COVID-19 COMPLICATIONS AND SUGGESTED MEASURES: MODERN TOOLS FOR INTERVENING PANDEMIC

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Abstract

Viral diseases are the most devastating health concern worldwide. Outbreaks of coronavirus (CoVs)-related acute respiratory diseases are responsible for the massive health/socio-economic breakdown in the last two decades including the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), the third reported spillover SARS-CoV-2 from an animal coronavirus to humans. After the H1N1 pandemic influenza (2009), SARS-CoV-2 (novel-beta coronavirus) causing COVID-19 has stretched across 215 countries in 5 major continents with 200,523,190 confirmed cases (4 August 2021; https://www.worldometers.info/coronavirus/). COVID-19 patients had cough, fever, dyspnea, headache, and respiratory failure, as well as shock, acute respiratory distress syndrome, and sepsis in severe instances. Independent of two preceding epidemics, SARS (2002) and MERS (2012), a knowledge gap about the emerging medical manifestations as well as complications of SARS-CoV-2 (2019-2020) infections in humans must be filled, with a focus on immunological complications and computational genomics for forecasting/ preparedness for a similar outbreak in the future. This paper aims to address aspects of this gap.

Keywords: Human Coronaviruses, drug repurposing, COVID-19, Comorbidities, Computational Genomics

Introduction

Coronaviruses (CoVs) have proved to be the most devastating pathogens of the 21st century gearing up the global focus on viral research once again. The major thrust of viral research in the pandemic condition is represented in Figure 1. Coronaviruses are members of the Coronaviridae family and can infect a wide range of animals (1). Their genetic material is non-segmented single-stranded RNA of positive sense, along with an envelope (E) and nucleocapsid (N). Due to the presence of bulbous surface projections which resemble a crown, the name 'corona' is given to the viruses and can be attributed to peplomers (2). The length of their genetic material can range from 26 to 32 kb. They are classified into four genera, namely alpha (α), beta (β), gamma (γ), and delta (δ). The beta and alpha viruses affect mammals, while the delta and gamma viruses attack birds (3). The viruses that are housed in the avian and zoonotic populations are mostly asymptomatic, though birds can get respiratory tract infection (RTI) or enteritis, while pigs and cows can get enteritis (4). Human coronaviruses (HCoVs) are the most common cause of RTI. Six HCoVs have been found so far, including HCoV-229E (α-CoV), HCoV-NL63, HCoV-KU1, HCoV-OC43, 'Middle East Respiratory Syndrome-CoV' (MERS-CoV) and 'Severe Acute Respiratory Syndrome-CoV' (SARS-CoV) as β-CoVs. The SARS and MERS epidemics in 2002-2003 and 2012-2013, respectively, as

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well as the COVID-19 (as named by WHO as Coronavirus disease 2019) pandemic in 2019-2020, highlighted the epidemic potential and clinical relevance of HCoVs with varying pathogenicity and high mortality rates (4-6). Mild cough, rhinorrhea (upper RTI) or tracheitis, severe cough, and bronchitis are all symptoms of the 229E, NL63, OC43, and HKU1 genes (lower RTI).

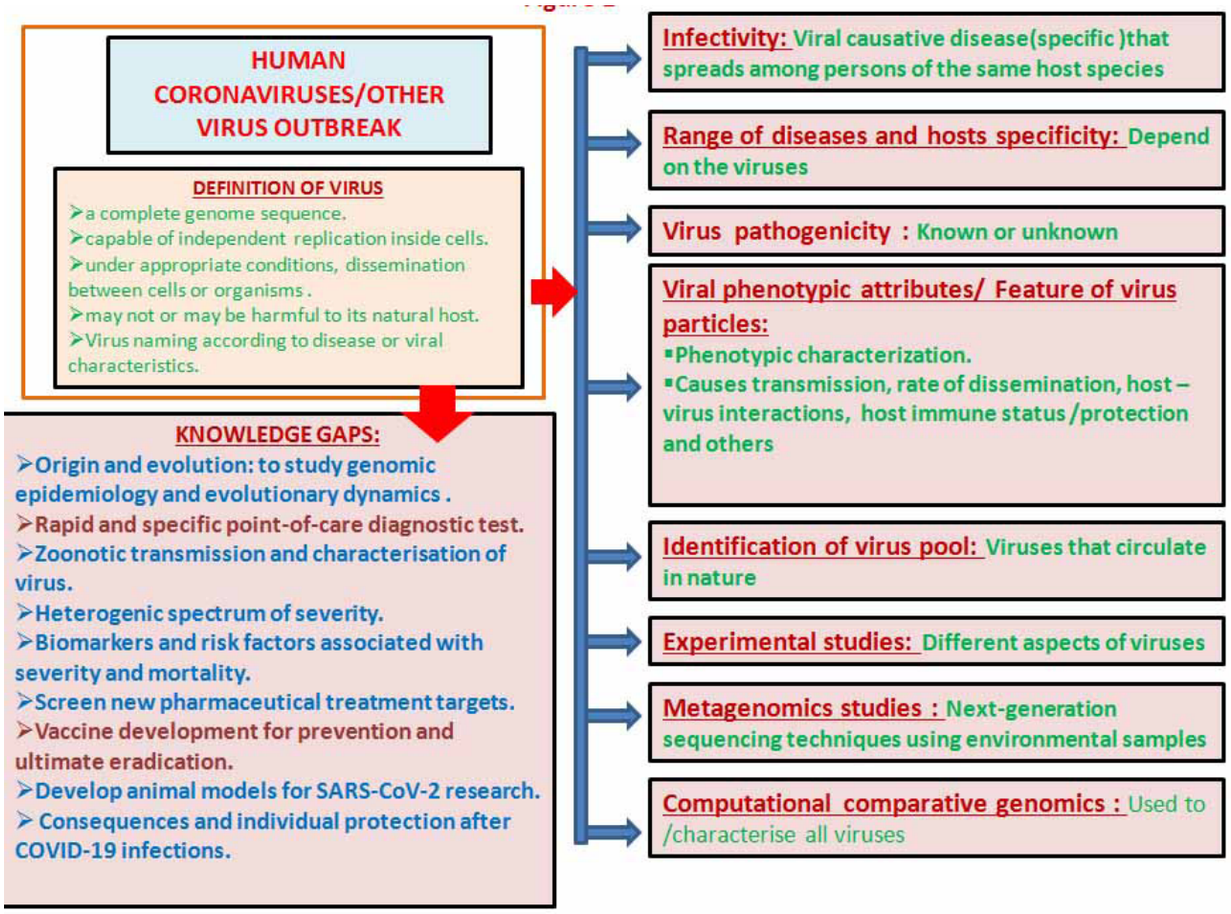

Figure 1: Major thrust of viral research. Infectivity, metagenomics, computational genome sequence, host-virus interaction, knowledge gaps and other related areas were noted.

MERS-CoV encompasses the "C lineage" of coronaviruses that generally infect humans and SARS-CoV and SARS-CoV-2 belong to the "B lineage" (7-9). Despite the fact that CoVs have been around for centuries (9), their origin is unknown. Bats are the principal reservoirs of both α- and β-coronaviruses, according to genetic and virological investigations. Before spreading to humans, the virus utilized palm civets and dromedary camels as intermediary hosts (9). Zoonotic coronaviruses cause infections by spreading from one species to another through a spillover event. The membrane, spike, and other structural proteins are all encased in a generic bilayer lipid envelope structure found in all coronaviruses (10) (Figure 2 & 3). The non-proteins (nsp1-nsp16) of the viruses were encoded by several genetic loci on the RNA. Coronaviruses have a 3'-polyadenylated tail and a 5'-methylated cap, with structural and nonstructural genes in between. The accessory genes (located at the 3' end of a genome) are intermingled among the structural genes, which plays an important role in viral pathogenesis (11). CoVs of animal origin have undergone genetic and evolutionary changes, resulting in altered CoVs that are extremely pathogenic and likely to be more lethal to humans (12).

The genome of CoV is divided into ten open-reading frames (ORFs). The coronaviruses' ORF1a and ORF1b located at 5' end of the genome occupy major regions of the genome and are translated to produce large polyproteins 1b and 1a (polyprotein AB in MERS-CoV) that encode for replicase and transcriptase, which self-sliced to form non-structural proteins that are responsible for virulence (13). In general, the viral RNA's capping and tailing enable it to connect to the host ribosome, which then interprets it. Proteases break the polypeptide into non-structural proteins as a result of this process (13). These non-structural proteins combine to generate "RNA dependent RNA polymerase"

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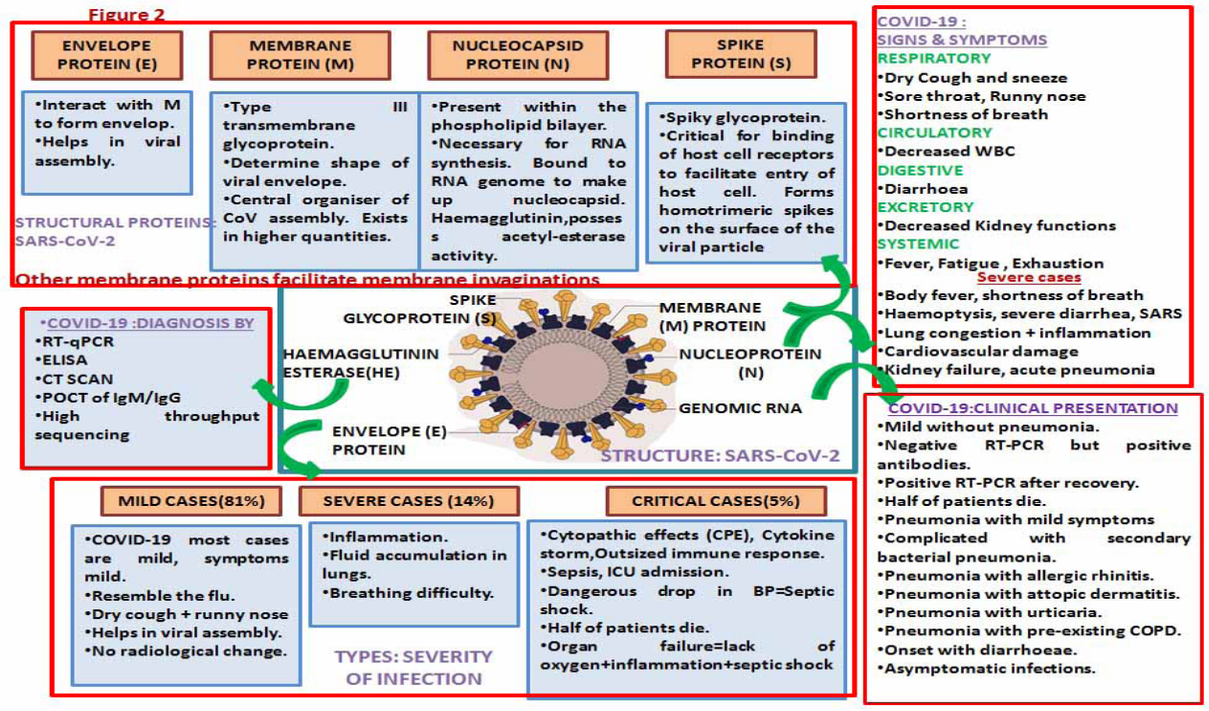

Figure 2: Details of COVID-19. The virus SARS-CoV-2 causes COVID-19 disease. The functions and location of the four structural proteins were given. The assembly of all structural proteins was not required to make virions. Non-structural protein helps in dispensing or compensating certain proteins. The severity of COVID-19 infection includes mild, severe, and critical. The diagnosis, signs, and symptoms of COVID-19 including the severe cases were mentioned. SARS=Severe Acute Respiratory Syndrome, ELISA=Enzyme linked immunosorbent assay, CT= Computer Tomography.

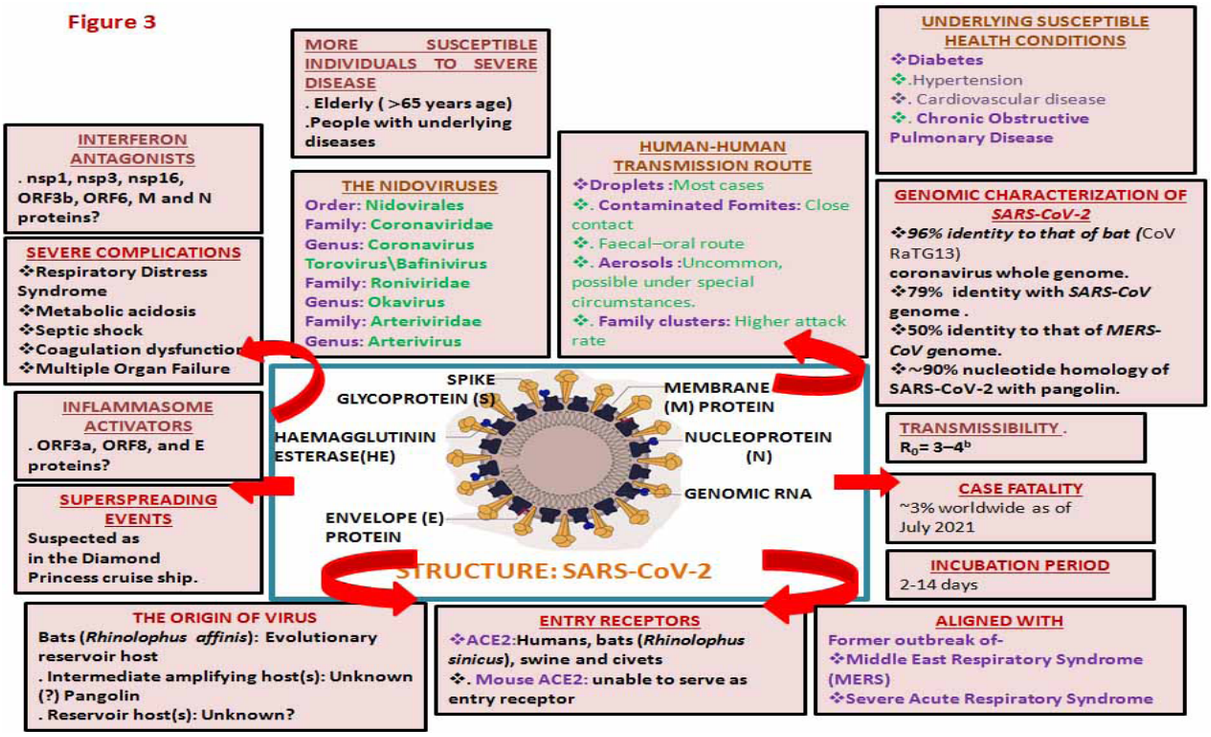

Figure 3: About SARS-CoV-2. The virus, its family, route of transmission in humans, entry receptors, the origin of the virus, transmissibility, comorbidities, antagonist and activators, genomic characterization, case fatality, and superspreading events were noted. The transmission rate of SARS-CoV-2 expressed as reproductive number (R0) comes within the range of 3-4, which is higher than that of SARS-CoV.

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(RdRP), which participate in replication and subsequent transcription. The endoplasmic reticulum is the location of translation, from which secreted proteins travel to the Golgi apparatus, where progeny viruses are gathered and released via exocytosis. All of these viruses have been linked to RTI in the vulnerable host and have been identified as a highly infectious zoonotic transmission.

The Adenine-Thymine percentage (AT%) in the SARS-CoV-2 genome was more elevated than the Guanine-Cytosine percentage (GC%) in other CoV genomes. SARS-CoV-2 has a lot of codons that finish in A or T. Pyrimidine-rich codons are preferred over purine-rich codons. SARS-CoV-2 possesses a lower effective number of codons (ENc) value than Bat SARS, SARS, and MERS-CoVs, indicating higher codon bias and gene expression potency, especially for the E and spike (S) genes. Furthermore, SARS-CoV-2 encoded the codons that were the most negatively biased and over-biased (14). Understanding the pattern of infection and comparing it to prior outbreaks can provide a lot of information on how to prepare for future outbreaks. Bioinformatics research provides a critical foundation for studying viral pathogen drug targets and accounts for significant progress in medication repurposing studies. Although COVID-19 vaccines are now available, the negative effects of already infected persons cannot be overlooked, as the virus has already had a significant influence on human populations, and reservoirs for the virus still exist. As a result, understanding the application of contemporary methods that allow researchers to evaluate past trends in infections, genetic similarities, and future implications in drug discovery, is a major study emphasis. This review focuses on the specifics of COVID-19, its genetic similarities to other viruses, the disease's associated immunological complexities, the use of modern bioinformatics tools for analysis, and the revalidation and repurposing of effective therapeutic options to combat these deadly infections.

COVID-19: Primary knowledge

More than 11,691,364 persons have current cases of the disease (11,613,499 have mild cases and 77,865 have serious or critical cases) throughout 215 nations at the time of lettering this article, resulting in the deaths of more than 3,990,613 people (5 July 2021). The number of suspected and confirmed cases, as well as the number of deaths, continues to rise, although there has also been a notable increase in the count of recovered COVID-19 patients. The virus was initially known as 2019-nCoV, but following characterisation and genomic sequence analysis, it was discovered to be a strain of SARS-CoV with 79% similarity, hence it was renamed SARS-CoV-2 on 11 February 2020 by the International Committee on Taxonomy of Viruses (ICTV) (5). The disease's strong transmissibility is due to the remaining genomic dissimilarity. The Chinese chrysanthemum bat (primary reservoir), which has a greater sequence homology to Bat-CoV-RaTG13 than pangolin, is thought to be the amplifying/intermediate host of SARS-CoV-2 (due to similarities to SARS-CoV) (15). As a result, SARS-CoV-2 is a zoonotic virus that has adapted to infect humans as a result of a spillover occurrence. Two changes in the S and N proteins may explain zoonotic transmission of SARS-CoV-2. The high pathogenic potential of SARS-CoV-2 is attributed to two hypervariable hotspots in the ORF8 genes and polyprotein, respectively, at locations 28,151 (Ser/Leu alteration) and 8,789 (synonymous variant) (16-17). Although this disease is very contagious, as evidenced by the large number of sick people, the incubation time varies from 0 to 24 days, with an average of 5 days (18), and there have been a few asymptomatic instances.

Comorbidity and immunological complications in COVID-19

COVID-19 has been conjugated to a number of comorbidities, encompassing type 2 diabetes, cerebrovascular illness, chronic obstructive pulmonary disease (COPD), kidney failure, and hypertension. Patients with one or more comorbidities have a poor prognosis. Obesity affects the epitope-profiling of SARS-CoV-2 receptors as well. Low-grade systemic inflammation caused by adipokines produces a rise in cytokines release in obese people, according to metabolism. Coronavirus entry is facilitated by impaired phagocytic cells and angiotensin-converting enzyme 2 (ACE2) receptors on the pancreas, resulting in temporary Type 2 Diabetes Mellitus (T2DM), pneumonia-like symptoms and rapid hyperglycemia. Lower insulin levels and increased lung inflammation are caused by increased furin expression, dysregulated immune response, decreased T-cell activity, and greater ACE-2receptors. COVID-19 has deadly comorbidities such as insulin resistance and the advanced glycation end product (AGE)-receptor of AGE (RAGE) signaling pathway. ACE-2 expression was considerably higher in active smokers and people with COPD. Males are more vulnerable to severe COVID-19 than females. The danger of infection is higher in the elderly. In comparison to elderly persons, children (often asymptomatic and silent carriers) have anti-SARS-CoV-2 immune memory, effective viral clearance, Th-2 biased immunity, low tendency to cytokine storm, controlled inflammation, and modest tissue damage. Coronavirus susceptibility is enhanced in elderly adults with immunosenescence, recurrent multimorbidity, and low-grade chronic systemic inflammation with substantial increases in inflammatory markers (IL-6and C-reactive protein). LDH, IL-6, D-dimer, ferritin, cardiac troponin, G-CSF, IL-2, IL-7, TNF-MCP-1, and MIP-1 were important biomarkers in ICU admitted patients (19-21).

COVID-19 causes hypoxemia, which necessitates the use of a ventilator in individuals who have a poor prognosis. Infection with COVID-19 causes severe lung damage due to a microbiota imbalance, the use of respiratory corticosteroids, an inflammatory response surge, inadequate immunity, and flowing mucus in COPD with elevated ACE-2 receptors. In intensive care unit (ICU) admitted COVID-19 patients with co-morbid COPD, there was a significant rate of mortality. Smokers and asthmatics have diminished IFN-secretion and a delayed innate anti-viral immune reaction, which can lead to serious

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consequences. Asthma is not a significant predisposition for COVID-19 infection. In COVID-19, significant case fatality rates are linked to hypertension and pneumonia symptoms. The treatment regime upregulates the expression of SARs-CoV-2 receptors in hypertensive individuals. COVID-19 infections, such as SARS and MERS, were found to have a higher prevalence in people with cardiovascular disorders. The causes are a weakened immune response and ACE-2 receptors in heart muscle cells.

Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactic dehydrogenase (LDH) levels cause liver damage in COVID-19 when ACE-2 receptors are localized on liver cells, SARS-CoV-2 targets (cholangiocytes, kuppfer cells). Hepatic disorders, medication toxicity, and psychological stress can contribute to serious liver damage. Cancer patients who are undergoing chemotherapy are at a heightened threat of contracting COVID-19 due to their weakened immunity. Human Immunodeficiency Virus (HIV) and hepatitis B infection, several respiratory ailments, renal abnormalities, and immunodeficiencies are among COVID-19's less prevalent comorbidities. With acute kidney damage, dipeptidyl peptidase-4, ACE-2 creates the target for viral entry (19-21).

The computational perspective of COVID-19 genomics

Marchler et al. (2017) used genomic sequences from the Genbank Reference database in their research (22). Virus genomes were acquired from GenBank using BLASTn with the query of 2019-nCOV. The Geneious (version 11.1.5) was used to predict the ORF of the verified genome sequences, and the Conserved Domain Database was used to annotate them (22). Geneious was also used to calculate pairwise sequence identities. Simplot software (version 3.5.1) was used to study potential genetic recombination, and MAFT software (version 7.450) was used to conduct phylogenetic analysis (23). Phylogenetic studies of the entire genome and important coding areas were performed with 1000 bootstrap replicates using RAxML software (version 8.2.9)(24) and the generic time-reversible nucleotide substitution model. Quite a few receptors that distinct coronaviruses attach to, like the ACE2 for SARS-CoV (25) as well as CD26 for MERS-CoV, have already been identified by bioinformatics research (26). However, recent molecular modelling researchers have discovered that the receptor-binding domains (RBDs) of SARS-CoV and 2019-nCoV are structurally similar. Though some amino acid changes were noted in SARS-CoV and SARS-CoV-2 in their RBD domain, but they use the same ACE2 as their receptor. Study in HeLa cells expressing ACE2 proteins showed this finding (27). More research is needed to see if these mutations impair ACE2 binding or modulate receptor tropism.

The genomic characterization of COVID-19 based on sequence homology with other SARS or coronaviruses is important, but studies on repurposing previous treatments in opposition to the COVID-19 endemic could help to spot treatment modalities (28), with recognized preclinical, pharmacodynamic, pharmacokinetic, and toxicology profiles, that can enter stage 3 or 4 quickly or be used straight in clinical platforms. One of the benefits of this strategy is that, in that situation, the typical quest for a vaccination can be avoided for the time being. Li (2016) studied the genome sequence of SARS-CoV-2 and determined that SARS is the closest disease to MERS and other human coronavirus infections, based on genome similarities between the two causative viruses (2). COVID-19-related genes were discovered using an AutoSeed pipeline (text mining and database searches) (29). Using those genes, molecular networks were created, leading to the discovery of 24 disease-related human trails and the recommendation of 78 medicines for repurposing (30).

Based on the alignment of sequences, SARS-CoV was the virus that was closest to SARS-CoV-2, and SARS was utilized as a keyword in text mining alongside the NCBI PubMed abstracts database, which was downloaded in December 2019 (31). Inside any sentence (also known as "sentence co-occurrence" in Natural Language Processing (NLP) approaches), all human genes co-occurring with the term "SARS" (full names, abbreviations, or synonyms) were used. The count of SARS co-occurrences was used to rank all of the genes. "MERS", "coronavirus", "viral pneumonia", and "HIV" were included to the text mining findings to improve the quality of the results. Because of its close resemblance to SARS-CoV-2, MERS was chosen (32) as it has been examined for a long time. Because of the nature and symptoms of SARS-CoV-2, the terms "coronavirus" and "viral pneumonia" were chosen (33). Despite the fact that HIV is not a coronavirus, "HIV" was selected as a keyword since HIV and SARS have comparable viral protein structures (34) and HIV medicines have been shown to be effective against SARS (35). Additionally, there are publication data and extensive research on HIV that can be used to enhance text mining analyses.

In addition to the text mining analysis data, six other keywords from reference databases, including DrugBank, DisGeNET, MalaCards, KEGG, Edgar, and also GWASCatalog, were used to enrich the search for SARS-related genes (36). These databases combine text-mining results with expert-curated content on topics such as pathways, genetic variables, and animal models. The findings of text mining and database searches were combined to create a final catalog of seed genes. Pseudoephedrine, andrographolide, tapinarof, chloroquine (small molecules), afelimomab, golimumab, and ibalizumab are just a few of the key medications discovered (biotech drugs). Repurposing drugs can help us treat COVID-19 without the need for a vaccine for the time being.

ACE2 was determined as the most important candidate gene associated with COVID-19 exposed of all the biomarkers incorporated in the study. To characterize the ACE2 interaction network and analyze ACE2 tissue expression that may have been modulated by SARS-CoV-2 infection, the network medicine approaches, bioinformatics tools,

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and publicly available datasets were used. According to the study, the top ACE2 interactors are particular miRNAs that act as regulators between ACE2, virus-infection linked proteins, and cardiac interaction networks, with lung and nervous system arrangements serving as a reference. In this study, SARS-CoV-2 risk groups were identified and treatment recommendations were made for them. To investigate the connections between other genes and ACE2, a PPI network was built in the virtual platform Cytoscape 3.7.2 using human interactome data from the StringApp 1.5.1 (Search Tools for the Retrieval of data for Interacting Proteins/Genes) database, which contains data on known and predicted protein interactions (37). The networks of interactions are made up of a set of genes (nodes) that are connected by edges that describe the functional linkages between them. Gene expression confidence scores >2 in a given tissue were assigned to interaction networks with tissue-specificity. So as to get better the interpretation of gene functions, The database of Gene Ontology (GO) using BiomaRtR package for mining the GO terms were used and further the genes connected with subsequent processes which comprises "Inflammation" (having 22 GO terms and 648 genes), "coagulation" (having 18 GO terms and 223 genes), "angiogenesis" (having 24 GO terms and 535 genes), "cardiac muscle functions" (having 176 GO terms and 524 genes), "muscle hypertrophy" (having 16 GO terms and 85 genes), along with "fibrosis" (having 23 GO terms and 263 genes) were recognized. Similarly, the data was extracted using genes that were likely connected to "viral infection" (with 120 GO keywords and 1047 genes). The list of disease-related genes was derived from the T2DiACoD database at http://t2diacod.igib.res.in/ (38). Datasets on nephropathy, CVD, atherosclerosis, and neuropathy were taken from this database. For the keyword "diabetes type-2," the genes related to diabetes were pulled from the domain StringApp disease database. For gene extraction and subsequent research, the GO word lists were used once more.

In silico investigation revealed that the ACE2/RAS, Apelin, and AGE-RAGE pathways are crucial in the COVID-19 infection (39). Pathway enrichment study revealed a significant link between Chagas disease and several disorders. Atherosclerosis, Alzheimer's disease, and malaria are all diseases associated with increased arterial wall shear stress (39). ACE2 plays an essential role in the cardiovascular system, and is hence accountable for a critical concomitant symptom, according to the findings.

COVID-19 genomics computational study has shown genomic sequence similarity with other related viruses, potential pharmacological targets, and biomarkers that could be employed as novel therapeutic options in the future. To make further advances into COVID-19 pathogenesis, however, both fresh computational and advancements in wet lab approaches are necessary.

In silico techniques to design drug repurposing approaches for COVID-19

Despite the availability of vaccines, COVID-19 research necessitates unique therapeutic implications, as many people remain infected and vaccination campaigns are difficult to reach complete populations within a year, particularly in underdeveloped countries. As a result, computational strategies for repurposing current medications are regarded as critical clinical interventions. Because SARS-CoV-2 infection typically activates innate and adaptive immune reactions in infected hosts, preclinical in vitro and in vivo studies on other CoV-induced diseases suggested that using alpha-interferon, arabinol, chloroquine phosphate, lopinavir/ritonavir, remdesivir, and other anti-inflammatory drugs could result in promising clinical outcomes for SARS-CoV-2 patients (40). Since the treatment options for SARS-CoV-2 infection are restricted to broad-spectrum antivirals, the diagnosis is dependent on detection of the viral genome in real-time PCR Test with particular virus probes (41). However, in many situations, the pharmacological treatment was ineffective (42). Molecular modeling is one method for creating repurposed pharmaceuticals. Shah et al. (2020) conducted a test of 61 pharmacological compounds that are already in use, and 37 of them were shown to interact with more than two protein structures of COVID-19 (43). According to the docking tests, HIV protease inhibitors and RdRp inhibitors were among the chemicals that showed potential for binding to the COVID-19 enzyme (43). In addition, COVID-19 therapies could include CGP42112A, an angiotensin AT2 receptor agonist, Methisazone, a protein synthesis inhibitor, and ABT450, a non-structural protein 3-4A inhibitor (43).

Drug repurposing algorithms use a variety of methods to rate pharmaceuticals, including molecular outlines (44), chemical organizations (45), adverse sketches (46), molecular docking (47), electronic health records (48), pathway examination, genome-wide association studies (GWAS) (49), and network perturbations. Recently the three pioneering network-medicine drug-repurposing techniques based on network diffusion, artificial intelligence (44, 50-52), and network proximity were evaluated (44, 50-53). They employed 918 medicinal compounds that had been scientifically screened to suppress growth and viral infection in cultured cells to assess the validity of such predictions (54). They have also looked at data from clinical trials to see what doctors think about promising treatment possibilities. On 15 April 2020, they deployed 12 pipelines to forecast the efficacy of 6,340 medications in DrugBank (55) against SARS-CoV-2, extracting and freezing the predictions in the form of 12 sorted catalogues, and indirectly figuring their effect by perturbing the host sub-cellular cascade. These medications cannot be found using standard binding-based methods since they don't target viral proteins or their hosts, but they can be prioritized

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using network-based methods (41). Drug repurposing tries to prioritize all accessible medications in order to focus experimental efforts on the most promising ones. As a result, the most acceptable performance metrics are the proportion of all positive outcomes in the top K rated pharmaceuticals (remind at K) and the number of positive outcomes in the top K ranked pharmaceuticals (accurateness at K) (56). Based on these techniques, 76 of the 77 drugs that demonstrate effectiveness in their trial display are "network therapeutics" (41). Chloroquine, penicillin, pentoxifylline, thalidomide, cortisol and other commonly used repurposed drugs created during the study by Viveriros et al. (2020) and Al-Horani et al. (2020) (57-58). The bulk of drug-gene interactions, according to the current study, are based on PPI (Protein-Protein Interaction) networks, gene enrichment, and functional annotations. All significant drug-gene interactions are based on ACE2 and its metabolic intermediates like ACE, ACE1, and S proteins, as well as certain actors like APOA, TMPRSS2, AGT, and others, which all play key roles in cardiovascular processes at various levels (42). The bulk of drug-gene interactions, according to the current study, are based on PPI networks, gene enrichment, and functional annotations. The bulk of drug-gene interactions, according to the current study, are based on PPI networks, gene enrichment, and functional annotations. All significant drug-gene interactions are based on ACE2 and its metabolic intermediates like ACE, ACE1, and S proteins, as well as certain actors like APOA, TMPRSS2, AGT, and others, which all play key roles in cardiovascular processes at various levels (42).

The effectiveness of this drug repurposing technique will be determined by whether such drugs compare favorably to virus-specific vaccines or small molecules, both of which have long been considered gold standards in modern therapeutic research (59). Using precision oncology information, it is possible to conclude that a broad-spectrum strategy will have basic problems. On the efficacy and off-target toxicity fronts, drug repurposing will have to compete with structure-based creation of preventative/therapeutic vaccines and small molecules (60). The CoV spike glycoprotein employed by SARS-CoV-2 at atomic resolution, as well as the human ACE2 enzyme as a cellular entry point, have recently been identified (59). These findings are expected to hasten the development of vaccinations and antibodies. However, such processes can take up to a decade and are hampered by the risk of epitope antigenicity being reduced as a result of the virus's genetic drift (60-61).

As a result, significant support from additional in silico approaches corroborating the results is required to corroborate the uniformity of the pharmacological targets described (62).

Conclusion

Virus illnesses are the most harmful form of infections because the most prevalent difficulty is the failure to develop effective vaccines within a reasonable time frame and successfully carry out mass immunization campaigns. Observing the pattern of a different viral outbreak, the mechanism of infection, genetic characteristics, and transmissibility, as well as computational approaches, allows us to investigate the similarities between them and solve the most vexing mysteries related to developing an effective combating method. SARS-CoV, MERS-CoV, and SARS-CoV-2 have been discovered to have significant sequence similarities and exploit a common pathway of infection among their hosts. They enter through the respiratory system and take advantage of common receptors found in respiratory tissues such as ACE2, APN, DPP4, and others. Despite this, the infection's severity and transmissibility are constantly increasing. Computational analysis aids in the repurposing of possible treatments, resulting in a significant reduction in the time required to find viable therapeutic options. Although these visible patterns emerge to aid in the development of efficient therapies in the susceptible host, they also fascinate us as we try to figure out why diseases are becoming more severe. Whether it is the intermediate host or the primary reservoirs through which the more diversified and virulent strain emerges is still a subject of ongoing research; however, the hunt for the most effective approach to manage such outbreaks in the future continues.

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Competing interests

The authors declare no competing interests.

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