Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Informatics in Medicine Unlocked 22 (2021) 100486

Contents lists available at ScienceDirect

Informatics in Medicine Unlocked

journal homepage: http://www.elsevier.com/locate/imu

Decoding information on COVID–19: Ontological approach towards design possible therapeutics

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ARTICLE INFO

Keywords:
Covid-19
Mortality rate
Ontology
Vaccine
Drug repurposing
Antiviral
Therapy
Decoding

ABSTRACT

To date, no effective preventive or curative medical interventions exist against COVID-19, caused by Severe Acute Respiratory Syndrome corona virus 2 (SARS CoV-2). The available interventions are only supportive and palliative in nature. Popular among the emerging explanations for the mortality from COVID-19 is "cytokine storm", attributed to the body's aggressive immune response to this novel pathogen. In less than a year the disease has spread to almost all countries, though the mortality rates have varied significantly from country to country based on factors such as the demographical mix of the population, prevalence of comorbidities, as well as prior exposure to viruses from the corona family. This review examines the current literature on mortality rates across the globe, explores the possible reasons, thereby decoding variations. COVID-19 researchers have noted unique characteristics in the structural and host-pathogen interaction and identified several possible target proteins and sites that could exhibit control over the entry of SARS CoV-2 into the host, which this paper reviews in detail. Identification of new targets, both in the virus and the host, may accelerate the search for effective vaccines and curative drugs against COVID-19. Further, the ontological approach of this review is likely to provide insights for researchers to anticipate and be ready for future mutant viruses that may emerge in future.

1. Introduction

COVID-19, a highly contagious respiratory illness caused by Severe Acute Respiratory Syndrome Corona virus 2 (SARS CoV-2), is believed to have spread from animals to humans at the local meat and sea food market at Wuhan, the capital city of Hubei province, China [1]. At first the disease was assumed to be incapable of spreading between humans. Though initial outbreak in December 2019 was reported only in Wuhan, soon cases were found in other parts of China among people not directly associated with Wuhan meat and seafood market, thus confirming that intra-human transmission was taking place. On January 30, 2020, World Health Organization (WHO) declared COVID-19 as global emergency [2], and on March 11, 2020, upgraded it to a pandemic [3]. By mid August 2020, 20.6 million confirmed cases and 749,000 deaths were reported globally [4]. As of mid-November 2020 these numbers have raised to 53.2 million confirmed cases and 1.3 million deaths, across 220 countries.

The rapidly accumulating research information related to COVID-19 from different parts of the world has created a huge glut of data some of which are not readily relatable. An ontological approach is expected to facilitate overall understanding of the biological process, furthering the likelihood of targeted drug development. Ontology can be defined as a

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https://doi.org/10.1016/j.imu.2020.100486
Received 1 September 2020; Received in revised form 20 November 2020; Accepted 20 November 2020
Available online 27 November 2020

set of concepts and categories in a subject area or domain that shows their properties and the relations between them. Generating molecular and genetic ontology involves analyzing proteins and genes in association with similar other molecules that may have control over various signaling pathways and developing common concepts. When the same ontological concepts describe two different species such as host and pathogen, it may provide fresh ways to understand the mutual interaction between their genes and proteins. Biological terminologies led by individual proteins and DNA's were programmed as huge data in computers with a facility to retrieve based on the user's command. The ontologies are terminologies or biological verbs collected from various research publications in the relevant area of research, and hence the retrieved information has high reliability for the ontological research application.

Accordingly, this review takes an ontological approach and summarizes the results of coordinated work of interdisciplinary experts who did not neglect any angle of the drug development. This allows maximum possible predictions for development of targeted drugs with no or minimal adverse effects. The ontology provides common terminology that furthers communications between experts in different specialties engaged in the same quest, such as pharmacology, vaccine designing, personalized medicine preparation, and new target identification. As individual departments tend to prefer specialists in their own discipline, institutions may need to appoint a team leader with interdisciplinary expertise and ontological skills. Being able to identify specific gene or set of genes, which are activated or suppressed during the disease condition helps in targeted development of the new drug. The traditional manual approach makes it tedious to identify a single gene or gene set in a large group of genes, whereas gene ontology can more quickly identify the most likely genes and their products which make the drug development process more reliable, faster and cheaper. Hence, gene ontology and different branches of biomedical ontology accelerates development of new drugs, new drug targets, as well as vaccine development. Various gene ontology consortia provide a platform that facilitates development of an integrated and controlled vocabulary of genes and gene products. Some of them-such as Gene Ontology (GO), Infectious Disease Ontology (IDO), and Vaccine Ontology (VO)-provide open source ontological databases to facilitate global cooperation. This paper discusses the utility of such databases in detail.

2. Historical Overview of COVID–19

The corona virus family contains four sub classifications: alpha, beta, gamma, and delta, long-known to infect non-human mammals and reptiles. The first infection on humans from a mutant zoonotic corona virus was the 2003 outbreak of Severe Acute Respiratory Syndrome (SARS). Since then, at least two more instances of previously non-pathogenic corona viruses infecting humans were reported, namely, Middle East Respiratory Syndrome (MERS) virus and SARS CoV-2 that causes COVID-19. Epidemiologists warn of the risk of more pandemics from mutated corona viruses in the future. In this context, the globally coordinated efforts of scientists to deeply understand and restrain this family of viruses from harming humans should be given top priority.

SARS CoV-2 has undergone minimal genomic modification/mutation from the SARS CoV-1, which was responsible for killing 774 people in the 2003 outbreak [5]. So far, three strains of corona viruses are believed to infect humans and potentially cause severe symptoms: MERS-CoV, SARS CoV-1, and SARS CoV-2. MERS virus is another species coming under the same genus that spread in Middle Eastern countries after its outbreak in 2012 and killed an estimated 858 people by 2019 [6]. Although these viruses come under the same family with similarities in the molecular aspects, mode of spread, and similar clinical conditions among humans, the exhibited behavior of each is different from each other.

This may be due to factors like rate of reproduction, zoonotic behavior, and type of clinical manifestation in the host. The reproduction rate of MERS is represented as $R0 = 1$, while for SARS CoV-1 it is between 1.7 and 1.9 and for SARS CoV-2 it is 2.5 making the latter reproduce faster than the other two [7]. Despite the lower reproduction rate, MERS CoV infections have higher fatality percentage (FP) since 2012, a total of 2,494 confirmed cases resulted in 858 deaths (FP: 34.4%). The lower reproduction rate of MERS may have provided longer time window for the healthcare systems to control the spread. Right from the receptor entry into the host cell and the use of antigenic peptides against host cells, MERS-CoV behaves differently from the other two corona viruses. SARS CoV-1 infection was detected in a total of 8, 089 people between 2002 and 2004, killing 774, representing an FP of 9.5% [9]. On the other hand, the SARS CoV-2 infection with its much faster reproduction rate, renders COVID-19 spread much faster [8] causing 20.6 million confirmed cases of COVID-19, while causing far lower FP 3.9% at 749,000 deaths.

3. Therapeutic Management of COVID-19

As of today, there is no specific treatment for COVID-19, and clinical management of the COVID-19 patients is through non-targeted therapies meant for management of the symptoms and preventing secondary bacterial infections, palliatives. As the infection spreads, there are also

Table 1
Types vaccines as listed by WHO and its mode of action.

S. No	Type of Vaccine	Mode of Action	Reference
1	RNA	Immunogenic region or the antigen of the microorganism's mRNA sequence will be loaded in the vector vaccine, directly triggering antibody production in the host system	verbek R et al. 2019
2	DNA	Immunogenic region or the antigen of the microorganism's DNA sequence is loaded in the vector vaccine, directly triggering antibody production in the host system	DNAvaccines -WHO
3	Live attenuated virus	A lab-weakened form of the pathogenic virusis used to induct immunity in the host system	Badgett MR et al. 2002
4	Inactivated virus	Particles of killed viruses grown in a controlled environment at the laboratory are introduced into the host. The viral antigens present in the particles stimulate the host immune system.	Petrovsky N et al. 2004
5	Non-replicating viral vector	The viral vectors used for the introduction of the antigenic region to the host cannot replicate inside the host cell. This calls for booster doses to keep immunity active.	Marjorie RG 2007
6	Replicating viral vector	As these viral vector scan replicate inside the host system, booster doses are not required.	Marjorie RG 2007
7	Virus-like particles	Artificially synthesized viral-like particles are introduced into the host system. This precludes the risk of causing virulence in the host system.	Zeltins A et al. 2013
8	Protein subunit	A protein subunit vaccine is prepared from a specific immunogenic protein part of the pathogen, which may directly induce immunity in the host system	Francis MJ 2018

Source: WHO 2020.https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

expectations of achieving herd immunity.

The proposed therapies can be broadly classified into three categories:(1) vaccines and new drugs [2], repurposing of existing antiviral drugs, and [3] non-antiviral drugs and accessory therapeutic management strategies.

4. Strategies of Vaccine Development

Esteban et al. in 2020 has extensively discussed vaccine development against COVID-19 [10], and the current review focuses on different aspects of designing vaccine using systems biology approach. Table 1 features the types of vaccines and vaccine platforms as per the WHO recommendation, except live attenuated and inactivated vaccine platforms, that are not amenable to ontology use among the listed eight. The excluded two categories use either whole virus or viral parts, hence there is no opportunity for vaccine design. All other remaining six platforms that are able to utilize the ontological approach are discussed here, particularly the methodology towards creating protein subunit vaccines, the most successful approach to date. Gussow et al. (2020) systems biology work revealed several antigenic portions of pathogenic and non-pathogenic corona viruses of all categories, as well as the possibility of currently non-pathogenic corona viruses gaining pathogenicity in the future. Gussow's extensive findings reveal that the enhancement of nuclear localization signals by nucleo-capsid protein and insertion on receptor binding motif (RBM) present in spike protein could render a corona virus potentially pathogenic. Consequently it might be surmised that the development of a protein subunit vaccine against RBM may provide immunity against COVID-19 [11]. In addition, common antigenic regions of current human corona viruses (SARS CoV-1, SARS CoV-2, and MERS) may remain unaltered in the sequence for a long period. Therefore, designing a protein subunit vaccine, targeting genetically conserved antigenic regions common to various species of corona virus is likely to yield preventive benefits that remain effective for several years.

A vaccine can be developed in a relatively short period, whereas understanding and mitigating its adverse effects and making it fit for human trials is a complex, challenging and time-consuming process. Until a decade ago, clinical trials used to be the only viable mode of evaluating the adverse effects of a vaccine. Currently different ontological processes make it easier to anticipate the impediments associated with vaccine production and its associated adverse effects.

Vaccine Ontology (VO) [12], part of the Vaccine Investigation and Online Network (VIOLIN) [13], provides several ontologically valuable pieces of information. The new technologies introduced by the VO and similar ontological databases help narrow down the likelihood and nature of adverse-effect-causing antigens. The latter could then be subjected to animal studies to evolve techniques to mitigate their adverse effects, and if successful, the vaccine could be considered for limited clinical trials. Many research groups use VO to improve the selection of effective and constructive antigen/antigens for the organism of interest and to predict its beneficial and adverse effects in their host systems. Hur et al. (2017) used VO and Interaction Network Ontology (INO) for selecting and narrowing down specific genes that can be utilized for vaccine development [14]. In another study performed by Xie et al. (2016), ontologically identified the adverse events (AE's) associated with the tuberculosis vaccine BCG as a treatment for bladder cancer. They reported many novel findings that include the genes associated with AE in the immune system, skin, and respiratory system while using against TB, whereas, they found genes associated with urinary complications in treating bladder cancer [15].

5. Failure of Antiviral and Non-Antiviral Drugs

Based on the emerging literature on COVID-19 pandemic and previous knowledge about the SARS and MERS outbreaks, scientists are working to modify the existing anti-viral drugs to treat COVID-19. Lopinavir and Ritonavir were used for previous corona outbreaks and HIV treatment as well. These drugs are designed to inhibit chymotrypsin-like cysteine protease known as the 3C-like protease which is also found in the COVID-19 virus. Lopinavir tends to show significant activity as a protease inhibitor *in vitro* whereas Ritonavir is co-introduced to increase the half-life of Lopinavir [16]. Despite several studies, Lopinavir/Ritonavir combination has failed to show beneficial effects against the COVID-19 virus, and is no longer recommended [17,18]. Another antiviral drug, Remdesvir, is now preferred for its comparatively beneficial effect to COVID-19 patients [19,20]. Remdesvir is a nucleotide analog, which is believed to prevent viral reproduction [21]. Even though this drug is claimed to be the best in the market, till now there is no published evidence against any drugs with clinical evaluation proof. Another antiviral candidate under investigation is Favilavir (Favipiravir), selectively designed to inhibit the RNA-dependent RNA polymerase (RdRp) in RNA viruses ([22]). Both of these drugs work on the same principle, but the problem is that these drugs are also capable of introducing a mutation in the viral genome that could make the virus even more dangerous. Even though these drugs are produced to inhibit viral reproduction, their beneficial effects are highly limited, and the adverse effects seem to be high that makes the drug fail in consecutive clinical trials [23]. After the COVID-19 outbreak, several research teams worked to modify existing antiviral drugs to deal with the new threat. Riva et al. 2020 has extensively analyzed more than 12,000 FDA approved small drug-like molecules, out of which they found 100 molecules to inhibit the viral replication, which included 21 known antiviral drugs. Besides, they identified selected compounds namely MDL-28170, ONO 5334, and Apilimod in possessing antiviral activity in iPSC-derived pneumocyte-like cells and primary human lung model [24]. While the above work was performed extensively in the combination of *in silico* and *in vitro* models, others employed purely *in silico* works to identify potent inhibitors of viral replication [25].

Several non-anti-viral drugs are used currently in the treatment of COVID-19 symptoms. Among them, Chloroquine (CQ) and Hydroxy Chloroquine (HCQ) are the most prominent. Originally used as anti-malarial drugs, these were also used to treat chemoprophylaxis, rheumatoid arthritis, and some blood disorders, and more recently, to treat HIV. SARS CoV2 uses endosomes in the host cell for its survival and Golgi apparatus for its reproduction. Both intracellular organelles are active only in the acidic environment. CQ and HCQ, being weak bases, makes the vesicles less acidic, hence makes the viral survival tougher [26]. Also, these drugs potentially inhibit the IL-6 mediated inflammatory pathway, thereby help prevent the cytokine storm inside the host system. The problems associated with CQ and HCQ are their strong adverse effects such as nausea, vision impairment, digestive disorders, and most importantly prolongation of QT interval, which could lead to cardiac arrest [27,28]. Despite the risks, CQ/HCQ is often used currently as a drug of choice to treat COVID-19. CQ/HCQ was officially approved by the FDA as an emergency alternative at the end of February 2020, which was revoked later, but the drug is still permitted in some other countries such as Brazil.

Tocilizumab is another anti-inflammatory drug, used for the treatment of rheumatoid arthritis. It is a monoclonal antibody that specifically inhibits the IL-6 signaling thereby reducing the severity of the COVID-19 [29]. The non-antiviral drugs discussed above are used as anti-inflammatory drugs to minimize secondary complications such as cytokine storm, rather than acting against the viruses. The mechanism of antiviral drugs discussed here was specified by the manufacturers, however, the inability of these drugs to stop viral replication indicates a need for more detailed studies related to host-pathogen interaction. Such in-depth understanding is vital to identify more vulnerability in the pathogen and develop drugs that target those.

Apart from pharmacological management, convalescent plasma therapy (CPT) is also used to treat COVID-19 patients. CPT provides a pool of antibodies against the virus and provides passive-artificial immunity. Even though CPT is believed to be effective in COVID-19

Fig. 1. Gene ontology database derived interaction of COVID-19's M protein with host genes. ATP1B1 and ANA6 are highlighted.

patients in the initial stages, it does not appear to have significant benefits in the acute stages of the disease [30]. Additionally, COVID-19 patients in the ICU affected by hypoxia and sepsis are recommended mechanical ventilation to maintain the oxygen levels [31,32]. Overall, the view about the pharmacological aspects of COVID-19 depicts the need for a better understanding of the patho-physiology of this virus. Mass analysis of huge data with a different type of experts, including pharmacologists, virologists, molecular biologists, biochemists, immunologists, and bioinformaticians, and to employ them together under one umbrella for the identification of a variety of targets for SARS CoV-2 on the host and the virus itself. To facilitate such an integrated approach, a few systems biology platforms are currently available to analyze high volume data. Their outputs facilitate better understanding of various aspects of the host-pathogen interaction. A few key features of these system-based approaches are discussed below.

5.1. Ontology-based approach for COVID-19

Gene Ontology (GO) is a widely used online database and consortium used to attribute genes and gene products of different species in biology, which programs a large amount of experimentally proven and published data, after the alignment under the specific vocabulary of terms [33]. It is programmed to collect and organize the huge database on the combinations of gene-gene/gene-protein or protein-protein between different species.

Numerous studies have benefited from the database accessible at the GO website *https://geneontology.org* using it to retrieve the information about host-pathogen interactions, and using the same to identify the most likely type of proteins that form pathogen interactions with the host at different levels [34–36]. The GO database was used in an important research by Gordon et al. (2020) after the COVID-19 outbreak. The researchers cloned and expressed 26 SARS CoV-2 proteins and identified its interactions with human proteins, and extensively used GO to gather the information on proteins interacting with the host cells, and used protein-protein interaction network analysis to discover a total of 332 high-confidence protein-protein interactions. They also reported that compound PB28 could serve as an antiviral drug that may work as an inhibitor of mRNA translation and a predicted regulator of sigma-1 and sigma-2 receptors [37].

Despite significant successes, a few wet-lab biologists appear to be under valuing such outputs as the oretical predictions by computer and not factual. The reality is that these computers are programmed to quickly compute multiple permutations and combinations from vast databases as per the command given by the attributes from the previous literature. Human mind also tests various permutations and combinations but so slowly that results that well-programmed data analysis can output in an hour may take six months for a small team. This will also cause waste of valuable man hours spent in largely routine work. In addition, gene ontology.org offers several additional tools to narrow down useable data from the varied information from diverse specialties. Along with molecular ontological tools, the site provides immuno-ontology platforms for immunologists to study the dynamics between the host's immune system against different types of pathogens and other variables [38]. The website also gives a separate link that provides basic understanding of the SARS CoV-2 interaction with human genes and proteins [39], namely, 1) the functions of human proteins exploitable by the virus to gain entry into human cell and 2) after viral entry, the functions of vulnerable human proteins within a cell.

Gene Ontology (GO) constitutes three major components: 1) molecular function, 2) biological process and 3) cellular component. The interactions of the given pathogen with the host will be displayed under three categories and the subcategories by highlighting "strongly reactive "in dark blue, "moderately reactive" in mild blue, and not highlighting "non-reactive". More such user-friendly options are built into the software.

A preliminary analysis of host pathogen interaction by GO was performed by selecting a membrane protein (M protein) of SARS CoV-2 and proteins from the host. The virus's M protein interacted with 30 host proteins showing high reactivity with sodium/potassium-transporting ATPase subunit beta-1 (ATP1B1), and moderate reactivity with Anoctamin-6 (ANO6) gene (Fig. 1). Interestingly, both these protein products of these genes are highly involved in lung disorders. ATP1B1 gene codes for the beta chain of Na^+/K^+ and H^+/K^+ ATPases and also codes the subfamily of Na^+/K^+ -ATPases. Na^+/K^+-ATPase is an integral membrane protein responsible for establishing and maintaining the electrochemical gradients of Na and K ions across the plasma membrane

Table 2
Lower COVID-19 infections in previously MERS infected countries in the Middle East.

Name of the Country	MERS pandemic			COVID-19% fatality till date 29th July 2020		
	Confirmed cases	Number of deaths	% fatality	Confirmed cases	Number of deaths	% fatality
Saudi Arabia	1030	453	44%	270,831	2,789	1.03%
United Arab Emirates	77	10	13%	59,546	347	0.58%
Jordan	19	6	32%	1,182	11	0.93%
Oman	6	3	50%	77,904	402	0.52%
Qatar	13	5	39%	109,880	167	0.15%
Kuwait	3	2	66%	65,149	442	0.68%

[40]. Another study reported that digoxin, a cardiacglycoside, is effective in preventing the entry of the Chikungunya virus by blocking Na^+/K^+ and H^+/K^+-ATPases pump after screening several clinically significant compounds through high-throughput screening [41]. Moreover, Li et al. (2019) reported that ATP1B1 is essential for normal lung function and the down regulation could lead to lung fibrosis [42]. These two studies revealed a strong link between ATP1B1 and viral entry into the host cell which has led us to suggest that this protein might be valuable in developing a drug against COVID-19.

Another human host protein, ANO6, has been found (via GO) to be moderately reactive with viral M protein. ANO6 is involved in the Cl^- transport in the lung and intestinal tissues. A recent study reported that ANO6 is essential for the expression and normal functioning of the CFTR genes and normal lung function. Decreased or no expression of ANO6 is reported to be associated with abnormal lung functions [43]. Thus, simple analyses using GO can give rise to many such interpretations. With increased collaboration between experts from various fields in GO platform, all 29 proteins might be speedily identified and analyzed for COVID-19's interaction with host proteins. That may well open a potential expressway for identifying more drug targets and positive therapeutics trategies, anticipating future viral mutations, and being ready to combat them. Dyer et al. (2008) have demonstrated a huge dataset analysis with protein-protein interaction (PPI) network pertaining to more than 190 pathogens. They reported that most of the PPI's (likely 98.3% of 10,477 host-pathogen PPI's) are viral associated. In their elaborate study, they revealed several GO processes and functions which may be helpful in the development of new targets to fight against pathogens [44].

In an earlier study, Karadeniz et al. (2015) revealed by their own GO modeling, many host-pathogen interacting genes for *Brucella*. They used several literature mining protocols and kernel-based methods to extract the host-pathogen gene interactions [45].

The above mass data analysis experiments demonstrate the high likelihood of researchers developing comprehensive understanding of pathogens' entry modes, survival strategies, reproduction, mutation potentials and vulnerabilities. Further, by refining the selection process by modifying and narrowing down variables, it is possible to open up a new dimension of biological research in the field of not merely COVID-19 virus, but the entire corona virus family. Hence, during this pandemic emergency, it is recommended that the scientists utilize the combination of modern approaches (such as host-pathogen interactions by GO process) to identify new drug targets, (i) high throughput virtual screening for the selection of best ligand to interact with drug target and (ii) molecular dynamic simulation studies to analyze the stability of the drug and the target protein. These procedures could possibly help researchers to accelerate their research against the COVID-19 pandemic to save millions of affected.

5.2. Lower Mortality among COVID-19 patients in previously MERS-affected countries

Studies of the COVID-19 infection in the Middle Eastern region yield some interesting patterns. Several of these countries were previously MERS affected. As per WHO, MERS was first reported in Saudi Arabia in June 2012, later it began spreading to more than 27 countries across the globe. but largely concentrated in the Middle Eastern region. The disease spread over 12 countries in the Eastern Mediterranean (EMR) region, of which 8 countries were listed with a significant number of diseases spread [46]. Surprisingly these 8 countries except Iran, has significantly lower fatality rates towards COVID-19 infection compared to all other countries. Table 2 depicts the percentage fatality of MERS infected countries listed in the MERS fact sheet released by WHO and their current situation in the COVID-19 (as of13th August 2020). Intruding on to the possible reason for the lower fatality for COVID-19 infection among MERS infected countries, it is known that MERS shares 50% of the genome with COVID-19. The shared regions are more antigenic and capable of developing host-pathogen interaction. Because of its strong antigenic nature, the population with mild exposure to MERS virus via air, aerosols, touch, or by any other mode even with a less pathogenic dose may provide a natural immunity among them. And therefore if people from those listed seven Middle East Countries, with a history of previous spread for MERS, might have gained immunity not only against its own, also possibly would expect to provide immunity against COVID-19 because of its sharing genomic nature. The current scenario depicted the same phenomenon as described above among MERS infected population, while it is not possible to see a similar picture among other groups of the population from other countries and the data sets were collected from the official website of WHO (Table 2). Further, even regions of the SARS CoV-1 infected population do not seem to have good immunity against COVID-19. Hence, it is possible to consider that the antigenic region of MERS CoV could be important for the development of subunit vaccines, which may help to fight not only against MERS and also against COVID-19 as well.

6. Comorbidity and Global COVID-19 Death Rates

COVID-19 infection is appears to be rarely fatal to younger individuals with healthy immune systems. Societies where COVID-19 mortality rates are high tend to have older residents with comorbidities [47]. Persons with pre-existing conditions such as diabetes, asthma, high blood pressure and obesity have higher risk of mortality from COVID-19. As on date, statistics that establish the extent and nature of comorbidity risk associated with COVID-19 are not available. Nevertheless, the relationship is evident when comparing the COVID-19 deaths of country or region with its usual leading causes of deaths. Fig. 1 is the graphical representation of different diseases/reasons leading to the cause of death among the listed top ten COVID-19 affected countries. It is essential to know the disease pathology at this moment to correlate the COVID-19 deaths with other conditions.

Against of SARS CoV-1 and MERS viruses the host system's innate and adaptive immune response includes large-scale production of type I Interferons (IFN). Meanwhile against SARS CoV-2, a major defense consists of production of cytokine pools in the host system. The host cells are reported to produce a large amount of pro-inflammatory cytokines including IL-2, Il-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α against SARS CoV-2. Sometimes this can escalate into a dangerous

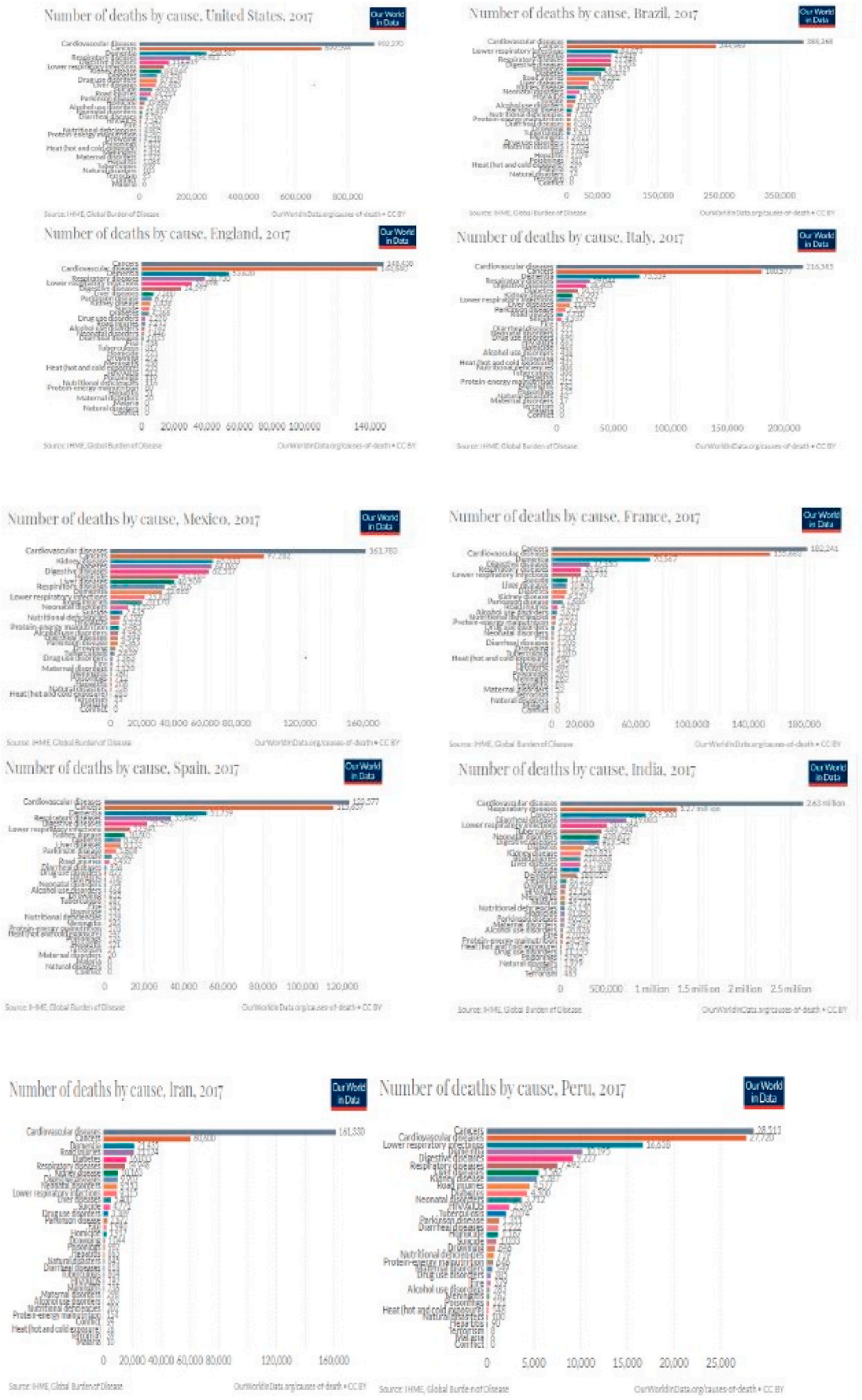

Fig. 2. Top 10 countries with the number of high death ratesfrom COVID-19 infection and the comorbidity details of the same. Source https://ourworldindata.org/.

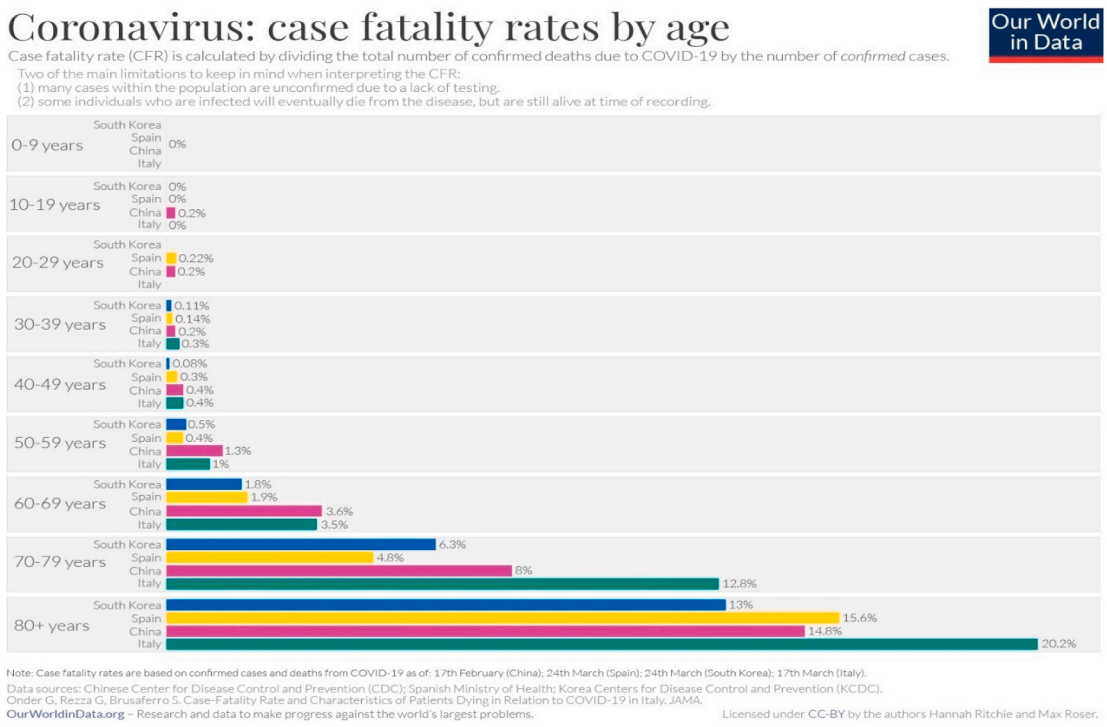

Fig. 3. Age-associated case fatality rate (CFR) in South Korea, Spain, China, and Italy. An increase in the age is directly proportional to the CFR and it is the only available data to date. Source https://ourworldindata.org/.

cytokine storm. Research shows that cytokine storm may lead to pulmonary inflammation, extensive lung damage, and acute respiratory distress syndrome (ARDS) [48]. Respiratory failure due to ARDS is believed to the main reason for COVID-19 related mortalities. Diseases like cardiovascular diseases (CVD), cancer, dementia, respiratory disorders, and lower respiratory infections are associated with the leading cause of death in these top 10 countries having high COVID-19 infection rates. A clear understanding of the comorbidity-induced aggravation of the disease should explain the higher COVID-19 death rates in these countries. Since some of these diseases are capable of elevating the inflammatory cytokine levels in the patient's body, susceptibility to cytokine storm increases, which further leads to the development of ARDS [49].

Wealthy countries such as the United States and European Union score high on all the above-mentioned disease conditions as depicted by their complete screening dataset of their citizens for the given condition. Several developing countries may also offer similar scenarios. However data from these countries are often incomplete and sometimes non-existent. In countries like India, reliable information on co-morbid states of the population infected by COVID-19 may be not available. Currently, there is growing understanding of the importance of the comorbidity conditions for the prognosis of patients with COVID-19. The developing world need to give great importance to generating comprehensive health datasets on their population which can be used to identify, target, and generate personalized treatment plans for the most vulnerable.

7. Ontological Approach to Comorbidity

As there are no specific databases or ontological approaches available to predict the comorbidity of any particular disease, research initiatives that predict comorbidity have been initiated. Ko et al. (2016) instigated the identification of comorbidity associated genes and pathways after collecting the information from four different disease databases, namely, OMIM (Online Mendelian Inheritance in Man), HPO (Human Phenotype Ontology), GAD (Genetic Association Database), and DO (Disease Ontology). From their experiments, they identified important genes and pathways commonly involved in different diseases including diabetes mellitus, ankylosing spondylitis, and other inflammatory spondylopathies. They reported that 40% enriched the sharing of GO terms for interleukin-10 receptor binding, regulation of immune response, and response to insulin for the above-mentioned diseases [50].

Table 3
Age-associated increase in COVID-19 death rate among different countries.

S. No	Name of the Country	Confirmed COVID-19 Cases	Confirmed COVID-19 Deaths	Population all age groups (000's)	Population aged b/w 50-100+ (000's)	Percentage aged b/w 50–100+	Percentage aged b/w 65–100+
1	United States	4,426,281	1,51,374	331,002	1,17,838	35.60%	16.63%
2	Brazil	2,484,649	88,634	212,559	54,278	25.54%	9.59%
3	United Kingdom	300,692	45,878	67,887	25,743	37.92%	18.65%
4	Italy	246,488	35,123	60,463	27,610	45.66%	23.30%
5	Mexico	402,697	44,876	128,934	27,249	21.13%	7.62%
6	France	183,804	30,223	65,274	26,155	40.07%	20.75%
7	Spain	280,610	28,436	46,753	19,324	41.33%	19.98%
8	India	1,531,669	34,193	13,80,004	2,67,742	19.40%	6.57%
9	Iran	296,273	16,147	83,994	16,942	20.17%	6.57%
10	Peru	395,005	18,612	32,971	7,437	22.56%	8.72%

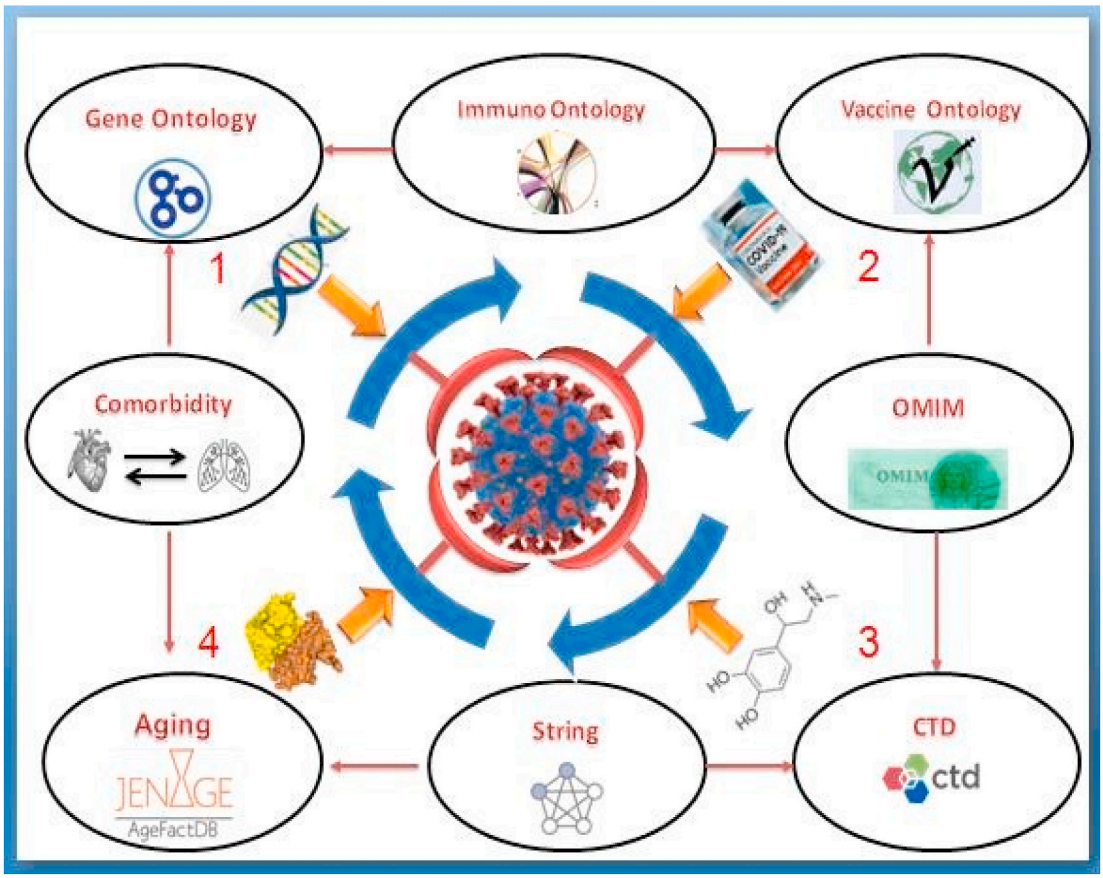

Fig. 4. Schematic representation needed for the development of new strategies against COVID-19. A combined effort of different systems biology approach may provide valuable information about 1) identification of new target gene, 2) development of new vaccine candidature, 3) development of new pharmacological agent, and 4) development of new protein target.

Hence, they strongly recommend that comorbidity, common pathways, and gene links should be incorporated into treatment plans. Since co-morbidity is associated with higher death rates (Fig. 2), the same phenomenon can be used to identify common signaling pathways in the case of COVID-19. Recently technological advancements have facilitated faster and more accurate identification of co-morbid genes. Zheng et al. 2018 performed the association of co-morbid genes in multiple sclerosis (MS), psoriasis, and obesity, thereby showing that in addition to genes and pathways, many drugs also shared common properties to treat these diseases [51]. Hence, we strongly believe that performing the comorbidity analysis for the COVID-19-induced clinical conditions may lead the researchers to identify some existing drug action-potential against the current pandemic. The data required for the analysis of comorbidity can be retrieved from OMIM, HPO, GAD and from DO databases.

7.1. Age and COVID-19

Age is an important parameter for the assessing COVID-19 death risk. As there are no authenticated reports available to date on age-based details of COVID-19 deaths, all agencies strongly suggest that the age is robustly associated with COVID-19 deaths correlating the few existing reports (Fig. 3). The aging process is known to reduce lung function, by progressive loss of elasticity of the lung tissue, thus reducing the efficiency of breathing. Above a mean age of 65 years, morbidities such as diabetes, hypertension, and/or CVD are likely to set in, accelerating any age-related reduction in respiratory efficiency, make them highly susceptible for severe COVID-19 infection and high risk of death. Table 3 shows the details of the aged populations in the top 10 countries with COVID-19 confirmed cases and deaths. Even though the case fatality rate (CFR) is low in the USA, the proportion of the aged population (>50 years) is high, making them stay at the top of the list. Italy, Spain, France in particular has more than 40% of the population in the age group of 50 years and above and relies upon the foremost reason for their COVID-19 attack and death.

The population and age-related details of the below table were collected from the World Bank and the COVID-19 data were compared manually.

A notable exception is Japan, which, despite 48% of the population being above 50 years, has very low CFR. The reasons might be speculated variously, perhaps a mix of healthier lifestyle practices, genetic factors, and higher levels of social discipline making the Japanese more likely obey instructions for social distancing, mask wearing and maintaining public hygiene.

Similar to VO and comorbidity databases, there are age-associated databases which provide information related to aging and related variables. JeneAge is one of such databases, exclusively dedicated for the ontological research of age-associated complications [52]. This database provides information regarding the collection and integration of aging phenotype data including lifespan information, dietary restrictions, and chemical compounds [53]. However, this database is still relatively underused by COVID-19 researchers. Hühne et al. (2018) used this database to study the gene network related to the lifespan [54]. The same strategy can be adopted to study likely age association of genes that are susceptible to SARS CoV-2 and other corona viruses.

The following schematic representation explains the importance of the integrated ontological approach to find out effective vaccine and therapies to tame SARS CoV-2 virus, and eventually the entire corona virus family.

8. Conclusion

COVID-19 pandemic has fundamentally disrupted the routine of human life, whether personal, socio-cultural, economic or political [55–60]. Research groups around the globe are investing time, effort, and resources to find a remedy for this unprecedented pandemic. Relying on the conventional approach to drug discovery or vaccine development needs to give way to integrated collaborative ones. Here, the modern ontological approach offers a powerful tool for revealing the secrets ofthe complex interactions between the genes and proteins of the pathogen and the host. New insights may lead to paradigm shifting breakthroughs in the design of novel drugs and vaccines. The published results and predictions made possible by the new bioinformatics tools is suggestive of the lower effectiveness of working as a single team or on a restricted focus towards drug discovery approach or vaccine development as explained schematically in Fig. 4.

Wars have produced some of the biggest advances in modern medicine. World War II gave us antibiotics. The emerging threat posed by future mutations in corona viruses is the new war, for which Covid-19 is, but the practice ground. Unlike how antibiotics vanquished bacteria, the ongoing war against viruses is far more complex and collaborative. The past failure of well-established drugs and vaccines against SARS CoV-2 should be studied carefully before getting into new drug development and shared with the worldwide research community to prevent wasteful repetitions. Classical methods need to give space to emerging open-sourced technologies such as gene ontology and other ontologies, which help evolve target identification tools, and common drug database information may help in the development of effective vaccines and remedies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The Open Access funding provided by the Qatar National Library. The language and technical editing done by The Editing Refinery, MD, USA is acknowledged.

References

[1] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of corona virus disease (COVID-19) outbreak. J Autoimmun 2020:102433.
[2] World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel corona virus (2019-nCoV). Available from: https://www.who.int/newsroom/detail/30-01-2020-statement-on-the-second-meeting-ofthe-international-health-regulations-(2005)-emergency-committeeregarding-the-outbreak-of-novel-corona virus-(2019-NCOV), accessed on April 7,2020..
[3] World Health Organization. WHO Director General's opening remarks at the media briefing on COVID-19 - March 11, 2020. Available from: https://www.who.int/dg/speeches/detail/whodirector-general-s-opening-remarks-at-the-media-briefing-oncovid-19_11-march-2020, accessed on April 5,2020..
[4] https://covid19.who.int/?gclid=Cj0KCQjwupD4BRD4ARIsABJMmZ_RpjQwB8pW6kx_004hJX5dv-xEUxgGpU1W-1zppW3wMEomTeAzXb0kaAgRREALw_wcB.
[5] www.who.int/csr/sars/en/..
[6] Middle East respiratory syndrome corona virus (MERS-CoV) summary and literature update–as of 20 January 2014" (PDF). World Health Organization; 2014. 20 January.
[7] Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? Clin Microbiol Infect 2020;26(6):729–34. https://doi.org/10.1016/j.cmi.2020.03.026.
[8] Hirano Toshio, Murakami Masaaki. COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. Immunity 2020;52(5):731–3. https://doi.org/10.1016/j.immuni.2020.04.003.
[9] https://www.cdc.gov/sars/about/fs-SARS.pdf.
[10] Ortiz-Prado E, Simbaña-Rivera K, Gómez-Barreno L, et al. Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Corona virus Disease 2019 (COVID-19), a comprehensive literature review [published online ahead of print, 2020May30]. Diagn Microbiol Infect Dis 2020;98(1):115094. https://doi.org/10.1016/j.diagmicrobio.2020.115094.
[11] Gussow AB, Auslander N, Faure G, Wolf YI, Zhang F, Koonin EV. Genomic determinants of pathogenicity in SARS-CoV-2 and other human corona viruses. Preprint.*bioRxiv*. 2020. https://doi.org/10.1101/2020.04.05.026450. 2020.04.05.026450. Published 2020 Apr 9.
[12] http://www.violinet.org/vaccineontology/index.php.
[13] http://www.violinet.org/.
[14] Hur J, Özgür A, He Y. Ontology-based literature mining of E. coli vaccine-associated gene interaction networks. J Biomed Semant 2017;8(1):12. https://doi.org/10.1186/s13326-017-0122-4. Published 2017 Mar 14.
[15] Xie J, Codd C, Mo K, He Y. Differential adverse event profiles associated with BCG as a preventive tuberculosis vaccine or therapeutic bladder cancer vaccine identified by comparative ontology-based VAERS and literature meta-analysis. PloS One 2016;11(10):e0164792. https://doi.org/10.1371/journal.pone.0164792. Published 2016 Oct 17.
[16] Ford N, Vitoria M, Rangaraj A, Norris SL, Calmy A, Doherty M. Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment. J Int AIDS Soc 2020;23.
[17] Yueping L. An exploratory randomized controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalizedwithmild/moderate COVID-19 (ELACOI), vol. 33; 2020.
[18] Cao B, WangY, Wen D, LiuW, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020;382:1787–99.
[19] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel corona virus (2019-nCoV) in vitro. Cell Res 2020;30:269–71.
[20] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236):1569–1578–1578.
[21] Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome corona virus. J Biol Chem 2020;295(15):4773–9. https://doi.org/10.1074/jbc.AC120.013056.
[22] Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci 2020;248:117477. https://doi.org/10.1016/j.lfs.2020.117477.
[23] National Center for Biotechnology Information. PubChem compound summary for CID 492405, favipiravir. Retrieved July 30, 2020 from, https://pubchem.ncbi.nlm.nih.gov/compound/Favipiravir; 2020.
[24] Riva L, Yuan S, Yin X, et al. Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing [published online ahead of print, 2020 Jul 24]. Nature 2020. https://doi.org/10.1038/s41586-020-2577-1. 10.1038/s41586-020-2577-1.
[25] Shah B, Modi P, Sagar SR. In silico studies on therapeutic agents for COVID-19: drug repurposing approach. Life Sci 2020;252:117652. https://doi.org/10.1016/j.lfs.2020.117652.
[26] Antiviral activity of chloroquine against human corona virus OC43 infection in newborn mice ls keyaerts, sandra Li, leen vijgen, evelien rysman, JannickVerbeeck, marc van ranst. Piet Maes Antimicrobial Agents and Chemotherapy Jul 2009;53(8):3416–21. https://doi.org/10.1128/AAC.01509-08.
[27] National Center for Biotechnology Information. PubChem compound summary for CID 2719, chloroquine. Retrieved July 30, 2020 from, https://pubchem.ncbi.nlm.nih.gov/compound/Chloroquine; 2020.
[28] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/OSE%20Review_Hydroxychloroquine-Cholorquine%20-%2019May2020_Redacted.pdf%20.
[29] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–4.
[30] Zhao Q, He Y. Challenges of convalescent plasma therapy on COVID-19. J Clin Virol 2020;127:104358. https://doi.org/10.1016/j.jcv.2020.104358.
[31] https://www.covid19treatmentguidelines.nih.gov/critical-care/oxygenation-and-ventilation/.
[32] Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with corona virus disease 2019 (COVID-19). Crit Care Med 2020;n48(6):e440–69. https://doi.org/10.1097/CCM.0000000000004363.
[33] http://geneontology.org/.
[34] Lovering RC, Camon EB, Blake JA, Diehl AD. Access to immunology through the gene ontology. Immunology 2008;125(2):154–60. https://doi.org/10.1111/j.1365-2567.2008.02940.x.
[35] He Y, Wang H, Zheng J, et al. OHMI: the ontology of host-microbiome interactions. J Biomed Semant 2019;10(1):25. https://doi.org/10.1186/s13326-019-0217-1. Published 2019 Dec 30.
[36] Lin Y, Xiang Z, He Y. Ontology-based representation and analysis of host-Brucella interactions. J Biomed Semant 2015;6:37. https://doi.org/10.1186/s13326-015-0036-y. Published 2015 Oct 5.
[37] Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020;583(7816):459–68. https://doi.org/10.1038/s41586-020-2286-9.
[38] Diehl AD, Lee JA, Scheuermann RH, Blake JA. Ontology development for biological systems: immunology. Bioinformatics 2007;23(7):913–5. https://doi.org/10.1093/bioinformatics/btm029.
[39] http://geneontology.org/covid-19.html.
[40] Bab-Dinitz E, Albeck S, Peleg Y, Brumfeld V, Gottschalk KE, Karlish SJ. A C-terminal lobe of the beta subunit of Na,K-ATPase and H,K-ATPase resembles cell

adhesion molecules. Biochemistry 2009;48(36):8684–91. https://doi.org/10.1021/bi900868e.
[41] Ashbrook AW, Lentscher AJ, Zamora PF, et al. Antagonism of the sodium-potassium ATPase impairs Chikungunya virus infection. mBio 2016;7(3). https://doi.org/10.1128/mBio.00693-16. e00693-16. Published 2016 May 24.
[42] Li B, Huang X, Xu X, Ning W, Dai H, Wang C. The profibrotic effect of downregulated Na,K-ATPase β1 subunit in alveolar epithelial cells during lung fibrosis. Int J Mol Med 2019;44(1):273–80. https://doi.org/10.3892/ijmm.2019.4201.
[43] Benedetto R, Ousingsawat J, CabritaI, et al. Plasma membrane-localized TMEM16 proteins are indispensable for expression of CFTR. J Mol Med (Berl) 2019;97(5):711–22. https://doi.org/10.1007/s00109-019-01770-4.
[44] Dyer MD, Murali TM, Sobral BW. The landscape of human proteins interacting with viruses and other pathogens. PLoS Pathog 2008;4(2):e32. https://doi.org/10.1371/journal.ppat.0040032.
[45] Karadeniz İ, Hur J, He Y, Özgür A. Literature mining and ontology based analysis of host-BrucellaGene-GeneInteractionNetwork. Front Microbiol 2015;6:1386. https://doi.org/10.3389/fmicb.2015.01386. Published 2015 Dec 9.
[46] https://www.who.int/emergencies/mers-cov/en/.
[47] Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020;55(5):2000547. https://doi.org/10.1183/13993003.00547-2020. Published 2020 May 14.
[48] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 Novel Corona virus in Wuhan, China. Lancet 2020;395:497–506.
[49] Kindler E, Thiel V, Weber F. Interaction of SARS andMERS corona viruseswith the antiviral interferon response. In: Advances in virus research. Elsevier; 2016. p. 219–43.
[50] Ko Y, Cho M, Lee J, et al. Identification of disease comorbidity through hidden molecular mechanisms. Sci Rep 2016;6:39433. https://doi.org/10.1038/srep39433.
[51] Zheng C, Xu R. Large-scale mining disease comorbidity relationships from post-market drug adverse events surveillance data. BMC Bioinf 2018;19:500. https://doi.org/10.1186/s12859-018-2468-8. Published 2018 Dec 28.
[52] http://agefactdb.jenage.de/.
[53] Hühne R, Thalheim T, Sühnel J. AgeFactDB-the JenAge ageing factor database-towards data integration in ageing research. Nucleic Acids Res 2014;42:D892–6. https://doi.org/10.1093/nar/gkt1073. Database issue.
[54] Hühne R, Kessler V, Fürstberger A, et al. 3D Network exploration and visualisationvisualization for lifespan data. BMC Bioinf 2018;19(1):390. https://doi.org/10.1186/s12859-018-2393-x. Published 2018 Oct 23.
[55] Muthuraman S, Al Haziazi M. COVID-19 impact on health, social & economy. Int J NutrPharmacol Neurol Dis 2020;10:159–60. https://doi.org/10.4103/ijnpnd.ijnpnd_64_20.
[56] Subramanian S, Mohamed S, Khanzadah T. The corona virus' impact on education – school students' perspective. Int J NutrPharmacol Neurol Dis 2020;10:166–7. https://doi.org/10.4103/ijnpnd.ijnpnd_59_20.
[57] Fernandes AJ. Impact of COVID-19: university students' perspective. Int J NutrPharmacol Neurol Dis 2020;10:168–9. https://doi.org/10.4103/ijnpnd.ijnpnd_60_20.
[58] Al-Balushi B, Essa MM. The impact of COVID-19 on children – parent's perspective. Int J NutrPharmacol Neurol Dis 2020;10:164–5. https://doi.org/10.4103/ijnpnd.ijnpnd_55_20.
[59] Prabhakar P, Punnaveetil S. COVID-19 impact – A physician's perspective. Int J NutrPharmacol Neurol Dis 2020;10:161–3. https://doi.org/10.4103/ijnpnd.ijnpnd_62_20.
[60] Essa MM, Hamdan H, Chidambaram SB, et al. Possible role of tryptophan and melatonin in Covid-19. Int J Tryptophan Res 2020. https://doi.org/10.1177/1178646920951832.