COVID-19

CAUSES, TRANSMISSION, DIAGNOSIS, AND TREATMENT

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Bentham Books

COVID-19: Causes, Transmission, Diagnosis, and Treatment

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ISBN (Online): 978-981-5256-53-6

ISBN (Print): 978-981-5256-54-3

ISBN (Paperback): 978-981-5256-55-0

First published in 2024.

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PREFACE

Since the ongoing pandemic has affected every individual, we need a book that is simple, precise, and easy to comprehend. I feel that very few books are available in the market aimed at the common person. Most books are written for college-going students, academicians, or researchers. This book covers all the aspects required to understand the present situation.

Generally, books are written for students, academicians, or researchers. However, this book is intended for the ordinary person to raise awareness. Therefore, it is written in a way that is coherent and understandable to the average person. Furthermore, the chapters' names and the contents' language are straightforward.

As we have already mentioned, the primary audience is the general masses. This book is written to include the role of all emerging technologies like Artificial Intelligence and Machine Learning, for predicting and diagnosing COVID-19 infection. Therefore, this book takes care of the primary and secondary audiences, without compromising the need and availability of the required material.

Since the primary audience is the general masses, we need to design the content so they can understand it easily and not lose interest. Readers will also learn all they need to know about emerging technologies (Machine Learning, Artificial Intelligence, Blockchain), so they can understand how these technologies can be used to diagnose and fight COVID-19. Due to this coherency, the reader goes to a higher level of understanding without realizing it.

Three key features:

1. Generally, books are written for students, academicians, and researchers. This is the only book written based on the needs of the general masses of the population. Since this pandemic has affected every strata of society, many people want to learn more about the causative Coronaviruses, the viral agent that causes this disease. For that, they will need to learn about the basics of cause, epidemiology, pathogenicity, transmission, diagnosis, treatment, and challenges. The above-mentioned characteristics are explained in detail in the first few chapters.

2. The book is organized in a way that the reader acquires knowledge from basic to advanced levels. After learning about the biology of the coronaviruses, readers will learn how Machine Learning, a common buzzword that everyone uses, is used to diagnose and fight COVID-19 infection. This book will also discuss the challenges we face in using these technologies to carry out such a task.

3. Along with Machine Learning, Artificial Intelligence (AI) and the Internet of Things (IoT) can also be used in the fight against COVID-19. This book will also use Blockchain technology to find and control the socioeconomic and educational post-pandemic impacts of COVID-19.

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CHAPTER 1

History of Coronaviruses

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Abstract: Over the past two decades, coronavirus-associated diseases such as SARS and MERS have challenged the public health systems globally. Around 2002-2003, a near-pandemic of a previously unknown β-coronavirus, named SARS-CoV, arose in China and 29 other countries. Not much attention was paid to it post-disappearance of this outbreak. An understanding of the coronavirus began only after alarming predictions of the virus's re-emergence began in 2007. Identification from previous studies revealed that bats have proven to be a major reservoir of animal coronavirus. SARS-related bat coronaviruses have all the essential components of SARS-virus, have along with similar genome sequences to that of SARS-CoV and SARS-CoV-2, and thus, are able to cause infection and transmit between humans directly. Later in 2012, another unknown β-coronavirus named Middle East respiratory syndrome (MERS-CoV), with close relation to the SARS-CoV, caused an epidemic limited to the Middle-East. The emergence of yet another bat-origin coronavirus, α-coronavirus, in China caused epizootic disease in pigs, thus named swine acute diarrhea syndrome coronavirus (SADS-CoV). Subsequently, unattended warnings of 12 years led to the most fatal bat-derived sarbecovirus, recognized as SARS CoV-2, springing up in November 2019, sweeping the globe. The predictions of SARS-CoV-2 to be a natural event with association to transmission directly from bats to humans or through an intermediate host have been essentially proven to be true. SARS-Cov-2 shares genetic properties with many other sarbecoviruses; this slies fully within their genetic cluster and is, thus, a naturally emerged virus.

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Based on the genomic structure coronavirus is mainly divided into four subgroups alpha, beta, gamma, and delta.

CoVs are fall under the family Coronaviridae, and subfamily Orthocoronavirinae. The virus is protected by receptor binding domain (RBD) that binds to ACE2 receptor found in kidneys, lungs, heart and gastrointestinal tract, which that promote viral entry into target cells.

Domestic animals can act as intermediary hosts in the transmission of viruses from natural hosts to people. Porcine Epidemic Diarrhea CoV(PEDC), which originated in pigs, was found to be similar to SADS-CoV. It has been transferred from bats to pigs. SADS-CoV was first found in rhinolophids or horseshoe bat, before the SARS epidemic Recombination of bat SARSr-CoVs, or recombined virus, infected and adapted to civets and humans. MERS-CoV is a zoonotic virus. It was transferred from dromedary camels to humans. The first confirmed cases of SARS-CoV-like viruses were found in raccoon dogs in live animal markets and palm civets. Another bat coronavirus, CoV RaTG13, was isolated from the *Rhinolophus affinis* bats.

Corona variants are classified into variants of concern (VOCS), variants of interest (VOI), variants of high consequence (VOHC), and variants being monitored (VBM).

Some common coronaviruses of human are 229E, NL63, OC43, and HKU1, which infect the upper-respiratory tract.

Keywords: ACE2 receptor, A570Y, ARCoV-2, APN, AIBV, BALF, CTD, CEACAM1, CoV-HKU5 strains, D614G, DPP4, Fatal pneumonia, GISAID, HCoV, HKU1, HCoV-OC43, MERS-CoV, NL63, N5014, Nsp, NTD, Orthocoronavirinae, Orf1a, PL-pro, PEPV, RaTG13, Rf4092, RBd, SARS-CoV-2, Spike (S1), SARS-CoV, SADS-CoV, SARS-CoV-2, SARsr-CoVs, TMPRSS2, TCOV(TECoV), TGEV, VOI, VBM, VOCs, VOHC, WIV16.

INTRODUCTION

Coronaviruses are enclosed, unsegmented, and single-stranded positive RNA genomes. They are identifiable by crown-like protrusions on their surface (the term “corona” comes from the Latin word “crown”). They belong to the Nidovirales subfamily within the Coronaviridae family. Coronaviruses are categorized into four groups: alpha, beta, gamma, and delta. Typically, alpha and beta coronaviruses impact mammals, causing respiratory issues in humans and gastroenteritis in various animal species [1].

B.1.1.7 (Alpha): The first problematic variant was labeled in the UK at the end of December 2020.

B.1.351 (Beta): First stated in South Africa in December 2020.

P.1 (Gamma): First identified in Brazil in January 2021.

B.1.617.2 (Delta): First identified from India in December 2020.

B.1.1.529 (Omicron): First identified in South Africa in November 2021 [2].

Among the four beta-coronaviruses known to infect people, the most serious pathogens are the SARS-CoV and MERS-CoV [3].

Till December 2019, only six different coronaviruses had been identified with capability of infecting humans. Among these, four coronaviruses (HCoV-NL63, HCoV-229E, HCoV-OC43, and HKU1) usually induced mild flu-like signs in individuals with a healthy immune system. The remaining two coronaviruses had caused global pandemics in the preceding two decades [4]. The first case of covid was reported as a common cold in 1960. According to a Canadian study in 2001, about 500 patients had a flu-like symptoms. Around 17-18 cases were confirmed by PCR to be infected with the coronavirus strain [5].

The SARS outbreak, which occurred between 2002 and 2003, was characterized by the development of the severe acute respiratory syndrome coronavirus (SARS-CoV) and had a 10% death rate. Likewise, in 2012, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) gave rise to a substantial pandemic with a notably high fatality rate of 37 percent [6].

Hundreds of different classes of bats found around the world have become a huge reservoir of coronaviruses. SARS-CoV, MERS-CoV, and SARSCoV-2, all cluster as closely associated coronaviruses in the SARS-like virus's arbovirus and merbecovirus (MERS-like viruses) phylogenetic groups. These two SARS viruses, like SADS-CoV, are derived from viruses that infect rhinolophids (Rhinolophus genus) or horseshoe bats. During the previous 15 years, scientists have also discovered worldwide reservoirs of coronaviruses over the past 15 years (in Africa, the Americas, the Middle East, Asia, and Southeast Asia, with a particular focus on China, which has been the epicenter of three out of the four recent crises).

Bats, belonging to many widespread genera and species, have now been identified as an important source of animal coronaviruses. According to a study in 20 countries with more than 19k species, mainly primates, and bats. These regions represented over 98% of the reported cases of coronavirus infections, with nearly 9% of over 12,000 randomly sampled bats found to be carrying one or more coronaviruses [7].

CHAPTER 2

Epidemiology of Coronavirus

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Abstract: More than 600 million people have contracted the COVID-19, and a substantial level of fatalities have occurred on a global scale. The pandemic has grown to pose a serious risk to humankind. Gaining knowledge about the dynamics of virus transmission and clinical manifestation, as well as possible causes of severe illness and mortality, requires an understanding of coronavirus epidemiology. To create global health policies that work, it is imperative to understand these elements. It is believed that bats are the original host of the coronavirus that causes severe acute respiratory syndrome. The most prevalent means of transmission is through airborne droplets. Other potential routes of infection include the fecal-oral pathway, sexual transmission, the vertical chain, and so forth. The incubation period of COVID-19 is two to fourteen days, during which asymptomatic carriers may spread the virus to other people. From mild symptoms like fever, coughing, and fatigue to life-threatening illness necessitating hospitalization, COVID-19 respiratory illness can range widely in severity. The impacts of the disease are more likely to affect the elderly and people with underlying medical disorders including Type 2 diabetes, obesity, or chronic heart disease. New strains of SARS-CoV-2 have evolved as the pandemic has expanded, wreaking havoc on countries with weak healthcare systems and low incomes. Social isolation, the use of masks, and vaccination campaigns have all helped reduce the spread of the virus.

Keywords: Aerosols, Coronavirus, COVID-19, Epidemiology, Fecal-oral route, Respiratory Syndrome, Respiratory infection, Symptoms, SARS-CoV-2, Transmission.

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INTRODUCTION OF EPIDEMIOLOGY OF CORONAVIRUS

Coronavirus is among the most common pathogens that are related to mild and moderate respiratory disorders [1, 2]. Despite the fact that coronaviruses have been isolated from a wide variety of animals, bats are generally considered to be their primary natural reservoir. The virus emerged at the tail end of 2019 [3, 4]. On March 11, 2020, a declaration was made by WHO labeling Coronavirus as a global pandemic in response to swift dissemination of the SARS-CoV-2. This beta coronavirus had never been observed before, but it is related to other coronaviruses, such as severe acute respiratory syndrome (SARS). It has also been associated with Middle East Respiratory Syndrome (MERS) [5, 6]. There are multiple ways that SARS-CoV-2 can spread from one person to another in a community; respiratory droplets are the most common [7]. COVID-19 manifests with a variety of severity levels and symptoms. Some patients develop an adverse type of disease that is characterized by acute respiratory distress syndrome and adverse effects on other organs. However, the vast majority of the disease is less severe or without symptoms [8, 9]. As a result of the COVID-19 pandemic, millions of people were infected, and thousands of lives were lost all over the world. This chapter discusses the epidemiology, geographical distribution, and clinical manifestations of COVID-19.

ETIOLOGY OF CORONAVIRUS

The name “Coronavirus” comes from the Latin term “corona,” which literally translates to “crown”. It is named so because of the appearance of cloverleaf structures, such as glycoproteins and proteins, on the surface of the virus when viewed through an electron microscope that looks like spherical particles with a ring of projections around them, like the corona of the sun [10, 11]. These single-stranded viruses with 80-120 nm diameters belong to the family Orthocoronaviridae. They are enveloped, non-segmented, positive-sense viruses and were first isolated from humans in 1965. They commonly cause mild respiratory diseases in humans [12]. The virus was officially named SARS-CoV-2 on February 11, 2020. This decision was based on evolutionary history and taxonomic classification. The viral spike (S) glycoproteins are accountable for mediating the cellular entry of the virus. These glycoproteins consist of two subunits, S1 and S2. S1 is in charge of binding to the receptor on host cells. S2 is responsible for the fusing of the viral and cellular membranes. An infection caused by the virus is dependent on the ability of the host cell receptor, angiotensin-converting enzyme 2, to bind to the virus. High levels of ACE2 are found in alveolar epithelia, making them a crucial target for SARS-CoV-2. The disease that occurs due to this virus has been named Coronavirus disease by the World Health Organization (WHO) [13].

ORIGIN/DISEASE BACKGROUND

Initial reports from the Chinese Centre for Disease Control (CDC) in early 2019 described a cluster of patients in Wuhan, China, with pneumonia of unknown origin. In these patients' lower respiratory tract epithelial cells, an unidentified beta-coronavirus, known as the 2019 novel Coronavirus (2019–nCoV), was found using genetic sequencing. It was also theorized that the virus was initially found in bats and “naturally” spread to humans, most likely through contact with infected aquatic and living animals at the Huanan seafood wholesale market. Within a matter of months following the original outbreak, the pandemic had spread to dozens of additional countries and territories around the world [14]. The principal mode of viral transmission from an individual who is infected to another individual is by direct or through respiratory droplets. As compared to coronaviruses that infect humans, the novel Coronavirus showed a higher degree of phylogenetic relatedness to two bat-derived coronavirus strains, such as a 79% similarity with SARS and a 50% similarity with MERS that have led to large outbreaks of varying clinical severity, ranging from mild illness that goes away on its own to illness that can kill. COVID-19 has caused a previously unseen human and health disaster and brought about a global financial crisis that will take a long time to recover from [15, 16].

GEOGRAPHICAL DISTRIBUTION

The disease outbreak caused by the Coronavirus rapidly spread throughout China and 229 other countries and territories. Some of these countries were geographically close to China, such as Thailand, Taiwan, Japan, Singapore, and South Korea. Due to its very high transmissibility rates, the virus's spread was not limited to countries near China or even the Asian continent. France was the first European country involved, and all patients there apparently had contact with their Chinese counterparts [17]. On January 30, 2020, the first coronavirus case in India was reported in the Thrissur district of Kerala. The patient was a student who had recently returned from studying at Wuhan University in China [18]. As of March 5, 2023, the Coronavirus COVID-19 has caused 680,656,727 confirmed cases and 6,805,186 deaths around the world [19]. The United States has the highest number of COVID cases, followed by India [20]. About a third of all cases were presumed to have happened in South Asia (including India).

EPIDEMIOLOGICAL DETERMINANTS OF CORONAVIRUS

Variants of Coronavirus

Viruses tend to mutate genetically to adapt to even minor changes in the environment and transfer from one host to another. Mutations help the virus to

CHAPTER 3

Replication and Pathogenesis of Coronaviruses

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Abstract: The COVID-19 pandemic has led to widespread illness, death, and economic disruption worldwide, leading to a critical need for effective treatments, vaccines, and diagnostic tools. SARS-CoV-2, belonging to the class of β-CoVs, is the virus accountable for COVID-19, and mediates entry into the host cell via its surface spike protein. Understanding its replication and pathogenesis is crucial for developing effective treatments and curbing the microbe's spread. Here, we dive deep into the genomic organisation of the SARS-Cov2 virion and its various structural components, highlighting the molecular mechanism involved in replication, ultimately leading to pathogenesis.

Keywords: COVID-19, Diagnostic, Genomics, Pandemic, Pathogenesis, SARS-CoV-2, Vaccines.

INTRODUCTION

Infecting both mammals and birds, coronavirus (CoV) is a zoonotic virus. This virus family induces respiratory tract infections (RTI) that range from mild to severe. It was first reported in 1937 and termed "coronavirus" for its crown-like appearance observed under the microscope in 1965. These viruses are non-segmented and enveloped, with a massive positive-sense genome. It is a member of the family Coronaviridae, the Orthocoronaviridae subfamily of the Nidovirales order. In addition, the subfamily is categorised into four genera: alpha coronavirus (α-CoV), beta coronavirus (β-CoV), gamma coronavirus (γ-CoV), and delta coro-

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navirus (δ-CoV). Their hosts can be bovis, pigs, humans, avians, *etc*. and they suffer from various sorts of infections such as pneumonia, diarrhea, enteric indication, renal failures, and so on. Both, α-CoV and β-CoV infections are prevalent in mammals. However, γ-CoV and δ-CoV infections are predominant in birds [1].

The coronavirus is not new to human beings and has existed for decades. Since the dawn of the 21st century, it has become a great threat to human life, necessitating immediate, researchful, and effective remedies. Pathogenic human coronavirus was first recognised in 2002 with the discovery of severe acute respiratory syndrome-CoronaVirus (SARS-CoV). To date, 7 human coronaviruses have been identified with disease severities ranging from mild to lethal. Human coronavirus associated with mild diseases is 229E and OC-43 (belonging to genera α-CoV) and NL-63 and HKU-1 (belonging to β-CoV). The two extremely detrimental human CoV (hCoV) are SARS-CoV, accountable for causing severe acute respiratory syndrome (SARS), and MERS-CoV, liable for triggering Middle East Respiratory Syndrome (MERS), both belonging to genera β-CoV [2].The outbreaks of SARS-CoV and MERS-CoV had a significant impact on human life in 2002 and 2012, respectively. The SARS-CoV outbreak first appeared in China in 2002, infecting 8422 people and resulting in 916 deaths. In 2012, the MERS-CoV outbreak originated in Arabian countries, with approximately 1800 individuals being infected [3].

Recently, in late December 2019, a novel virus surfaced in China, causing severe pneumonia-like symptoms in patients, predominantly those who had visited the seafood market in the city of Wuhan. The pathogen was certified to be a virus using Polymerase Chain Reaction (PCR) and Next Generation Sequencing (NGS) techniques, which revealed that the virus was new and distinct from any previously known viruses, as it did not demonstrate complete similarity to any known virus. Also, the clinical symptoms were much more severe and distinguishable from any of the other known viruses [3]. It has caused a great infestation influencing almost all countries across the globe and killing millions of people [4]. SARS-CoV-2 (β-coronavirus) is a virus that is closely related to SARS-CoV. The SARS-CoV-2 NGS result shows 79% homology with SARS-CoV and 50% with MERS CoV. However, SARS-CoV-2 has a higher transmission and infectivity rate than SARS-CoV and MERS-CoV [5].

Both the corona viruses, MERS-CoV and SARS CoV were discovered in bats and inflicted human beings through different intermediate hosts; civet cats in case of SARS-CoV and the intermediate in MERS CoV were dromedary camels [6, 7]. Furthermore, SARS-CoV-2 shares 88% of homology with two bat-derived coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21.

Genomic Organisation of SARS-CoV-2

CoVs have the largest genomic size of any RNA virus, ranging in length from 26 to 32 Kbp. SARS-CoV-2 being the largest CoVs have positive, single-stranded RNA genome of 29,891 nucleotides and 9,860 amino acids present within the nucleocapsid, which is further encapsulated by an envelope [8, 9]. Club-shaped spikes protrude from the surface, like a solar corona. The GC content is only 38%, which is very low compared to other CoVs.

The ORF number differs across CoVs. However, the SARS CoV-2 genome consists of 10 ORFs; out of which ORF-1 is the longest and accounts for $2/3^{rd}$ of viral RNA. It encodes for polyprotein-1a, polyprotein-1b and 1-16 non -structural genes. ORF1b overlaps with 1a followed by shorter sub-gRNA (sgRNA). The remaining 9 ORF are involved in encoding structural gene-protein Spike (S), Envelope (E), Nucleocapsid (N), Membrane(M) and other accessory proteins [10].

Structural proteins are located at the 3' end of the remaining one-third of the genome. Generally, 4 structural genes are required by most CoV to produce a functional and complete viral particle. Some CoVs may encode additional structural proteins like Hemagglutinin Esterase (HE) protein, which, however, is lost in SARS-CoV-2 [11]. Not just limited to structure formation, these genes are also involved in other aspects such as entry inside the host, replication, *etc*.

The coronavirus genome is structured as 5' UTR-Replicase-S-E-M-N-3' UTR followed by a poly A tail. The structural genes are present with genes that code for auxiliary proteins. For SARS-CoV-2, five ORFs that encode accessory genes have been identified as ORF6, ORF7a, ORF3a, ORF7b, and ORF8. Also, ORF3b and ORF9b are formed due to the leaky translation of sgRNA of the nucleocapsid protein [12 - 14].

Structural Proteins of the SARS-CoV-2

Spike Protein

The SARS-CoV-2 virion membrane features glycoprotein projections known as the spike protein, which belongs to the class I type of transmembrane protein. This protein plays a critical role in identifying the host cell receptor, mediating binding to it, and subsequently merging with the membrane to enter the host cell. The spike protein comprises homotrimers of the S protein, with each corona virion typically containing around 50 to 100 of these trimers. The S protein has a molecular weight of 150KDa and is divided into three regions being the outer ectodomain region, intracellular region which has a short tail (C fragment) and a

CHAPTER 4

Transmission Cycle of SARS-CoV-2

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Abstract: The COVID-19 infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), progressed to a global pandemic and led to millions of deaths worldwide over the years since its COVID-19 origin. Coronavirus transmission is a zoonotic spillover, which means that virus transmission can occur from a vertebrate animal to a human host. The CoV genome underwent continuous recombination and evolution, which resulted in interspecies transmission and the virus' recurrent emergence as a pandemic. The SARS-CoV-2 infection primarily results in respiratory symptoms, like pneumonia, that range from mild to severe in severity, along with alveolar injury ultimately leading to acute respiratory distress syndrome (ARDS) and death. This chapter outlines the SARS-CoV-2 transmission pathways, how the disease spreads by infected people, and the consequences for the prevention and control of infection, both inside and outside healthcare facilities. This section also covers modes of transmission like horizontal, fomite, fecal-oral, nosocomial, and animal-to-human transmission of SARS-CoV-2.

Keywords: COVID -19, Modes of transmission, SARS-CoV-2, Transmission cycle.

INTRODUCTION

In December 2019, researchers discovered an unexplained source of pneumonia in Wuhan that was later identified as a novel strain of coronavirus, SARS-CoV-2, isolated from the respiratory epithelium of patients. SARS-CoV-2 is a single-

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stranded RNA virus of the genus Beta coronavirus. It is considered to be an extremely contagious and pathogenic coronavirus [1 - 4].

The disease caused by the new coronavirus, originally known as 2019-nCoV, was referred to as coronavirus disease 2019 or COVID-19 until it was officially renamed SARS-CoV-2 on February 11, 2020, by the WHO and the International Committee on Taxonomy of Viruses (ICTV) (2019-nCoV or COVID-2019) [1, 5, 6].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative factor behind COVID-19 infection. Since its discovery, SARS-CoV-2 has been responsible for millions of deaths worldwide. The World Health Organization (WHO) declared it a pandemic due to the virus' unprecedented global impact. Until the outbreak in Guangdong, China, the SARS-CoV virus was primarily believed to infect animals only, but later it was transmitted to and among humans [7]. The SARS-CoV-2 virus first impacted the lower respiratory tract in humans in the Chinese province of Guangdong in 2002, and then again in Wuhan in 2019. It was found that the Huanan seafood wholesale business was associated with the hospitalization of patients in Wuhan. There was a possibility of zoonotic infection from the market because live animals including chicken, bats, snakes, frogs, rabbits, marmots, and hedgehogs were sold there. In addition, the National Health Commission of the People's Republic of China disclosed that human interaction with wild bats was the most likely route for the transmission of SARS-CoV-2 [1 - 4].

Transmission Cycle

When the SARS-CoV-2 virus infects patients, it causes pneumonia symptoms along with alveolar injury that eventually results in acute respiratory distress syndrome (ARDS). When an individual eats an infected animal as food, this results in the virus transmission from the animal to the human. Furthermore, when an infected person comes in close contact with a healthy individual, the virus is transmitted among them as well [5].

Furthermore, the process by which the coronavirus transmits from a vertebrate species (animals) to a human host is known as “zoonotic spillover.” The CoV genome underwent continual recombination and evolution, which caused cross-species transmission and contributed to the virus' recurrent emergence as a pandemic [4].

To develop viable therapies against SARS-CoV-2 and preventive approaches to contain the progression of the disease, it is important to determine the source of origin and the transmission of the virus [5]. The transmission of the SARS-CoV-2 virus is primarily linked to Wuhan's seafood market, which has spread substantially to cause an outbreak of the pandemic. Several coronaviruses are believed to be transmitted by bats, which also are considered to be the major source of SARS-CoV and SARS-CoV-2 in humans. Although the underlying mechanisms for virus zoonotic spillover is unrecognized yet, it is thought that from this region, the spillover actually occurred from bats to civets and eventually to the neighboring residents or was attributed to involvement in the trade of diseased animals [4].

SARS-CoV-2 is primarily transmitted by three factors: the host, the environment, and the virus [10]. The novel coronavirus is believed to spread between humans by respiratory droplets that are released through an infected person's sneeze or cough [4].

The transmission cycle for SARS-CoV-2 is illustrated in Fig. (**1**).

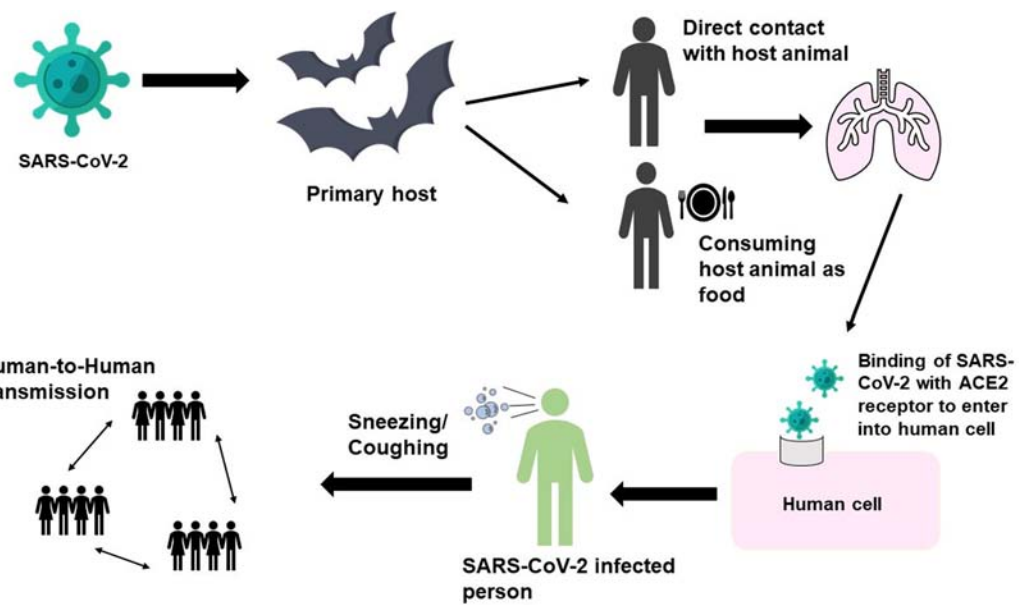

Fig. (1). Transmission cycle of SARS-CoV-2.

Although the transmission cycle is still unknown, scientists have identified particular pattern to limit the transmission of disease. Considering these patterns, some strategies were made by WHO to obstruct the transmission of coronavirus, which are mentioned at the end of the chapter.

CHAPTER 5

Symptoms and Diagnostic Techniques of COVID-19

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Abstract: COVID-19, an outbreak that has disrupted people's normal lives and lifestyles worldwide, has evolved to rank among the top few major causes of death. The virus spreads through direct and contact transmission and is thought to have a zoonotic origin. Fever, cough, and myalgia are symptoms of the symptomatic phase, which progresses to severe respiratory failure. It also includes pulmonary symptoms, which involve the severe acute respiratory syndrome coronavirus 2.

Human antibody detection, viral antigen detection, and viral gene detection are used as the foundation for the diagnostic tools developed thus far; however, viral gene detection via RT-PCR has proven to be the most reliable method. It is one of the more delicate approaches, which is also well-known for being highly advised for both qualitative and quantitative products. There is another sensitive method too that can precisely amplify a target nucleic acid known as loop-mediated isothermal amplification or LAMP.

On the other hand, amplification of nucleic acid tests is the test that identifies COVID-19, which works by identifying the RNA (ribonucleic acid) sequences responsible for generating the viral genetic material. Diagnostic systems based on CRISPR for COVID-19 have advantages like early screening (30 minutes from crude extract to result), sensitivity and accuracy, mobility, and the absence of specific laboratory equipment. Some other diagnostic techniques are CBNAAT and TruNAT, along with some other serological assays that use the ELISA KIT. Lateral flow immunoassay, Enzyme-linked immunosorbent assay, and chemiluminescence immunoassay (CLIA) are some of the other reliable diagnostic techniques.

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Keywords: Computed tomography, COVID-19, CBNAAT, CRISPR, CLIA, diagnostic techniques for COVID-19, iFlash assay, Isothermal amplification, Manifestations of COVID-19, RT-PCR, SARS-CoV-2, TruNat, Spike protein, (crRNA).

INTRODUCTION

COVID-19 cases are divided into three categories: mild, severe, and critical.

Critical patients experienced respiratory failure, acute cardiac injury, septicemia, and numerous organ failures whereas, serious patients displayed dyspnoea, increased respiration rate, and blood oxygen levels, whereas patients with mild symptoms developed mild pneumonia.

The emergence of new and evolving SARS-CoV-2 variants has increased the requirement for better, more flexible diagnostic techniques for the detection of SARS-CoV-2 infections. On the other hand, it is currently more difficult to develop quick and effective diagnostic technologies because of novel variations and the range of symptoms presented by infected individuals. At least 65 million people are expected to be affected by Long COVID, and the incidence is continuously increasing. Medical science has made tremendous progress in defining the illness, treating various physiological and pathological alterations and comorbidities, and showing its similarities to other colds and flu, such as postural orthostatic tachyarrhythmia disease and so forth. It also includes pulmonary symptoms, which involve the severe acute respiratory syndrome coronavirus 2. (SARS -CoV-2). Its other symptoms involve endocrinology manifestations along with neurological symptoms and olfactory dysfunction. As mentioned in Fig. (**1**), there are various diagnosis techniques which are useful for detecting the presence of a virus in a body. The virus can potentially enter the central nervous system of the human body and lead to primary and secondary encephalopathy. One typical symptom seen in COVID-19 patients is myalgia. Systemic inflammation and a cytokine storm have also been suggested as the pathophysiological underpinnings of myalgia.

Those who suffer from serious COVID-19 disease have elevated levels of lactate dehydrogenase and serum creatinine. Endothelial dysfunction, venous and arterial micro- and macrovascular problems, and stroke caused by SARS-CoV-2 can result from endothelial cell infection. It causes vasculitis and localized inflammation in the cerebral artery walls. Recently, post-mortem findings in the pulmonary, renal, heart, and colon following SARS-CoV-2 infection have revealed an inflammatory response and the death of endothelial cells. Pro-inflammatory cytokines collecting in the arterial endothelium may raise the blood-to-brain shield's permeability. It has been studied that COVID-19 patients who arrive with severe meningeal encephalitis do not exhibit SARS-CoV-2 or any other viral pathogens in their CSF. Hence, the absence of SARS-CoV-2-RNA in the CSF may suggest that factors that go beyond a direct serious infection, such as an altered nervous system and peri-infectious irritation, may be involved.

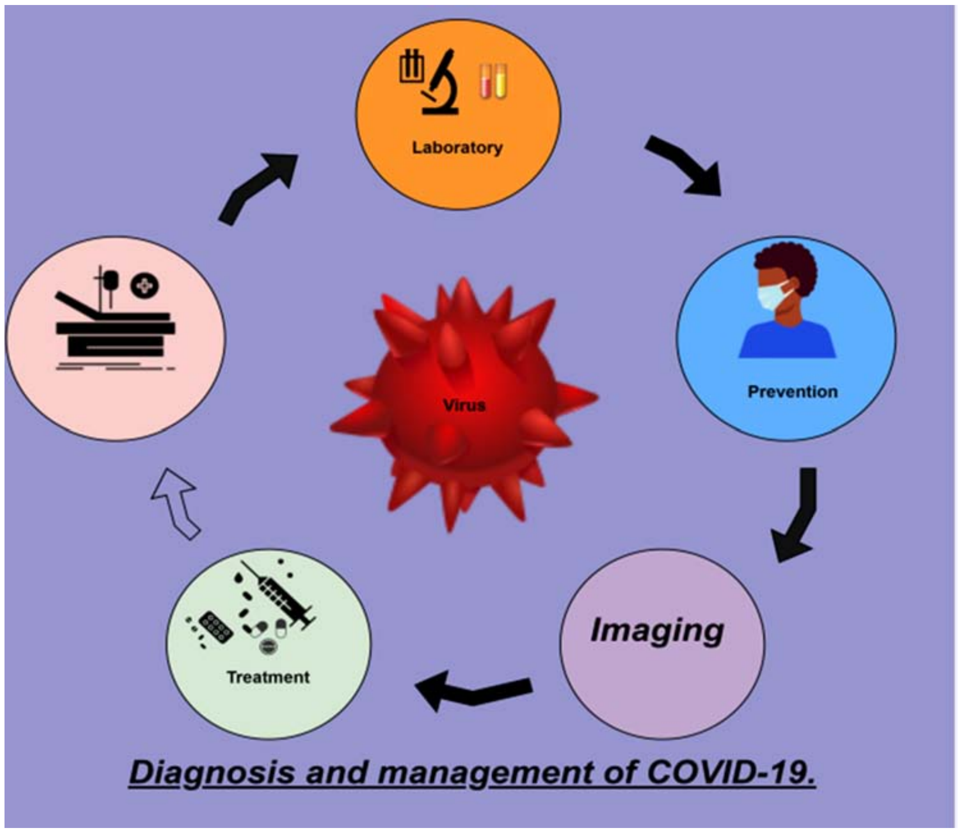

Fig. (1). Diagnosis and management of COVID-19.

In this review, we will focus mostly on the diagnostic methods of COVID-19 and manifestations. Several diagnostic methods have been demonstrated to be effective in identifying the illness; hence, we will focus on all methods that are efficient and regarded as the gold standard for the identification of COVID-19.

Asymptomatic Illness

A major issue has been COVID-19. Asymptomatic, mild, moderate, and critical symptoms have all been assigned to it. An asymptomatic illness exhibits no symptoms; according to a study, just one in five cases of illness exhibits signs.

CHAPTER 6

Treatment Options for COVID-19 Infected Patients

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Abstract: The world witnessed the outbreak of the most dreadful zoonotic infection, COVID-19, by the last month of 2019. The prompt dissemination of SARS-CoV-2 by intermediate hosts in the human community paved the way for the WHO declaration of a pandemic in 2020. In patients, the severity of this infection ranges from asymptomatic to critical state, leading to complications like acute respiratory distress syndrome (ARDS). The different diagnostics investigated the rapid spread and complexity of the disease. The omics and sequencing technologies helped to identify the virus's structure and potential targets for drug discovery against the virus. Different therapeutic agents like antivirals, antibiotics, *etc.*, are administered to reduce the infection. The various treatment options discussed in this chapter include different types of drugs and their combinational therapies, monoclonal antibodies, immune modulating treatments, promising vaccine developments, CRISPR-Cas13 therapy, experimental therapeutic interventions, non-pharmacological interventions, *etc.* This study also concentrates on the various challenges these clinical medications have faced. By rectifying each challenge, new beneficial treatments can be made possible with the fewest side effects.

Keywords: Antiviral, ARDS, Challenges, COVID-19, CRISPR-Cas13 therapy, Pharmacological interventions, Non-pharmacological interventions, SARS-Co--2.

INTRODUCTION

Even though there had been a history of the severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) outbreaks in 2002 and 2012 respectively, the havoc caused by the Corona Virus Disease 2019 (COVID-19) in the human population is uncountable [1]. The three identified

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significant beta coronaviruses were SARS-CoV-1 which caused SARS, MERS-CoV which caused MERS, and SARS-CoV-2 which caused COVID-19. The source of these viruses was suspected to be from intermediate zoonotic hosts like civets, camels, bats, *etc.* Among these, due to the most dangerous and contagious actions of the SARS-CoV-2 virus, COVID-19 was declared a pandemic by WHO in 2020 [2]. However, the spreading of the community was caused by human-t--human interactions. Many strategies are being implemented to regulate the community's spread of COVID-19 [3] like contact tracing, quarantine, precise diagnostic testing, wearing face masks, *etc.*

Immunity is the ability of the host body to defend against infections caused by bacteria, viruses, toxins, *etc.* Simply, it is the disease resistance of the body. The body has two types of immunity, namely innate and acquired immunity. In the case of COVID-19 infection, both types play an important role. The first defense mechanism called innate immunity activates pathogen recognition receptors (PRR) and thereby facilitates natural killer cells (NK cells) and type 1 interferon (INF) production. Acquired immunity helps in the cytotoxic T cells (Tc) and B cell activation [4].

Coronaviruses are spherical, crown-shaped with many projections at their surface and a positive single-stranded RNA genome of 26-32 KB size. The virus contains 4 structural proteins, 9 accessory proteins, and 16 nonstructural proteins (NSP1 to NSP16). Structural proteins include spike glycoprotein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein (N) [5]. About 16 nonstructural proteins formed from two open reading frames (ORF1a, ORF1b) and their respective Replicase polyproteins (pp1a, pp1ab). NSP forms a replicase-transcriptase complex with multiple enzymes like two cysteine proteases called the main protease (NSP5 or M^{PRO} or $3CL^{PRO)}$ and papain-like protease (NSP3 or PL^{PRO}) [6]. Remaining are NSP7-NSP8 primase complex, NSP10 & NSP16 (methyl transferases), NSP12 (RdRp), NSP14 (exoribonuclease), NSP13 (helicase triphosphatase), and NSP15 (endonuclease) [7]. Highly variable accessory proteins (ORf3a & 3b, ORF6, ORF7a &7b, ORF8, ORF10, *etc.*) are formed by the interspersed ORF and they help in the formation of sub-genomic mRNAs (sg mRNAs) [8]. Among structural proteins, the S protein is involved in binding and cell membrane fusion with that of host cells as it contains 2 subunits namely, S1 and S2. The main functions of NSPs include viral replication, RTC formation, *etc.* Even if the exact molecular functions of accessory proteins are unknown, they are thought to be the major determinant of infection and will modulate the response of the host [8]. SARS-CoV-2 possesses ORF3b and ORF10 (complement of 3’ORF), which is the only difference noticed from SARS-CoV-1. The genomics helped to reveal the host range, cellular tropism, and mutations of coronavirus by sequence analysis of the S protein and its RBD (Receptor Binding Domain). The viral entry is through the host cell receptors like ACE2 (expressed in type 2 alveolar cells in the lung) and DPP4 (expressed in epithelial and endothelial cells of the lungs, liver, kidney, *etc.*) in SARS and MERS as they are highly conserved ectoenzymes in mammals, thus facilitating the interhuman transmission, respectively [9, 10].

Studies on the pathogenicity and viral features of COVID-19 have improved the pharmacological treatments and thus combat against this dreadful disease. Inhibiting the viral invasion, inhibiting the viral proliferation inside the host, and increasing the immunity of the host are the major methods that prevent and cure COVID-19. Such steps are being practiced in developing and discovering antiviral drugs by exploring the potent targets [11].

The proliferation and subsequent progression of coronavirus happen in the host body through different steps. The former step is the attachment between host-virus cell membranes due to viral invasion by receptor binding and receptor-mediated endocytosis [11]. For receptor binding, the viral body needs RBD, and endocytosis needs the S2 subunit or clathrin receptor. This will lead to viral nucleocapsid entry and its content release. The next step is the growth and establishment of the virus through processes like replication, transcription, and translation. The new viral particles are released, and they get transported *via* Golgi vesicles to the cell membrane surface, followed by exocytosis. This will cause community spread by aerosol transmission [3].

The interruption to any of these processes will inhibit the viral activity and thus prevent further transmission between individuals. So, the drugs that efficiently compete with RBD, drugs that inhibit endocytosis, the drugs that inhibit the replicase expression, replication, transcription, and translation, the drugs that interfere in viral assembly at ERGIC, the drugs that can activate the host's complement system, and IFNs are highly used in COVID-19 treatment. This study deals with various pharmacological and non-pharmacological interventions being used in the field of COVID-19 infection.

IMPORTANT TARGETS FOR PHARMACEUTICAL TREATMENT

About 26 viral proteins are expressed in COVID-19 affected humans and are found to interact with various human proteins in several biological processes [7]. These can be utilised for drug targeting as it is very important for the survival of viral metabolism inside host cells.

NSP1- involved in the replication of DNA

CHAPTER 7

Challenges Posed by COVID-19

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Abstract: SARS-CoV-2, the viral inciting agent of one of the deadliest pulmonary infections known as novel Coronavirus Disease (COVID-19) has resulted in millions of deaths. With the first incidence being reported in the city of Wuhan, China, in December 2019 and dealing with a pathogen capable of quick as well as easy transmissibility, undefined symptoms, non-availability of therapeutics and acclimatization/adaptation to COVID-19 scenario can be acknowledged as the phase I challenges faced by the world. The novel and enduring COVID-19 pandemic that the world has been witnessing for the past few years has advanced to the huge and exhaustive phase II challenges that encompass the implementation of one of the longest complete global shutdowns, unusual practice of work-from-home practices, immense pressure on the healthcare sector, suspension of daily activities, majorly closing of schools and colleges, no social gatherings, the urgency to develop anti-COVID therapeutic/vaccine, lack of awareness/negligence, antimicrobial resistance and emergence of variants that fuelled the spread of the infection. Despite the combined efforts that might have flattened the curve of the infection, it remains a major trigger for rolling out post-COVID challenges, being a serious concern for every facet of the society that includes continuous deterioration of mental health, financial instability, and fear of death. This chapter focuses on addressing the challenges and threats that prevailed during and post-COVID period. Additionally, it also summarizes strategies to combat the setbacks posed by SARS-CoV-2 infection.

Keywords: COVID-19, Infection, Pathogen, Therapeutic, SARS-CoV-2, Vaccine, Variants.

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INTRODUCTION

Individuals suffering from atypical viral pneumonia were initially observed at the centre of pandemic, Wuhan, China, towards the late 2019. Later, the International Committee on Taxonomy of Viruses (ICTV) and the World Health Organization (WHO) coined the disease and viral pathogen associated with it as Coronavirus disease-2019 (COVID-19) and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. According to the WHO update on COVID-19, the death toll stands at over 6.9 million with over 759 million confirmed cases **[Ref-Who Report https://covid19.who.int/].** The mode of transmission is primarily via respiratory droplets and contact routes, and the median latency period is around 4-5 days prior to symptom outset [2, 3]. The symptomatic COVID-19 patients often experience fever/chills, dry cough, shortness of breath(dyspnoea), upper airway congestion, loss of smell (anosmia) and loss of taste (ageusia) [1, 2]. Interaction of SARS-CoV-2 with the ACE2 receptor mediates its entry inside the pulmonary tract (the primary and potential target), wherein the virus replicates causing life-threatening acute respiratory distress syndrome (ARDS) [1, 4]. The underlying pathogenesis can be categorized into three stages: **a. Proliferative Stage**- the initial stage of the infection that is marked by SARS-CoV-2 infiltration into pulmonary parenchyma through the molecular gateway (ACE2 receptor). Activation of early innate defenses and the appearance of mild constitutional symptoms are hallmarks of this stage. **b. Pulmonary Stage-** the second stage of COVID-19 progression is defined by elevated signs of inflammation, tissue damage and impaired pulmonary function. **c. Hyper inflammatory Stage-** During this stage, the course of the disease advances to systemic inflammation, high levels of pro-inflammatory cytokines (IL-2, IL-6, IL-7, IL-10, C-reactive protein (CRP) thereby creating a '**Cytokine Storm**', a major cause of lung damage associated with life-threatening complexities including MOF, ARDS, septic shock, hemorrhage/coagulopathy, acute heart/liver/kidney injury, and secondary bacterial infections [1].

Due to the sudden outbreak worldwide, mass widespread and unknown outcomes of novel COVID-19, it was declared as a public health emergency on 30 January 2020 [5] followed by the very first shutdown in Wuhan on 23 Feb 2020 [4]. Owing to the health crisis globally and recurring COVID-19 waves, the world has faced multiple lockdowns/complete shutdowns for COVID-19 containment. Also, preventive guidelines were issued on a regular basis by competent authorities. Despite these efforts, COVID-19 continues to pose serious threats and challenges to public health. The deadly virus can be considered a global challenger as it has acutely affected different facets of society ranging from public health to the global economy. This chapter calls into question an in-depth understanding of these challenges, thereby necessitating appropriate measures to overcome these challenges as depicted in Fig. (**1**).

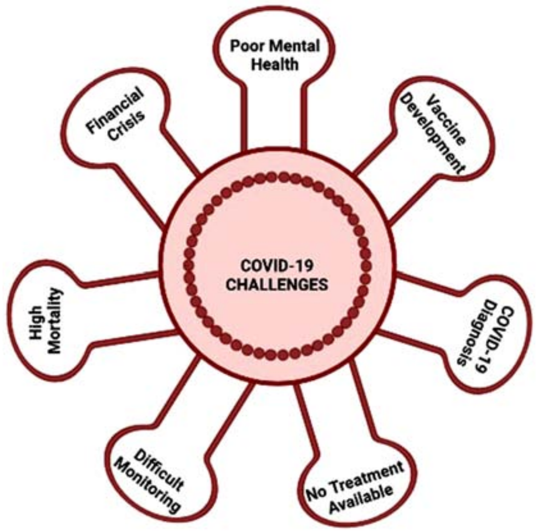

Fig. (1). Depiction of different challenges posed by COVID-19 pandemic caused by novel SARS-CoV-2 virus.

The challenges posed by Coronavirus (COVID-19) pandemic are enlisted below-

Challenge: Mental Health of Healthcare Workers

COVID-19 can be attributed, credited, and regarded as a primary cause of disruption to health and health services worldwide. Frontline workers or health care workers (HCWs) including doctors, nurses have been 'diligent and committed heroes' in putting their undying efforts in the fight against ongoing COVID-19 pandemic [6]. Though being frontline fighters, HCWs have also been identified as a 'vulnerable/risk group' who suffered a decline in mental well-being/subjected to/prone to a decline in mental well-being [7]. HCWs can be described as the 'second victim' of COVID-19 pandemic as they have faced challenges not only limited to their professional space but at personal levels too, a reason for their mental health deterioration [6]. The tally of crisis for HCWs began with initial challenges, such as diagnosis, contact tracing, quarantine, and treatment of suspected or confirmed COVID-19 cases. With the upsurge in COVID-19 cases, HCWs faced mental challenges with meagre resources of personal protective equipment, patient overflow and continuous exposure to COVID-19 hot zones, prolonged work shifts, and extensive media coverage [8], clearly described in Fig. (**2**).

CHAPTER 8

The Impact of COVID-19 on the Economy and Roadblocks to Recovery

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Abstract: An enormous global economic crisis was brought on by the COVID-19 epidemic, which first appeared in 2020. This paper analyzes the challenges standing in the way of an efficient recovery while also looking at the many economic effects. Severe economic contractions were first caused by widespread lockdowns and supply chain disruptions, mainly impacting the services, tourism, and hospitality industries. Fiscal and monetary measures were swiftly implemented by governments and central banks to lessen the effects, but a number of barriers to recovery have persisted.

In this research, several obstacles are outlined, such as unequal vaccination coverage, enduring health fears, and uneven economic recovery rates. The public's uneven adherence to safety measures and inconsistent worldwide response coordination have added to ongoing uncertainty. The pandemic has also highlighted pre-existing disparities and the need for extensive policy changes. In order to provide fair access to vaccines, the report promotes targeted aid for vulnerable sectors, investments in digital infrastructure, and international cooperation.

In conclusion, the COVID-19 outbreak highlighted weaknesses in the world's economies and prompted a reassessment of traditional economic paradigms. Despite continued recovery efforts, a number of challenges—from health issues to structural inequalities—remain in the way. Building a more robust and inclusive post-pandemic economy requires an integrated strategy that includes both short-term alleviation and long-term systemic improvements.

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Keywords: COVID-19, Economic impact of COVID-19, Macroeconomics, Microeconomics.

COVID-19 INFECTION

On 11th March 2020, the SARS-Cov2 Virus infection was declared a global pandemic by the World Health Organization. The SARS-CoV-2 virus brings on a highly contagious respiratory ailment called COVID-19. Since the disease's initial discovery in Wuhan, China in December 2019, it has spread worldwide and influenced almost every facet of life.

When an infected individual talks, coughs, or sneezes, respiratory droplets that are the primary means of COVID-19 transmission are released, it can spread through touch, mainly touching any parts of the face or contact with the nose, mouth or eyes epithelium after touching a surface exposed to the virus. Mild to severe COVID-19 symptoms might include fever, coughing, exhaustion, loss of taste or smell, and breathing difficulties. For elderly folks and those with existing medical issues, the illness can be more deadly. The mode of transmission of the virus is human-to-human transmission via droplets or direct contact; it has also been observed that this virus can show its effect even after 14 days.

STATISTICS OF COVID-19- MORBIDITY, MORTALITY

As the pandemic progresses, the figures for COVID-19 morbidity (the rate of illness incidence) and mortality (the rate of death due to the disease) constantly shift. According to WHO statistics from September 2021, over 4.5 million fatalities and over 220 million confirmed COVID-19 infections worldwide. These figures demonstrate the pandemic's intensity and substantially influenced world health.

The United States had the most confirmed cases and fatalities then, with over 40 million cases and 640,000 deaths. This placed a heavy load on the healthcare system, and the nation has been dealing with the pandemic's impacts for more than a year.

With over 33 million cases and 440,000 confirmed deaths in India, and over 21 million cases and 590,000 deaths in Brazil, respectively, both countries similarly experienced high rates of confirmed cases and fatalities. These nations had considerable increases in cases and deaths during the epidemic, straining their healthcare systems and highlighting the necessity of international collaboration in combating the pandemic.

The percentage of confirmed patients that pass away due to the illness is known as the case fatality rate (CFR). According to the global CFR average of 2%, there were two COVID-19-related deaths per 100 confirmed cases worldwide. The CFR varied significantly between nations, with some reporting more excellent rates than others. However, the CFR varied according to several variables, such as age, underlying medical disorders, and access to treatment.

The risk of developing serious disease and passing away from COVID-19 was greater in older persons and those with underlying medical disorders. Efforts have been made to prioritize vaccination and other preventive measures for these susceptible groups. It is crucial to remember that anybody can get COVID-19, therefore, preventative measures including social isolation, mask use, and immunization remain crucial.

In conclusion, the figures on COVID-19 morbidity and death show how seriously the pandemic has affected the world's health and the necessity for ongoing efforts to stop the disease's spread through vaccines, preventative measures, and international collaboration.

THE OVERALL IMPACT OF COVID-19

The overall impact of COVID-19 has been widespread and multifaceted, affecting nearly every aspect of life worldwide. Some of the key impacts of COVID-19 include:

1. Public health impact: With millions of verified cases and fatalities globally, the epidemic has devastated public health. In several nations, the epidemic has overburdened healthcare systems, causing a lack of medical supplies, hospital beds, and healthcare professionals. The epidemic has also interfered with standard medical care, which might have long-term health effects including delayed diagnosis and treatments.

2. Economic impact: COVID-19 has had a considerable negative economic impact, especially on small enterprises and low-income workers. Many firms' closures or reduced capacity has resulted in job losses and financial difficulties. The epidemic has also impacted global supply networks, resulting in some goods and services shortages.

3. Social effect: COVID-19 has altered social behaviour, resulting in lockdowns and social distance measures that influence people's everyday routines and activities. Social disparities, notably those related to access to healthcare, education, and work prospects, have also been brought to light by the epidemic.

CHAPTER 9

AI-Based Diagnosis of Novel Coronavirus Using Radiograph Images

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Abstract: The therapeutic value of artificial intelligence (ML) in the diagnosis of viral illnesses has been illustrated by the outbreak of COVID-19. This chapter digs into the modern uses of Artificial Intelligence and Machine Learning (ML) algorithms for COVID-19 diagnosis, with a focus on chest imaging procedures like as CT and X-rays. Additionally, we explored ML's strengths, such as its capacity to analyze enormous datasets and detect patterns in medical imagery. But there are still issues to deal with, like the scarcity of data, privacy issues, and machine learning's incapacity to evaluate the severity of health conditions. However, several machine learning methods, such as decision trees, random forests, and convolutional neural networks, are reviewed in this research concerning COVID-19 diagnosis. Subsequently, we highlight the efficacy of several models in COVID-19 screening, such as XGBoost and Truncated Inception Net. Moreover, the chapter discusses potential strategies for machine learning in COVID-19 diagnosis, emphasizing the crucial role of collaboration among data scientists and healthcare experts. It is imperative to confront data bias and incorporate more comprehensive patient data than just chest imaging. All things considered, machine learning presents a potential pathway toward quick and precise COVID-19 diagnosis; nonetheless, conquering existing obstacles is necessary for ML to be widely used in healthcare institutions.

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Mohammad Sufian Badar (Ed.)

Keywords: Artificial Intelligence (AI), COVID-19, Chest X-ray, Computed Tomography (CT), Computer-aided Diagnosis (CAD), Deep Learning (DL), Diagnostic Imaging, Ground-Glass Opacity (GGO), Machine Learning (ML), Radiological Analysis, Variants of Concern (VOC).

INTRODUCTION

With the outbreak in December 2019, there have been almost 776 million officially verified cases of COVID-19 worldwide [1]. The World Health Organisation(WHO) proclaimed it a global pandemic in March 2020 following the first report in December 2019, and on April 21, 2020, two million cases and 120,000 fatalities were reported [2]. The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was the new coronavirus that triggers COVID-19 [3]. However, SARS-CoV and Middle East Respiratory Disease Coronavirus (MERS-CoV) are two other coronaviruses that have previously been identified [4]. SARS-CoV-2 is thought to be less lethal but much more contagious than earlier coronaviruses [3]. The primary transmission pathways for SARS-CoV-2, the etiological agent of COVID-19, are predominantly through the inhalation of respiratory droplets and aerosols. These particles are expelled by an infected individual during respiratory activities such as coughing, sneezing, or speaking [5]. Consequently, implementing measures to curb the spread of SARS-CoV-2 was challenging due to the virus's high transmission capability. Furthermore, SARS-CoV-2 has been associated with several distinct variants including delta, omicron, and delta-cron (a combination of Delta and Omicron variants) [6]. Furthermore, the rapid mutational capacity of SARS-CoV-2 is exacerbating public health challenges and exerting a significant toll on the global economy and healthcare infrastructure [7]. However, respiratory difficulties, fever, body aches, coughing, and other symptoms are common with COVID-19, and they can lead to multi-organ failure or even death. Given that the initial symptoms of COVID-19 are similar to those of the ordinary influenza, prompt diagnosis at an early stage is essential [8]. Subsequently, early and efficient large-scale screening for SARS-CoV-2 infection, coupled with the rapid implementation of appropriate medical interventions, remains a cornerstone in mitigating the impact of the COVID-19 pandemic. The RT-PCR test, while serving as the current gold standard for diagnosing active COVID-19 infection, presents limitations. These include being labor-intensive, requiring specialized equipment and trained personnel, and potentially yielding false-positive (FP) or false-negative (FN) results [9 - 11]. However, the limitations of RT-PCR testing, particularly sensitivity and turnaround time, can be particularly concerning during periods of exponential viral spread. Additionally, supply chain disruptions and resource limitations may further exacerbate these issues, hindering timely identification and isolation of infected individuals. This, in turn, can contribute to ongoing community transmission due to both false-negative results allowing unknowingly infectious individuals to remain unisolated and delays in testing allowing the virus to propagate [12].

While RT-PCR remains the gold standard for diagnosing active SARS-CoV-2 infection, chest imaging modalities such as computed tomography (CT) and chest X-ray can play a complementary role. These imaging techniques may provide valuable insights into lung involvement and disease progression, aiding in patient management and treatment decisions [13]. While chest imaging, particularly computed tomography (CT), can be a valuable tool in managing patients suspected of COVID-19 infection, it is not a definitive diagnostic test for the virus itself. RT-PCR remains the gold standard for diagnosing active SARS-CoV-2 infection. However, chest CT findings, such as Ground-Glass Opacity (GGO), can be suggestive of COVID-19 pneumonia, particularly when presenting with a characteristic bilateral, peripheral, and multifocal distribution. It is important to note that GGO is a non-specific finding and can be seen in other respiratory illnesses. In some cases, particularly in the early stages of the disease, GGO may appear as a solitary lesion in the lung periphery [14]. Moreover, the high volume of chest CT scans generated during COVID-19 outbreaks presents a significant workload for radiologists. Manual analysis of these images is labor-intensive, prone to inter-reader variability, and susceptible to observer fatigue. This can lead to missed or misdiagnosed cases, particularly when COVID-19 pneumonia mimics other viral infections. Furthermore, subjective interpretation can lead to inefficient allocation of healthcare resources. Subsequently, advancements in artificial intelligence (AI)-powered Computer-Aided Diagnosis (CAD) systems offer promising solutions [15].

COVID 19- ETIOLOGY, CLINICAL IMAGING, AND PROGNOSIS

Coronaviruses are named for their characteristic crown-like appearance under an electron microscope. This crown-like morphology is due to the presence of spike proteins projecting from their outer lipid envelope. Among the six identified genera of coronaviruses, only the α-coronavirus and β-coronavirus genera encompass strains known to infect humans. Within these two genera, there are seven human coronaviruses identified [16]. The above-mentioned classification is shown in the following Table **1** [17]:

CHAPTER 10

Use of Machine Learning in Diagnosing COVID-19 Infection

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Abstract: The world has witnessed the most devastating pandemic due to the rapid spread of COVID-19, an infectious disease caused by severe acute respiratory syndrome coronavirus (SARS-CoV2 virus). The public health emergency of international concern arose due to the sudden outbreak of COVID-19 where both medical and socio-economic structures remain entirely altered not only in developed countries but also in developing countries. In this crucial scenario, advanced technologies like machine learning (ML) and deep learning (DL) assisted the researchers and helped governments and other health officials (including frontline workers) to manage the outbreak. ML is a sub-branch of computer science, where, machines can analyze large datasets and derive inference from that variable data structures. With the help of suitable algorithms, computers can imitate human behavior by analyzing results and the machines can perform in less time with great accuracy. During the pandemic, due to the scarcity of human resources, ML aided in the diagnosis of patients, forecasted communal transmission, and also helped in the development of effective antivirals and vaccines. In this chapter, we have highlighted the importance of various state-of-the-art ML tools, algorithms and computational models useful in the diagnosis and management of COVID-19. The circumstantial applications of ML are also discussed with real-time case studies. Lastly, the challenges faced by ML in COVID-19 supervision and future directions are also discussed. This chapter will help the researchers and students to understand how this powerful tool is employed to fight COVID-19 and can assist in future health emergencies due to emerging pathogens.

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Keywords: Computers, Computational models, COVID-19, Deep learning, ML, Socio-economic, SARS-CoV-2, Vaccine development.

INTRODUCTION

The global pandemic, named coronavirus disease (COVID-19), has ruled the world for the past two years and was first reported in Wuhan, China, in December 2019. Since then, 627 million confirmed COVID-19 cases have been reported globally [1, 2]. After the first report in December 2019, in March 2020, it was declared a global pandemic by WHO, and on 21st April 2020, two million cases were reported associated with 120,000 deaths [3]. COVID-19 was caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) [4].

Other coronaviruses were reported earlier: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Compared to the previous coronaviruses, SARS-CoV2 is considered less fatal but most contagious [5]. The plausible mode of transmission of COVID-19 can be either through direct contact or through the small aerosols released by the infected person while talking, sneezing, or coughing. The high transmission capacity of SARS-CoV-2 made it challenging to take control measures on the spread of the disease. Several different variants of SARS-CoV-2 (delta, omicron, and delta-cron (mixed infections arise due to delta and omicron variants) were also reported from other parts of the world. The fast mutating ability of SARS-CoV-2 is worsening the health status of individuals and also affects considerably health infrastructure and the global economy [6, 7]. The common symptoms of COVID-19 include coughing, fever, body ache, difficulty breathing, etc. where, patients with comorbidities are mostly affected, which could end up in multi-organ failure or death [8]. Due to the similarity of primary symptoms of COVID-19 matches with common influenza, it is mandatory to identify COVID-19 at the preliminary stage.

Several identification systems have been reported for COVID-19, which include rapid antigen tests, antibody detection, reverse transcriptase (RT) PCR, next-generation sequencing, computed tomography (CT) of the chest, and X-rays. Among the techniques mentioned above, RT-PCR tests are usually used as confirmatory tests. However, studies showed that RT-PCR from nasopharyngeal and throat swabs give positive results in only 30-70% of cases. There are few reports of false negatives being reported as well. Among the other pathological tests, CT scans of the chest and X-rays are proclaimed to have 98% and 69% sensitivity, respectively. But identifying infection through CT-scan and X-rays requires expert radiologists [9, 10]. There are several kit-based identification methods also available in the market which are routinely used for the detection of COVID-19. But the positivity yield associated with those kits focuses on the demand for developing more advanced, accurate techniques to help patients in the early phases of diagnosis and prevent rapid dissemination.

In searching for more modern and accurate diagnostic techniques, researchers from different parts of globe try their best to develop universal diagnostic systems that apply to other variants of COVID-19 diagnosis. AI (AI) is one of the promising techniques that utilize previous instances, and without explicit programming, it speeds up the diagnosis process of COVID-19. With the help of two subsets of AI *i.e*. ML (ML) and deep learning (DL), the tracking, diagnosis, and treatment process have become much easier and faster [11]. ML is a system that depends upon machine intelligence based on the previous reference datasets, and deep learning (DL) is an advanced system that simplifies the learning of the machines [12]. ML approaches can be sub-divided into two broad categories viz. supervised and unsupervised learning. In supervised learning, the data are labeled, and it trains the machine in a guided manner, and two algorithms are used namely classified and regression. In unsupervised learning, without actual guidance and labeled data, different algorithms are employed for the training of machines. The algorithms employed could be subdivided into clustering and association [13]. Both machine and deep learning are used for patient diagnosis through the analysis of images of CT scans, and X-rays and they also help to track the epidemiological trend. In this chapter, we have highlighted the importance of ML techniques in the diagnosis of COVID-19 and illuminated new insights into the real-world applications of ML with some real-time case studies.

ROLE OF MODERN TECHNIQUES IN THE DIAGNOSIS OF COVID-19

The COVID-19 pandemic has wreaked havoc all over the world in the past two years. Different preventive measures have been taken for the early detection of the SARS-CoV-2 viral genome to control the outbreak, such as the detection of the viral antigen and their antibodies or viral nucleic acids. Furthermore, detecting the infection in its early stage [14 - 16] and its timely treatment can decide the quarantine period to stop the infection chain, increase the cure rates, and reduce the treatment costs of other serious ailments. However, the shortage of medical centres, dependable caretakers, and deficiency of diagnosis equipment creates difficulty in tracking down the infection and monitoring the pandemic. Recent advances in the technologies and healthcare sectors, along with the widespread use of smartphones, give rise to the development of various effective diagnosis equipment to fight against the current pandemic. Since the beginning of the pandemic, researchers have successfully implemented nucleic acid assays,

CHAPTER 11

Future Technologies for Coronaviruses (COVID-19)

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Abstract: The ongoing battle against coronaviruses demands innovative approaches and cutting-edge technologies to enhance our ability to detect, prevent, and respond to outbreaks effectively. This chapter explores the forefront of advancements in robotics, drones, Genetic Engineering technologies, and nano-technology, presenting a comprehensive overview of their potential roles in shaping the future of pandemic management. By embracing these innovative solutions, we have paved the way to not only enhance our response capabilities during the current pandemic but also to establish a robust framework for tackling future viral threats.

Keywords: Active and passive targeting, AMBU Ventilator, Autonomous-Robotics, COVID-19, CRN, CRISPR-Cas, Gene therapy, Mobile edge computing (MEC), Nanotechnology, Nanocarriers, Nano-based vaccines, Nanoparticles, RNAi, Telerobotic system, UAVs/Drones, Vaccine delivery methods.

EXPLORATION OF ROBOTICS IN PANDEMIC MITIGATION STRATEGIES

Integration of Robotics in Combating Coronaviruses

The workload of frontline personnel had been significantly reduced by the intelligent robot systems' capacity to assist in diagnosis, risk assessment,

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monitoring, telehealth care, disinfection, and various other tasks during this pandemic. The public and media have shown a great deal of interest in the use of robots in public areas, hospitals, and quarantine facilities. Although robots have been used in industrial settings such as automotive plants since the 1960s, they are now able to help us in places where humans are at high risk of being infected, like hospitals.

With robots and artificial intelligence (AI), humans are reducing the impact of coronaviruses, after two years of combating the virus. Professionals are replaced by robots as they have special benefits in enhancing the productivity and preventing the spread of viruses. Robots that measure temperature, such as the DROID team developed by UBTech Robotics in China, have monitored China, and have monitored people's health in public areas [1].

Robots used in telemedicine have the potential to reduce the direct contact between sick patients and their carriers. With a single sampling success rate of over 95%, the COVID-19 throat swab intelligent sampling robot has improved the standardisation of biological sample research topics and guaranteed specimen quality.

"This pandemic has created an interesting new landscape for advancements in consumer-facing robotics," says Bernd Schmitt, the Robert D. Calkins Professor of International Business and Faculty Director of the Centre on Global Brand Leadership at Columbia Business School. "Not only has the pandemic created many new immediate uses for robots, but I predict it will also change consumers' perceptions of service robots from one of relative skepticisms to acceptance, and more quickly than we previously expected."

Robotics Techniques and Tools

The most recent advancements in robotics research are the distribution of healthcare resources, diagnosis of symptoms or viruses, and detection techniques and tools.

COUGH RECOGNITION NETWORK (CRN)

A cough recognition network is built using an Mel-spectrogram and the CNN model. When compared to alternative techniques, CRN performs exceptionally well in cough recognition. Generalisation test findings indicate that CRN can adjust to cough monitoring in a variety of diverse everyday scenarios. The correct recognition rate of the datasets used is 98%. It can be seen that the model can still achieve good recognition performance even if a variety of different sounds are mixed. It is anticipated to lessen the exposure of healthcare workers and offer a viable option for managing illness during the COVID-19 pandemic [1].

AUTOMATED AMBU VENTILATOR

Automated AMBU Ventilator with Negative Pressure Headbox as shown in Fig. (**1**) and Transporting Capsule in Fig. (**2**) for COVID-19 patients transfer is a low-cost construction, flexible usage unit, and airborne prevention that could be manufactured without a high level of technology. It is possible to adjust the oxygen flow rate, rhythm, and volume using this automated AMBU ventilator. An HEPA filter was used to purify the dangerously expired air. The air treatment systems are integrated inside a small-sized patient transport capsule. The machine's future development concentrates on ensuring seamless integration with imaging technology, validating standardisation, conducting tests on human subjects, and eventually undergoing commercialization [2].

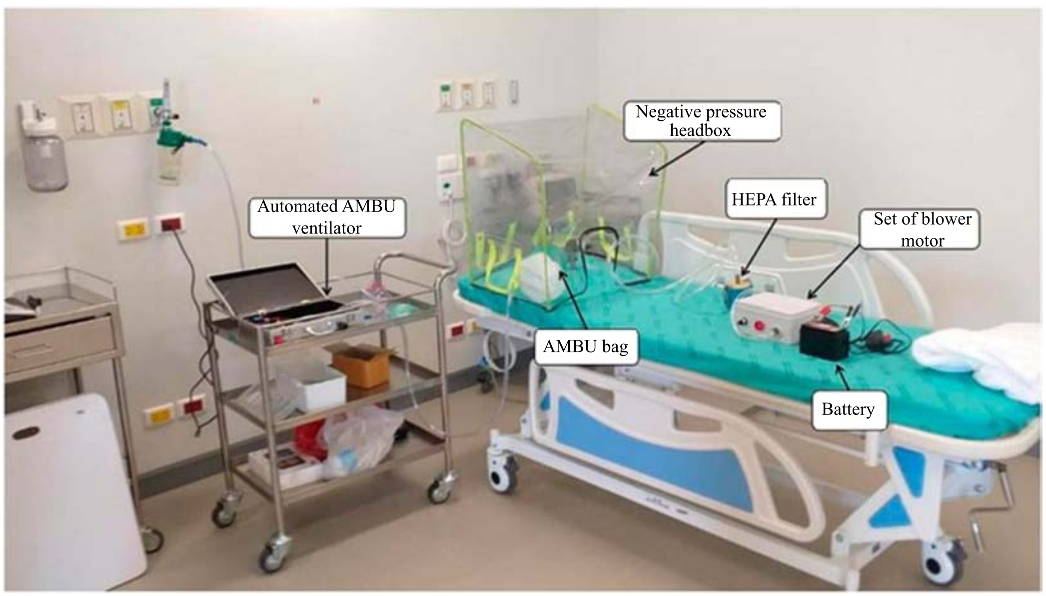

Fig. (1). Automated AMBU ventilator with the negative pressure headbox prototype.

AUTONOMOUS ROBOTIC POINT-OF-CARE ULTRASOUND IMAGING FOR MONITORING OF COVID–19–INDUCED PULMONARY DISEASES

An automated robotic system as shown in Fig. (**3**) makes it possible to stage and diagnose COVID-19 patients by POCUS (Point-of-care Ultrasound) scanning their lungs. An algorithm is created to determine the best orientation and position of an ultrasound probe on a patient during a CT scan to photograph target spots in

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Mohammad "Sufian" Badar

Mohammad "Sufian" Badar, PhD was born and raised in Nazra, Madhubani, Bihar, India. He has been working as an Assistant Professor in the Department of Computer Science and Engineering, School of Engineering Sciences and Technology (SEST), Jamia Hamdard, New Delhi, India. Before that, he served as a Senior Teaching Faculty in the Department of Bioengineering at the University of California, Riverside, CA, USA. He served as an Analytics Architect in CenturyLink for over a year in Denver, CO, USA. He is also the Academic Director of SPI Darbhanga, Bihar, India (Salfia Paramedical Institute Darbhanga).

He has an excellent academic record with an MS in Molecular Science and Nanotechnology and a Ph.D. in Engineering from Louisiana Tech University Ruston, LA, USA, respectively. He has published two books with Springer Nature and Elsevier respectively, "A Guide to Applied Machine Learning for Biologists", and "Diagnosis and Analysis of COVID-19 using Artificial Intelligence and Machine Learning-Based Techniques".

He is currently in the process of developing a device that, using Biosensors, can correlate the physiology of the human body with the emotion recognition algorithm, giving us a clear measure of the amount of stress hormones in the body.