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COVID-19: What We Know So Far
A Narrative Review

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Abstract

Objective: Since the emergence of the COVID-19 pandemic at the end of 2019, the number of affected cases has not stopped rising. Similarly, the number of scientific publications and pre-prints has been increasing exponentially, with an effort to understand this disease more and find a proper solution. The purpose of this article is to review the current understanding of the novel coronavirus.

Background: The latest COVID-19 pandemic caused by the SARS-CoV-2 has spread globally ever since it emerged in Wuhan's city in China. This rapidly spreading disease has changed our lives in unimaginable ways, spreading fear and uncertainty due to the lack of knowledge and the flooding with new information, which lacks the scientific method and cannot be critically appraised. The purpose of this article is to gather some of the best knowledge that has been published so far in a unified narrative review, making it easy for the scientific community to review the most accurate and recent understandings about COVID-19.

Methods: We screened relevant articles using a specified number of keywords and specific databases, including PubMed and Embase. We selected peer-reviewed English published material related to the topic, except for a few pre-prints that we deemed necessary to include. We also screened the reference lists of these articles to find relevant publications with the same criteria.

Discussion: This narrative overview comprises several subsections that discuss the epidemiology, virology, pathogenesis, clinical manifestations, diagnostic methods, and management of the disease. We also presented a section on the implications of the disease in pregnancy. We wrapped up the review with a special division regarding the response to COVID-19, which has been diverse in different countries.

Conclusion: COVID-19 has been a serious global health threat with a high transmission and case fatality rate, particularly in vulnerable populations. Epidemiologic models have so far guided the response, but

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they need to be interpreted carefully, with an understanding of their limitations. The disease's response has varied among different countries; with no current vaccine or standard treatment, the world stands in fear, maximizing preventive strategies to reduce the damages caused by this virus. This manuscript presents a summary of everything that is so far known about COVID-19 to make it easier for the medical community to overview the disease that has changed the world.

Keywords: coronavirus, COVID-19, SARS-CoV-2, epidemiology, patients, cases, virus, China, epicenter, clinical manifestations, SARS-CoV, MERS, pathogenesis, diagnosis, symptoms, complications, RT-PCR, CT-scan, FDG PET, imaging, findings, management, treatment, hydroxychloroquine, remdesivir, ivermectin, colchicine, corticosteroids, tocilizumab, lopinavir-ritonavir, vitamin C, ascorbic acid, Traditional Chinese Medicine, monoclonal antibodies, convalescent plasma, prevention, measures, infection, control, vaccine, pregnancy, transmission, risk factors, response, Taiwan, Italy, United States

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Introduction

In December 2019, a cluster of severe pneumonia cases of unknown etiology started surfacing in Wuhan, the capital city of Hubei province in China. The number of cases increased exponentially, and the scientific community started investigating respiratory samples to determine the etiology. On the 31st of December 2019, the Chinese health authorities raised their concern to the World Health Organization (WHO). On the 7th of January 2020, the investigations' results came positive for a type of coronavirus named 2019 novel coronavirus (2019-nCoV), which is almost identical to the Severe acute respiratory syndrome coronavirus (SARS-CoV) and homologous to that in bats. In retrospect, some of the first reported cases were noted to have a common origin, the Huanan market, a live animal and seafood market. Samples taken from the live wild animals at the market tested positive for the same virus. When cases that had no connection to the market started emerging from regions near Wuhan, a health crisis due to a virus with a human-to-human transmission was declared. By the 1st of March 2020, 79,968 cases and 2873 deaths were confirmed in China [1].

Progressively, countries like Korea, Japan, Thailand, Italy, France, Spain, and the United States of America recorded cases of people infected with the virus, with a history of contact with people coming back from China. The first mortality recorded worldwide was on the 11th of January 2020 in China. The WHO named the disease coronavirus disease 2019 (COVID-19) and the virus was later called Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The WHO soon urged officials to start implementing preventative measures. COVID-19 had become a global health crisis and a public health emergency of international concern. On the 11th of March, 2020, the WHO declared it a pandemic. As of the 25th of October, 2020, 43,270,814 cases were recorded with 1,157,818 deaths, spreading over 215 countries and territories, and two international conveyances [2]. Parallel to this rise in the number of cases and mortality, the number of articles related to the COVID-19 pandemic has been increasing exponentially in a global effort to understand the disease and develop proper treatment and prevention strategies. The purpose of this article is to unify the so far accumulated knowledge and review the current understandings concerning COVID-19, including, but not limited to, its pathogenesis, diagnosis, and treatment.

Methods

After a preliminary literature review, we set an outline that divided the work into subsections. We screened relevant articles related to the topic using specific keywords and databases, performing the searches using MEDLINE, PubMed, and Embase and selecting only peer-reviewed publications in English. We also screened these articles' reference lists and included some of the relevant publications and a few high-quality pre-prints.

The keywords we used to conduct our search included combinations of Medical Subject Heading (MeSH) terms and supplementary terms. From the significant number of articles yielded through this approach, a subset of high-quality studies was selected. It is possible that some of the relevant articles were missed, as the database is still increasing exponentially, but the selected articles allow a rich overview of the topic.

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Discussion

I. Epidemiology: Global trends, characteristics of the outbreak, and epidemiologic models

a) Global Trends

The latest coronavirus outbreak COVID-19 caused by the SARS-CoV-2 has been spreading worldwide ever since it had suddenly emerged in Wuhan's city in China by the end of 2019, thus accounting for the third severe outbreak of novel coronaviruses [3]. With the continuous population growth, epidemics become more likely. SARS-CoV in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 were responsible for the two previous epidemics that exhibited distinct dynamics compared to the current one due to differences in clinical characteristics, transmission, severity, and mortality [4,5]. Before these three recently detected coronavirus types, this group of viruses had been recognized as a cause of mild to moderate common cold in humans with bats as a major natural reservoir [6-8].

All human coronaviruses (CoVs) probably have a zoonotic origin, and early investigations identified bats (*Rhinolophus affinis*) as the probable progenitor source of the SARS-CoV-2 because they carry CoVs with a 96% nucleotide identity match to the latter [9]. Malayan pangolins (*Manis javanica*) CoVs were found to possess a 99% sequence identity to SARS-CoV-2, making them possible intermediate hosts [10]. The enormous number of travelers to the Chinese New Year contributed to the spread of the novel virus, similar to the 2003 SARS-CoV, but this time with a seven-fold increase in tourism flux [11]. Subsequently, the virus likely transmitted to humans and has evolved during unrecognized human-to-human transmission [12].

At the start of the outbreak, China was the primary epicenter with the highest reported cases and mortality. Cases outside China were mostly limited to travelers from the country. On the 3rd of February 2020, COVID-19 was reported on the Diamond Princess Cruise Ship, which had first departed from the Japanese shore. The cruise ship conditions exacerbated the already highly transmissible nature of SARS-CoV-2, making it the largest coronavirus spread outside China with more than 19% infections on board (with more than 700 out of 3711 passengers and crew affected) [14]. By mid-February 2020, COVID-19 had begun to spread in countries like South Korea, Japan, Italy, and Iran. After Chinese authorities' strict interventions, the disease got controlled in China, while cases started being registered exponentially in Italy, shifting the epicenter to Europe [15,16]. As of the 26th of March, cases in the United States surpassed any other country, affirming its new spot as the pandemic's epicenter with New York state suffering the most [17]. Six months after the disease's emergence, South America was registering an increasingly high number of infections, with Brazil being considered the new epicenter of the disease [13].

b) Characteristics of the outbreak: Severity spectrum, R0, CFR, and seasonality

Understanding the COVID-19 outbreak's basic epidemiology is of paramount importance to help define, contain, prevent, and treat the disease. Most interventions have so far been unable to stop this new virus from spreading. SARS-CoV-2 is a new virus, and epidemiological data is vital to overcoming the pandemic [3].

Most infectious diseases exhibit a spectrum of severity that ranges from asymptomatic to death. Such clinical classification of COVID-19 provides information about the distribution of cases along the severity spectrum, which offers insight into the disease's prognosis and mortality. COVID-19 affects people of all ages, and its clinical severity was defined and classified into four groups: asymptomatic, mild, severe, and critical *(Table 1)* [18]. In adults, most cases (81%) are mild, but in the critical group, mortality exceeds 50% [3]. Asymptomatic infections could occur at any age but are most frequent in younger populations [19]. In the pediatric population, the disease is mainly asymptomatic or mild (90%), constituting a significant source of disease spread in the community [18].

Furthermore, the infectivity of this novel virus or its tendency for horizontal transmission is high. The reason is the high viral load in the upper respiratory tract and the transmission potential from asymptomatic and mildly symptomatic patients [20]. The infectivity period for COVID-19 begins before symptoms, making it even harder to control its spread due to the added challenge of presymptomatic transmission on contact tracing [21].

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Table 1: Spectrum of the infection: COVID-19 clinical severity classification. Abbreviations: SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-PCR: reverse transcription polymerase chain reaction; PaO2: partial pressure of oxygen, arterial; FiO2: Fraction of inspired oxygen

Disease Severity Spectrum	Diagnostic Criteria
Asymptomatic	• Positive SARS-CoV-2 RT-PCR test. • No associated clinical signs or symptoms.
Mild	• Symptoms of acute upper respiratory tract infection **without pneumonia**: fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing • Mild pneumonia cases
Severe	• Rapid progression within one week. • Dyspnea with central cyanosis • Respiratory rate ≥ 30/min • Oxygen saturation less than 92% • PaO2/FiO2 <300 • Lung infiltrates > 50% within 24-48 hours
Critical	• Acute respiratory distress syndrome (ARDS) or respiratory failure • Shock • Multiple organ dysfunction/failure

We consider two parameters when categorizing an infectious disease and determining its burden. The first one is the reproduction rate, which determines the disease capacity to spread, translated as the probability of disease transmission. The base reproduction number of disease transmission (R0) indicates the number of secondary cases due to initial infection, reflecting disease spread in a population with no previous exposure to the virus [3]. To successfully halt the spread of a disease in a community, R0 should be below 1. In a review of 12 studies, R0 was 3.8 (1.4–6.49). We can calculate different R0 values using modified methods and assumptions, even in the same geographic region. It seems that we need more data to determine a more accurate R0 value [22].

The second parameter is the case fatality rate (CFR), which measures the disease's severity and its capacity to kill those infected [3]. It is the proportion of reported death cases with the disease within a specified time, and it depends on the case definition, the case detection, and the treatment availability. It is still challenging to calculate the accurate CFR of COVID-19, with the main challenge being the denominator's determination (the actual number of infectious cases). The best estimate of CFR was 0.99%, as determined on board the Diamond Princess cruise ship. In this situation, the denominator data was fairly accurate because the imposed quarantine on all passengers eliminated other confounding factors by providing a population living in a defined area, yet, the CFR was still lower than that of MERS (34.4%) and SARS (9.5%) [23, 24]. The absence of a gold standard for the diagnosis and treatment of COVID-19 increases the CFR; the level of preparedness, health care capacity, and resource availability also affect disease outcome: wherever testing and contact tracing are not widely available, the CFR skews to higher estimates [25, 26]. The broad spectrum of clinical presentations made the definition of a case difficult. Estimates of the CFR have changed over time as the case definition was modified to include very mild and asymptomatic infections [4].

R0 and CFR define transmissibility and severity, which are the most critical factors in determining an outbreak's public health impact [27]. With COVID-19, an apparent high transmission rate

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and CFR have confirmed the serious global health threat by this disease.

Most respiratory infections increase in the winter, and we attribute this to closer contact in closed spaces. Scientists proposed that COVID-19 would decline during the warmer summer season due to the possibility of seasonal transmission of SARS-CoV-2. However, in Australia, COVID-19 has been spreading amidst the summer, and it may be early to confirm its seasonality. In comparison, when a new strain of influenza emerged in Vietnam, the typical seasonality pattern did not evolve until a few years later [28]. Thus, COVID-19 transmission may not be seasonal during its early years, or it may be independent of climatic changes [3].

c) Epidemiologic Models

With the uncertainty about the evolution of the COVID-19 pandemic, epidemiologic models have become tools for policymakers and have made headlines as predictors of future trends. The certainty that these simulated models convey is appealing, but we should interpret such estimates with caution. A basic understanding of their validity, usefulness, and limitation is necessary before developing response strategies. COVID-19 epidemiologic modeling generally falls within one of two categories: *(1)* forecasting and *(2)* mechanistic modeling. While there are also other approaches, we will discuss these two model types as they tend to explore different outcomes over different time scales and deal differently with uncertainty [29].

Forecasting models have a statistical framework, and they fit a curve to pre-existing data and extrapolate future outcomes without accounting for the underlying process leading to the pattern. In such models, data from the past, or a different geographical area, are used to project COVID-19 in another area. Their statistical nature does not consider disease transmission, making the forecast limited to only a few weeks. These forecasting models cannot predict long-term epidemiologic dynamics, such as the peak and the second wave of an outbreak, and cannot predict intervention efficacy [29]. An example of this model is the study conducted initially by the Institute for Health Metrics and Evaluation (IHME), which used data from China and Italy to predict disease outcomes in other regions [30].

On the other hand, mechanistic models do account for transmission by using assumptions about various parameters controlling the disease spread and immunity. Thus, as opposed to the statistical models, such frameworks allow for long-term future prediction of the pandemic trajectory under different disease assumptions and accounting for implemented preventative measures. The mechanistic simulation explores a non-linear process's future possibilities, a task impossible to achieve by intuition. However, it is limited by our knowledge of the virus and the disease [31]. This model approach has been used to guide policymakers in the United States and Britain by projecting the 2-years-mortality under various social distancing measures.

Uncertainties bound all models due to our limited knowledge of the disease and the models' structure itself, not to mention the inherent uncertainties about future human behavior. Until knowledge expands, we must use modeling systematically to explore the various assumptions rather than make robust future projections of COVID-19 dynamics. Hence, only with a proper understanding of their basics and limitations, models can provide insightful guidance through this pandemic [29].

II. Virology

Coronaviruses are: enveloped, positive-sense, non-segmented, single-stranded, ribonucleic acid (RNA) viruses, six of which are known to cause human disease [32, 33]. The family has an immense genetic density among RNA viruses (up to 32 kb) [33], allowing frequent genome recombinations and wide genetic variability. The previous two major coronavirus pandemics were caused by zoonotic viruses SARS-CoV and MERS-CoV, mainly due to the increasing Human-Animal interface. We could explain that new coronaviruses emerge periodically in humans by cross-species and occasional spillover infections between populations [32].

The virus behind the new COVID-19 pandemic was initially isolated from bronchoalveolar lavages of symptomatic patients and analyzed using RT-PCR targeting consensus regions. All viral reads were in favor of lineage B of the genus Beta-Coronaviruses, with more than 85% similarity with a bat SARS-like CoV [32]. The initial taxonomy was 2019nCoV but was later modified to SARS-CoV-2 by the International Committee on Taxonomy of Viruses [32].

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Genomic organization of SARS-CoV-2 was read as a 5' non-translated UTG, a replicase complex, structural proteins (Spike S, Envelope E, Membrane, and Nucleocapsid proteins N2 and N2) coding sequences, several other non-structural open reading frames, and 3′ UTR. This arrangement is typical of subgenus sarbecovirus [32-34]. Sarbecovirus is classified into three clades; *(1)* the SARS-CoV-related strains from Rhinolophus sp. from Bulgaria and Kenya form clade 1, *(2)* the 2019-nCoV from Wuhan and the bat-derived SARS-like strains from Zhoushan in eastern China form clade 2, and *(3)* the SARS-CoV strains from humans and other similar SARS-like coronaviruses from bats from southwestern China form clade 3 [35].

Although it shares many similarities with other Beta-Coronavirus, the SARS-CoV-2 was different from the SARS-CoV and MERS-CoV and was thus classified in a different clade under the sarbecovirus subgenus [1]. Further support of this phylogenetic difference came from the analysis of RNA-dependent-RNA polymerase (RdRp) gene sequencing [35]. Seven conserved replicase domains in orf1ab were 94.4% identical between SARS-CoV-2 and SARS-CoV, suggesting the belonging to the same species, the SARS-CoV-related strains which form clade 1. However, when looking at the total genome sequence, the new virus responsible for COVID-19 was more similar to his bat-derived SARS-like strains than to SARS-CoV (79%) and MERS-CoV (less than 50%) [35]. Further, full genome sequencing showed the highest similarity with BatCoVRaTG13, both having longer S genes. This phylogenetic similarity suggests that the novel CoV might have originated in bats [36]. Although genomic sequence similarities suggest a bat reservoir, some facts point to an intermediate host. Most bat species are hibernating in December, and no bats were being sold at the seafood market [35]. This led to a potential intermediate host theory, namely the Malayan pangolins, who were found to possess a 99% sequence identity to SARS-CoV-2 [10].

The new virus also showed several variations in the S gene with modified residues at the receptor-binding site, further distinguishing it from other SARS-CoV members [34]. This S gene encodes the spike protein dictating host tropism [35]. The spike protein is composed of S1 and S2, mediating receptor binding and cell membrane fusion, respectively [35]. The SARS-CoV-2 shows 50 conserved amino acids in S1 compared to SARS-CoV, despite falling into different clade [35]. In summary, although the full genome sequence of SARS-CoV-2 was similar to the bat-related coronaviruses, the receptor-binding domain is closest to that of human SARS-CoV.

As previously mentioned, by holding one of the most significant genomes, coronavirus family members tend to go through frequent recombination processes. However, recombination might not explain the emergence of this novel virus [35].

Phylogenetic analysis has identified three SARS-CoV-2 variants, differentiated by amino acid changes, the A, B, and C variants. The A-type (ancestral type) is the most closely related to the BatCoVRaTG13 ancestor. Recent data showed that the B-type is confined to East Asia; the virus underwent environmentally driven immunologic adaptations to that specific area, rendering it unable to survive anywhere else. Every single B-genome outside that area has undergone evolutionary mutations making them more fit to survive. All this leads to a potential founder effect scenario and the viral need for a mutation to survive elsewhere [37].

Comparison with SARS and MERS

Coronaviruses are a branch from the Nidovirales family that uses mRNA for replication. The family is subdivided into four categories, the α, β, γ, and δ coronaviruses, with the α and β categories encompassing the strains that infect humans. The α coronaviruses are HCoV-229E and HCoV-NL63; in general, HCoV stands for human coronavirus, and we follow it by the strain. The β coronaviruses include HCoV-HKU1, HCoV-OC43, MERS-CoV, SARS-CoV, and SARS-CoV-2 [38].

The SARS-CoV outbreak began in Guangdong, China, and is considered to date the most severe disease caused by a coronavirus [38]. Over nine months, 8086 cases and 774 deaths occurred with a mortality rate of 10%, as the virus spread over 24 countries. The disease was considered to have originated from bats with transmission through direct human-to-human contact. SARS-CoV was contained by a quarantine that lasted for five months [39].

The MERS-CoV outbreak affected the Middle Eastern area, and more specifically, Saudi

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Arabia, where it first emerged. The disease was thought to have started by coming in close contact with infected camels or possibly consuming these animals' products (milk, meat). Similarly, disease transmission occurred through human-to-human direct contact. The outbreak started in June 2012 and spread to a few surrounding countries [40]. The final WHO report counted 2519 cases and 856 deaths, with a mortality rate of 34.4% [17].

The SARS-CoV-2 has around 80% genetic similarity to SARS-CoV in terms of structure and is considered to have originated from bats. However, phylogenetic analysis defined the SARS-CoV-2 as a novel beta coronavirus. The virus initially spread in China with a reproductive number (R0) of 2.86, closely similar to the R0 of SARS-CoV (2-4) but higher than that of MERS-CoV (<1). The virus is transmitted through droplets and contact with fomites. Symptoms of COVID-19 include mainly fever, dry cough, and dyspnea, whereas SARS-CoV causes more of a flu-like spectrum, including fever, fatigue, cough, myalgias, and headaches. *Table 2* summarizes the main differences between the three outbreaks [17].

III. Pathogenesis

After excluding the receptors used by other Coronaviruses such as dipeptidyl peptidase-4 (DPP4) or aminopeptidase N, and with the results of three-dimensional structural analysis of the receptor-binding domains of SARS-CoV-2, the cell receptor might be an Angiotensin-converting enzyme 2 (ACE2), just like in the case of SARS-CoV [35, 36, 41]. Several other studies using serine protease inhibitor, camostat mesylate, against transmembrane serine protease 2 (TMPRSS2) showed impaired SARS-CoV-2 cell entry, supporting a need for this serine protease for spike (S) protein priming [36, 42, 43].

The postulated mode of entry is through an endosomal pathway. After the degradation of protein S by endosomal proteases and the virus's entry inside the target cell, the genome is released, replicated, and translated into the respective protein products. Once formed, the genomic RNA assembles with the nucleocapsid (N) protein, bud into the endoplasmic reticulum ER-Golgi system before being released by exocytosis [42] (Fig. 1).

The antigen presentation of SARS-CoV-2 mainly depends on major histocompatibility complex (MHC) class I, but also MHC II to a lesser extent. SARS-CoV-2 antigen detected in ciliated epithelial cells of nasal mucosa in primate-based studies fits respiratory transmission. Other studies suggested that the route of spreading is human-to-human via direct contact or droplets [36]. Recent studies in human cases have shown that presymptomatic and asymptomatic cases can also shed the virus [44]. Laboratory results showed a decrease in lymphocyte count with an increase in neutrophils to lymphocyte ratio of more than 5, along with an elevation of C-reactive protein and proinflammatory cytokines (high systemic immune-inflammation index of >500) [45]. There was a decrease in T cells (especially CD8+ T cells) and increases in IL-6, IL-10, IL-2 and IFN-γ levels in peripheral blood in more severe stages of the disease. Higher levels of the PD-1 marker in T cells and decreased NK cell numbers were also seen*; all that sets the stage for pathogenesis based on persistent cytokine release syndrome and a potential cytokine storm in response to pathogen-associated molecular patterns [42]. This results in suboptimal viral clearance manifesting as cellular apoptosis, vascular damage, and leakage [8]. The alveolar and bronchial lumens fill with fibrin, cellular protein-rich fluid, and hyaline membrane formation occur [44].

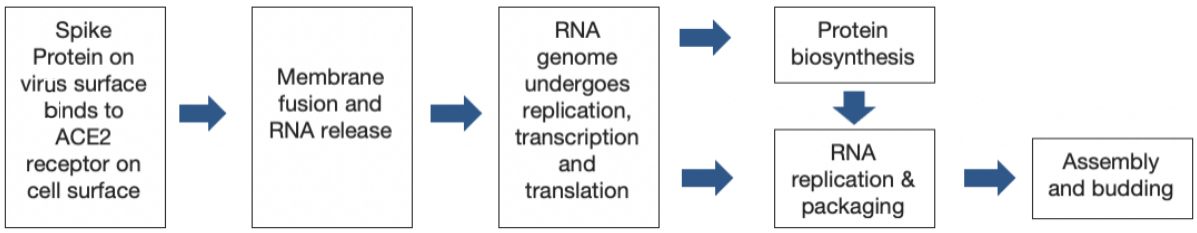

Figure 1: The putative life cycle of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Abbreviations: ACE2: Angiotensin-Converting Enzyme 2; RNA: ribonucleic acid

Abbreviations: IL: interleukin; IFN: interferon; PD-1: programmed cell death protein 1; NK: natural killer

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Table 2: Comparison between SARS-CoV2 with SARS-CoV and MERS.

	SARS-CoV2	SARS-CoV	MERS-CoV
Demographics			
Date	December 2019	November 2002	June 2012
Location of Detection	Wuhan, China	Guangdong, China	Jeddah, Saudi Arabia
Age, years (range)	49, (all ages)	39.9, (1-91)	56, (36-66)
Male: Female ratio	2.7:1	1:1.25	3.3:1
Confirmed cases	4,864,881	8096	2519
Mortality rate	3%	10%	34%
Incubation Period	7-14	2-7	5-6
Clinical Presentation			
Fever	88.7%	99-100%	98%
Dry Cough	67.7%	66%	83%
Dyspnea	45.6%	46%	72%
Diarrhea	6.1%	20%	26%
Sore Throat	13.9%	17%	21%
Myalgias	35%	49%	32%
Headache	8%	39%	-
Fatigue	29.4%	69.6%	-

The virus presents a wide range of tropism, targeting alveolar, myocardial, and tubular cells, along with ileal, esophageal, and bladder endothelium [42].

Experimental studies on human airway epithelial cells showed cytopathic effects of the virus, namely a lack of cilia beating, starting 96 hours post-inoculation. Viral particles were found inside inclusion bodies and free extracellularly, which goes with the Coronaviridae family [32]. Necrosis and tissue destruction were observed in cytokine release syndrome, leading to pulmonary edema, alveolar hemorrhage, reactive hemophagocytosis, and eventual acute respiratory distress syndrome (ARDS) [42].

IV. Clinical Presentation

a) Incubation

SARS-CoV-2 has an incubation period of 14 days [46]. Some reports showed a prolonged period extending to almost 24 days [47,48] Based on data from 291 patients who were able to provide accurate information regarding dates of exposure, a mean incubation period was calculated as four days (interquartile range [IQR], 2 to 7) [5].

Another study showed that a mean incubation period of 5.2 days (95% confidence interval [CI], 4.1 to 7.0) [48]. A model study based on 181 publicly reported confirmed cases with

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identifiable exposure windows and onset of symptoms estimated that 97.5% of those who develop symptoms will do so within 11.5 days (CI, 8.2 to 15.6 days) of infection [49].

b) Clinical Features

1) Demographic Factors

i) Age

Based on the report released by the Chinese Center for Disease Control (Chinese CDC) containing 44672 confirmed cases, most of the cases were 30-79 years of age (87%) [50, 51]. Recent meta-analyses based on China's studies mirrored the above distribution with a reported mean age of 50 years old [52,53]. In New York, a study conducted on 5700 hospitalized patients showed a median age of 63 years old (interquartile range [IQR] 52-75) [54].

In Italy, the distribution of cases was shifted to include a higher percentage of elderly patients. Patients older than 70 years old accounted for 37.6% of total cases in Italy, while that same age group accounted for only 11.9% of patients in China [50, 55]. The rest were distributed as follows: 0-18 years old, 1.2%; 19-50 years old, 24%; 51-70 years old, 37.3%. This was because Italy has one of the oldest populations with a median age of almost 47.3 [55].

ii) Gender

Initial reporting based on a study with 99 patients showed that males have a higher incidence of COVID-19 infection, with males comprising 68% of the cases versus 38% in females [56]. In another report based on 1099 patients from China, males made up 58.1% of the cases [57]. This difference could be potentially due to the increased innate and adaptive immune protection attributed to estrogen and the X chromosome [58].

Recent epidemiological meta-analyses based on Chinese patients reported conflicting results. Some still report an increased incidence in men, while others report equal rates [59]. The previous epidemics SARS-CoV and MERS-CoV showed a propensity to infect more males than females [60, 61].

2) Clinical Manifestations

SARS-CoV-2 showed similar presenting signs and symptoms compared to SARS-CoV, with fever, dry cough, and dyspnea being the most commonly reported [47, 57, 62].

A retrospective study based on 1099 laboratory-confirmed COVID-19 cases established that the most common presenting symptom was fever, which was present in 43.8% of the patients on admission, and later increased to include 88.7% of the patients during their hospitalization. Cough and fatigue were the second and third most common symptoms, affecting 67.8% and 38.1% of patients, respectively. Gastrointestinal symptoms, including nausea or vomiting (5.0%) and diarrhea (3.8%), were less common. [57].

A study showed that, on admission, the most common presenting symptoms were fever (83%), cough (82%), and dyspnea (31%), with the remainder of symptoms being gastrointestinal manifestations with diarrhea (2%) and nausea/vomiting (1%). The study also noted that 90% of cases presented with more than one sign or symptom, and patients presenting with the triad of fever, cough, and dyspnea occurred in 15% of admissions [56]. Recent meta-analyses mirrored the previously described findings with fever and cough being the dominant symptoms, followed by dyspnea, fatigue, and myalgias. They confirmed gastrointestinal symptoms as a rarer manifestation of SARS-CoV-2 [53, 59, 63, 64].

One meta-analysis based on 30 studies with a combined patient count of 53000 estimated an incidence rate of respiratory symptoms at 79.1%, gastrointestinal at 7.7%, and neurological symptoms at 6.1% [52]. Another meta-analysis based on 35 studies (6686 total patients) revealed a higher gastrointestinal manifestation at 15%, with a loss of appetite, nausea or vomiting, and diarrhea being the most commonly reported. Pooled analyses also showed that 10% of patients presented with only gastrointestinal symptoms, contributing to a delayed diagnosis. Additionally, subgroup analysis found that patients with severe COVID-19 were more likely to report gastrointestinal symptoms (Odds ratio 1.60 [95% CI 1.09-2.36]), specifically abdominal pain. Ultimately, it was also reported that patients with gastrointestinal symptoms were at an increased risk of severe disease and ARDS progression. It was cautioned not to overlook the gastrointestinal symptoms during the initial presentation and management of hospitalized patients [65].

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Compared to SARS-CoV and MERS-CoV, SARS-CoV-2 showed less incidence of gastrointestinal symptoms. Upper respiratory tract symptoms (rhinorrhea, sneezing, or sore throat) were also less common, suggesting a more localized affinity of the virus for the lower respiratory tract [47, 62]. Specifically, a meta-analysis based on five retrospective studies (1556 total patients) concluded that when it came to upper respiratory tract symptoms, pharyngodynia was present in 12.4% of the cases while nasal congestion and rhinorrhea were less common [66].

The initial studies from China did not document symptoms of anosmia and dysgeusia well. However, a study based on 202 patients from Italy showed that 64.4% reported an altered sense of smell or taste. The onset of these symptoms was mostly reported as occurring after other symptoms (26.7%), but 11.9% reported having these symptoms first, and 22.8% reported that the symptoms occurred simultaneously. Six patients (3%) reported alteration in smell or taste as their only symptom [67]. A study conducted in Iran showed that out of 60 patients, 59 (98%) had smell dysfunction, validated by an odorant test. 25% of the patients had anosmia, and the rest had varying degrees of hyposmia [68].

Another epidemiological study from Iran with 10069 participants concluded that 48.2% of patients exhibited anosmia or hyposmia, and 83.4% reported a decreased sense of taste. Of the patients who had an altered olfactory sense, 76.2% reported that the loss of smell was sudden [69]. A recent meta-analysis based on ten multinational study compilation (1627 patients) served to identify the prevalence of olfactory and gustatory dysfunction in confirmed patients. A particularly significant subgroup analysis that used studies that implemented validate methods to assess olfactory dysfunction showed a prevalence of 86.6% among 714 patients. This trend has even led to the suggestion of using sudden onset olfactory dysfunction as a potential screening tool, especially when no other symptoms are evident [70]. A position already inferred from previous studies [67, 71-73]. This prompted the recent Centers for Disease Control and Prevention (CDC) expansion of its list of symptoms to include new-onset loss of taste and smell, backed by the American Academy of Otolaryngology-Head and Neck Surgery and ENT UK (ear, neck and throat, United Kingdom) [74, 75]. A suggested mechanism is that the nasal epithelium might be susceptible to COVID-19 infection due to the increased expression of angiotensin-converting enzyme 2, an integral receptor for SARS-CoV-2 entry (Fig.1). Subsequent neuroepithelial disruption provokes an inflammatory reaction causing olfactory neuronal damage and, or impaired neurogenesis [76, 77]

3) Clinical Course & Classification of Manifestations

The Chinese CDC implemented a classification system of asymptomatic, mild, severe, and critical to classify patients based on their manifestation, as was touched upon earlier *(Table 1)* [18, 50, 51]. Based on the data from 44415 cases, it was reported that 81% (36160) were categorized as mild cases, 14% (6168) as severe, and 5% (2087) as critical cases [50]. Another category is the patients diagnosed with a positive viral nucleic acid test with no presenting symptoms. These asymptomatic cases accounted for 1.2% (889) of the 72314 cases pooled by the Chinese CDC *(Table 1)* [18].

A study of 41 admitted patients from Wuhan, China, established a rough timeline of the disease course from its onset. The median time from onset of symptoms to first hospital admission, shortness of breath, ARDS, mechanical ventilation, and Intensive Care Unit (ICU) admission were 7.0 days (4.0-8.0), 8.0 days (5.0-13.0), 9.0 days (8.0-14.0), 10.5 days (7.0-14.0), and 10.5 days (8.0-17.0) respectively [47].

Another study conducted on 138 patients from Wuhan, China reported similar timeframes, with time to first hospital admission at 7.0 days (4.0-8.0), dyspnea at 5.0 days (1.0-10.0), and ARDS at 8.0 days (6.0-12.0) [78].

4) Clinical Outcomes and Complications

Severe complications have been reported in the management of SARS-CoV-2 infection. Acute respiratory distress syndrome, arrhythmias, shock, and acute kidney injury are among the complications encountered. Many complications have been listed when it came to cardiovascular system reports, including myocardial injury/myocarditis, acute myocardial infarction, heart failure/cardiomyopathies, and dysrhythmias, with cardiovascular shock being

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the most severe complication [79]. Multiple reports and studies have highlighted the increased risk of pre-existing comorbidities, especially hypertension and cardiovascular diseases, complicating these patients' prognosis and management [50, 80-82]. Some studies have indicated a nearly 5-fold increase in case fatalities when comparing to patients without cardiovascular disease. Based on pooled data from the Chinese CDC, CFR was elevated in patients with cardiovascular disease (10.5%) compared to an overall CFR of 2.3% [50, 51]. When profiling for risk factors, the top 3 associated comorbidities were hypertension, diabetes, and cardiovascular disease [53, 56, 57, 64, 83-85]. A meta-analysis based on 10 Chinese studies with a cumulative patient count of 2209 reported that 21% had a history of hypertension, 11% had diabetes, and 7% had established cardiovascular disease[84]. Studies from New York identified hypertension (56.6%), obesity (41.7%), and diabetes (33.8%) as the most commonly associated comorbidities; this addition of obesity may be attributed to the overall high rate of obesity in the United States [54]. The suggested pathogenesis of cardiovascular complications in COVID-19 is centered around the myocardium's direct infection via ACE-2 receptor viral entry and the myocardial damage induced by the subsequent cytokine storm triggered by the infection [86, 87]. Of note, contrary to initial concerns regarding the use of angiotensin-converting-enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs), studies demonstrated no harmful association between the use of ACE inhibitors or ARBs in COVID-19 patients [88].

The most common complication encountered in critically ill patients is hypoxemic respiratory failure and subsequent progression to ARDS [89]. A retrospective study based on 201 hospitalized patients in Wuhan, China, reported that 41.8% went on to develop ARDS with subsequent need for ICU admission (26.4%) and mechanical ventilation (33.3%) [84]. Of the 67 (33.3%) patients requiring mechanical ventilation, 44 (65.7%) died [89]. The study showed that the average time from admission to developing ARDS was two days (IQR 1-4 days) and that all fatality cases had ultimately developed ARDS and required mechanical ventilation. The study additionally highlighted risk factors showing that patients with an initial presentation of dyspnea and higher body temperatures were more likely to progress to ARDS, which was also more common in patients with hypertension or diabetes [89].

Another study based on New York cases reported that out of the 1150 adult patients, 257 (22%) were considered to be critically ill, which was identified as having hypoxemic respiratory failure requiring mechanical ventilation or high-level supplemental oxygen. Patient profiling revealed that most critically ill patients were men (67%) and that Hispanic and African Americans were disproportionately more represented (62%). 51% of patients initially required non-invasive respiratory support (non-rebreather mask, High flow nasal cannula, and non-invasive ventilation). However, 79% of critically ill patients later required invasive mechanical ventilation [90].

A study from Lombardy, Italy, based on the outcome of 1591 patients referred for ICU admission, reported that 82% of these patients were males, solidifying the trend that males are disproportionately more likely to suffer from a worse clinical outcome. Of 1300 patients with respiratory data, 99% required respiratory support, with 11% requiring non-invasive ventilation and 88% requiring invasive mechanical ventilation [91]. This was concurrent with the outcomes reported in New York [90].

Out of 44672 patients recorded by the Chinese CDC, 1023 patients (2.3%) died from the infection. No death occurred in patients less than nine years old, whereas patients in older age groups had higher mortality than the rest of the population, with the CFR of 70-79-year-old patients being 8.0%, and that of patients older than 80 years old reaching 14.8%. Based on the severity of the disease, no death occurred in patients with mild or severe disease, whereas critical patients had a CFR of 49% [50, 57].

In Italy, the overall CFR was higher than in China (7.2% versus 2.3%). The CFR in patients younger than 69 years old was similar in both countries. However, in 70-79 years old, Italy had a CFR of 12.8%, and in patients older than 80 years old, the CFR was 20.2% [50, 55, 92].

This difference in CFR has not yet been explained, but the disproportional distribution of cases in these age groups highlighted previously may play a role in the observed difference [50, 55, 92]. On the other hand, a WHO-China Joint

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Mission on Coronavirus Disease 2019 Mortality report, pooling 55924 confirmed patients, reported a CFR of around 21.9% of patients older than 80 years old in China, which matches the rate of 20.2% in Italy [92, 93].

5) Special Population: Pregnancy and COVID-19

Studies involving pregnant patients remain insufficient. A systematic review involving 385 patients showed that pregnancy did not appear to increase the risk of severe illness. The majority of patients (95.6%) presented with mild disease, with a few presenting with severe (3.6%) or critical (0.8%) illness, only 4.4% requiring intensive care unit admission (ICU), of which 35.3% needed intubation. One case of mortality occurred. In terms of presenting symptoms, all patients showed similar clinical data to non-pregnant female patients, with fever being the most common finding, followed by cough and dyspnea [94]. These results oppose previous epidemics and pandemics caused by respiratory viruses, which had a much higher fatality rate for pregnant patients than for the general population. During the 2009 flu pandemic, pregnant patients with H1N1 were at an increased risk of obstetrical complications, higher hospitalization rates, and death compared to non-pregnant women [95]. In 2004, results from the SARS outbreak showed higher rates of pulmonary complications in pregnancy, leading to increased ICU admissions, and pregnant patients suffered from a higher mortality rate than non-pregnant ones [96]. Data concerning the MERS infection during pregnancy are scarce, but most show the deleterious outcome of the infection on pregnant patients, including respiratory failure and fetal death [97]. Understanding the impact of COVID-19 on pregnant patients is essential since the physiological changes in pregnancy might increase the risk of severe disease, morbidity, and mortality. These changes include an increase in oxygen demand, a decrease in total lung capacity, and a decrease in the Th1-helper cells population, which puts the patient in a state of mild immunosuppression [98]. These alterations may increase the susceptibility to the virus and worsen the prognosis. Therefore, given the experience with other coronaviruses, and the lack of information concerning SARS-CoV-2, pregnant women should be considered an at-risk group for COVID-19. Strict preventive measures, similar to the general population, should be taken to prevent the spread of the infection and the maintenance of routine checkups.

There has been no actual data that confirms the vertical transmission of SARS-CoV 2 during pregnancy. To date, no study has yielded positive results confirming the passage of the virus from the infected mother to the fetus [99, 100]. To detect a possible intrauterine transmission of the virus, cord blood sampling, nasopharyngeal swab, placental tissue sampling, or amniotic fluid studies should be implemented. There was one reported case of an infected neonate who tested positive for SARS-CoV-2 36 hours after delivery. His mother had developed COVID-19 pneumonia before delivery. However, no specific sampling was realized to confirm an intrauterine transmission, and the throat's swab was collected 30 hours after delivery. Therefore, no conclusion could be made regarding this subject [101]. To this day, no studies showed that pregnant women are at an increased risk of complications compared to other individuals, and studies involving COVID-19 positive patients in the third trimester showed assuring results. Data concerning the first and second trimester are still unavailable [102]. Complications of COVID-19 during pregnancy are mainly related to hyperthermia leading to preterm labor. Although data are still low quality, premature rupture of membranes, fetal heart rate abnormalities, and congenital malformations were described without an inherently increased risk [82].

In terms of delivery, cesarean delivery indications are not affected by COVID-19 [103]. As per the American College of Obstetricians and Gynecologists (ACOG), delayed clamping of the umbilical cord might decrease the risk of passage of the virus from the maternal blood to the fetus. However, this approach was not applied by many institutions. Skin-to-skin contact after delivery was forbidden; however, the WHO advised the opposite [83]. In a recent study, researchers suggested not removing the vernix caseosa from the fetus before 24 hours. It contains antimicrobial proteins that may protect the fetus. Others suggested bathing the newborn directly after delivery to remove any possible remaining pathogen [104].

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To date, there is no evidence that breast milk transmits the virus [105]. The minimal information reported showed that breast milk samples from infected patients appeared free from the pathogen. However, since breastfeeding requires close contact between the mother and her infant, virus spreading may be possible via respiratory droplets. Thus, to avoid this potential transmission, mothers with confirmed COVID-19 or who are symptomatic with a suspected infection should take all possible precautions, including strict hand washing and use of a facemask before each feeding [105].

An additional option to minimize transmission via respiratory droplets is to consider having another healthy caregiver feed the expressed breastmilk to the infant until the mother's recovery, provided that the other caregiver follows hygiene precautions. In such cases, the mother should practice hand hygiene and wear a mask before each pumping session.

If expressing breast milk with a manual or electric breast pump, the mother should wash her hands before touching any equipment. If possible, the mother should use a dedicated breast pump, and a healthy person should clean the pumping equipment. After each pumping, all parts that come into contact with the breast milk should be washed, and the entire pump should be appropriately disinfected [106]. Women who choose not to breastfeed must take similar precautions to prevent transmission through close contact when a formula is used.

V. Diagnosis

1) Reverse transcription polymerase chain reaction (RT-PCR)

The current diagnostic test recommended for the diagnosis of COVID-19 is a reverse transcriptase polymerase chain reaction RT-PCR to detect the SARS-CoV-2 target sequence. The samples for testing are mostly nasopharyngeal swab-based samples but can also be from the mid-turbinate, anterior nares, or the oropharynx. Expectorated sputum could be the testing sample in patients who have a productive cough. For intubated patients, a lower respiratory tract collection could serve as a sample [107]. In patients with gastrointestinal symptoms, stool samples should be collected and tested. Different sampling sites provide various benefits for the diagnosis of the disease *(Table 3)*. The viral genes, targeted based on the CDC and the WHO, include the nucleocapsid genes N1 and N2, the envelope gene E, the RNA polymerase gene RdRP, and the spike gene S, all of which have a high analytic sensitivity and specificity for the virus with minimal cross-reactivity [108]. The WHO recommendations state the need to detect at least two viral genes [109]. A positive RT-PCR result generally confirms the diagnosis. Patients with an initial negative result and a high suspicion should be re-swabbed. Samples from the lower respiratory tract should be tested when possible, based on the WHO and CDC [110]. Further investigations with computed tomography (CT) scans could enhance sensitivity for disease detection [110].

Table 3: Different modalities for specimen collection and diagnosis of COVID-19. Abbreviations: CT Scan: Computed Tomography Scan; RT-PCR: reverse transcription polymerase chain reaction; ELISA: enzyme-linked immunoassay

Specimen	Analytical Tool	Benefits
Lung Scan	CT Scan	Available earlier Checks severity and possible infection
Nasopharyngeal Swab	RT-PCR	Increased accuracy - Can be used to monitor disease progression
Tissue Sample after Autopsy		
Stool		
Plasma and Blood	ELISA	Detection of immune individuals and antibody for potential use
Fingertip Blood	Rapid Detection Test	Rapid processing - Easily accessible - Inexpensive

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A study showed that the viral load in the lower respiratory tract samples is higher than that in samples collected from the upper respiratory tract, which could help the false-negative results. It also showed that the viral load in samples collected from sputum was high during the early infection and progression stages of the disease and decreased during resolution [111].

The new recommendations by the Infectious Disease Society of America (IDSA) suggest a nucleic acid amplification test in symptomatic individuals in the community suspected of having COVID-19 even in clinically low suspicious patients. The recommendations state collecting nasopharyngeal or mid-turbinate or nasal swabs rather than oropharyngeal swabs or saliva for the testing [112].

As for other PCR modalities, droplet digital PCR ddPCR was better in detecting low viral load than the conventional RT-PCR [111]. Multiplex real-time reverse transcription polymerase chain reaction (rRT-PCR) could also be a modality with higher sensitivity for the detection of SARS-CoV-2 [109].

In a case series of discharged and cured patients, 11 of 69 patients showed a positive RT-PCR result at around 14 days after discharge. This highlights the notion that some patients might recover clinically but still harbor the virus as carriers. The study shows that initial symptoms of fatigue, elevated creatine kinase levels, and the number of initial symptoms can be associated with recurrent positive RT-PCR. Hence, this is notably important when it comes to following up with patients [113].

2) Serology

Studies showed that Immunoglobulin G (IgG) and Immunoglobulin M (IgM) antibodies against the virus are detectable during the middle and late stages of the disease. IgM antibodies were produced earlier than IgG antibodies, with IgM seroreactivity peaking at day 9 (after the onset of symptoms) and IgG antibodies peaking at day 12 [114]. IgM antibodies had a high specificity and a positive predictive value of up to almost 100%. However, the sensitivity and negative predictive values were around 73.2 % and 80 %, respectively. Hence, IgM antibodies can be useful markers for the diagnosis, but acute infections would be undetected in patients with a seronegative IgM. IgG antibodies also had a high specificity and negative predictive values of 95% and 94.8%, respectively, indicating the ability to diagnose based on a seropositive IgG with a high clinical suspicion [115]. Serological testing in COVID-19 may help examine exposure. However, several limitations, such as challenges with the false positives, possible cross-reactivity with other coronavirus strains, and delayed seroconversion, might limit serological testing usage. Further studies are needed to guide the proper usage of those tests [114].

In addition to molecular testing, serological testing has played a crucial role in estimating the disease burden in most people with varying presentations. Antibody testing has been used in the diagnosis of COVID-19 patients in conjunction with molecular testing. Although serological testing results can be hard to interpret, antibody detection tests can help diagnose patients, identify cases with protective immune status, document previous infections, and plan public health responses. As for the humoral response, several studies have shown that most of the patients seroconvert two weeks after symptom onset, with almost all patients being seropositive by day 28. IgM and Immunoglobulin A (IgA) response peaks at days 7 to 14 and wane down with IgG plateauing around days 15 and 21. The severity of the disease also contributes to the antibody response, whereby more critical cases have a delayed but more robust response. However, in this review, subclinical infections Anti-SARS-CoV 2 response is yet to be determined. In addition to that, little is known whether seropositivity can be protective against reinfection or whether it can indicate immune protection for infected individuals. As for the virus's cross-reactivity, areas where SARS-CoV and MERS-CoV widely circulate can potentially be a concern for cross-reactivity of SARS-CoV-2 serologic assays. Serological testing is essential in guiding the process of vaccine development. Antibodies targeting different proteins can aid in the process of selecting a promising target for vaccine candidates. While the receptor-binding domain (RBD) specific IgG is a promising target, it remains the most variable region of the genome, which presents a challenge [116].

Asymptomatic patients

In a study of 37 asymptomatic individuals with RT-PCR confirmed SARS-CoV-2 infection, individuals had a longer vital shedding duration

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with significantly lower virus-specific IgG levels in the acute phase. Data suggests that asymptomatic patients have a weaker immune response to the virus with a reduction in the IgG levels and neutralizing antibody levels in the early convalescent phase compared to symptomatic patients. Symptomatic patients had a significantly higher level of pro and anti-inflammatory cytokines than asymptomatic patients [117].

3) Laboratory Studies

The main laboratory finding in SARS-CoV-2 infected individuals is lymphopenia. More than 40% of patients have it, suggesting that the virus acts on the lymphocytes, as does SARS-CoV. A more severe decrease in absolute lymphocyte count correlates with a worse disease outcome. Other laboratory findings include an increase in inflammatory markers, with an increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), along with a prolonged prothrombin time (PT), elevated lactate dehydrogenase (LDH), low albumin, and low hemoglobin [56, 118].Several laboratory findings are associated with worse outcomes *(Table 4)* [119-121].

Table 4: Lab findings associated with increased adverse effects in patients. Abbreviations: WBC: White Blood Cells; LDH: Lactate Dehydrogenase; PT: Prothrombin Time; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CRP: C-Reactive Protein; ↑: increased; ↓: decreased

↑ WBC	↑ total bilirubin
↑ Neutrophil count	↑ creatinine
↓ lymphocyte count	↑ cardiac troponin
↓ albumin	↑ D-dimer
↑ LDH	↑ PT
↑ ALT	↑ procalcitonin
↑ AST	↑ CRP

4) Imaging

a) Ultrasound

In a case of COVID-19 pneumonia, lung ultrasound (US) findings showed bilateral diffuse pleural line abnormalities with underlying consolidation and whitened and thickened lung area and irregular vertical artifacts. Those findings were suggestive of interstitial - alveolar damage. Bedside US is essential in reducing the risk of medical personnel exposure and the transport of potential COVID-19 patients throughout the hospital. Lung US is also helpful in differentiating, based on the findings, the high-risk from low-risk patients using a radiation-free modality that is readily accessible to healthcare providers [122].

b) Computed Tomography Scan (CT Scan)

Computed Tomography scans (CT scans) of the chest are part of the diagnostic workup of the novel coronavirus SARS-CoV-2, with specific imaging findings being frequent in COVID-19. Consolidations and ground-glass opacities (GGO), with bilateral, peripheral posterior/subpleural, and multilobar involvement, are the most common findings and typical signs of COVID-19. Those findings are similar to radiographic findings in SARS and MERS [123, 124]. Consolidations increased with the progression of the disease through week 2 of the presentation. Ground glass appearance was found to progress and coexisted with the consolidations with the disease's progression through weeks 1-2 of presentation [125]. Other imaging findings included reticular patterns, crazy paving patterns, and, less commonly, airways changes such as bronchiectasis and bronchial wall thickening, pleural changes such as pleural thickening, multifocal irregular nodules (commonly seen in viral cases of pneumonia), and the Halo Sign [125]. Few studies observed cases with reversed Halo Sign, which is seen in organizing pneumonia [125, 126]. Findings such as pleural effusion, lymphadenopathy, and round cystic changes on CT were findings that were not common in previous SARS-CoV infections [127].

Pure GGO, GGO with reticular and/or interlobular septal thickening, and GGO with consolidation were the main findings. GGOs were more common in patients less than 50 years old, whereas those older than 50 years old had more consolidations with an organizing pneumonia pattern and greater lung volume involvement [128]. Subclinical patient imaging findings were mostly unilateral multifocal ground-glass appearance, which evolved into bilateral diffuse disease with a decrease in the GGO and increased consolidations as patients became symptomatic [127]. A meta-analysis of 34 retrospective studies involving 4121 patients in China validates the above and states that a

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bilateral multilobar involvement being the most common presentation of patients [129].

CT scan findings of patients with the COVID-19 progressed throughout the disease. With the presence of findings even before symptoms, findings on CT scan increased significantly with the initiation of symptoms and peaked on days 6-11 with a prolonged persistence of the findings. Ground glass opacities were predominantly seen during days 6-11 [130]. An increase in radiological findings on CT scans from the subclinical period through weeks 1 and 2 of the disease was evident, followed by a decrease over the third week, showing that the radiological findings are consistent with the clinical course of the disease [127]. Imaging findings ranged from minimal in the early stages of the disease and peaked around days 9-13. After two weeks, they progressed to the absorption stage, where consolidations gradually resolved with extensive GGO being observed [131].

The CO-RADS is a categorical system developed to assess lung involvement with SARS-CoV-2 on chest CT *(Table 5)*. The COVID-19 Reporting and Data System CO-RADS was divided into five categories, from category 1 to 5, in increasing suspicion of involvement of the lungs by the SARS-CoV-2. Table 5 further details the subcategorization [132].

c) RT-PCR and CT Scan Correlation

Researchers noticed that imaging features of COVID-19 are also present in RT-PCR negative patients with typical symptoms. With several studies showing the limited sensitivity of RT-PCR testing, the CT scan's sensitivity was compared to that of the RT-PCR. The study showed that the CT scan has better sensitivity (98%) than the RT-PCR (71%), supporting CT scan to screen for SARS-CoV-2 in patients with high suspicion who tested negative with RT-PCR [133]. Considering the lack of sensitivity of the RT-PCR and its long processing time, and because most patients with SARS-CoV-2 have a characteristic CT scan, with 60% having typical imaging findings before the positive RT-PCR results, the CT scan can be a useful tool in the detection of the virus [131, 134]. For RT-PCR negative patients, 81% of the patients with RT-PCR negative and CT scan findings were reclassified as probable cases. The same study reports that 90% of patients had CT findings consistent with COVID-19 before positive RT-PCR results. Given the CT scan's high sensitivity for the diagnosis of SARS-CoV-2, the chest CT should be considered a screening modality for patients with a high pretest probability [135]. Thus, cases with a typical clinical picture, with an exposure history and CT findings consistent with SARS-CoV-2, should be highly suspicious of the virus even with negative RT-PCR results. Those patients should be isolated and re-swabbed [136]. A recent meta-analysis presented the CT with a sensitivity of 94% and 89% for the RT-PCR.

In comparison, the CT's pooled specificity was 37% and hence a gap between the positive predictive value of the CT and the RT-PCR in low prevalence regions. Hence using a CT scan in low prevalence regions could result in a large number of false-positive results. The American College of Radiology also recommended against the use of CT scans to screen the virus or as a first-line test. The Society of Thoracic Radiology and American Society of Emergency Radiology agreed on this as well [137].

d) Fluorodeoxyglucose positron emission tomography (FDG PET)

The FDG PET scan findings in a study done on four patients with COVID-19 previously found to have peripheral GGO and/or consolidations

Table 5: CO-RADS categories and level of suspicion

Category	Level of suspicion	Summary
CO-RADS 1	Very low	Normal or non-infectious
CO-RADS 2	Low	Typical for other infections but not SARS-CoV-2
CO-RADS 3	Equivocal	Features compatible with SARS-CoV-2 but also other diseases
CO-RADS 4	High	Suspicious for SARS-CoV-2
CO-RADS 5	Very high	Typical for SARS-CoV-2
CO-RADS 6	Proven	RT-PCR Positive

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showed a higher tracer uptake of the lesions reflecting a high inflammatory process. Lung tumors with GGOs are unlikely to be FDG-avid. In addition to that, although the virus is not known to cause lymphadenopathy, the PET CT scan showed increased nodal uptake in 3 out of the 4 cases; however, no evidence of disseminated disease. Nonetheless, it is still not recommended to use 18F-FDG PET/CT imaging in the emergency department in the setting of infection. However, it might be a modality that can be used when reaching the diagnosis is challenging [138].

VI. Management

A) Prevention

1) Infection Control

In the absence of licensed vaccines or antivirals, non-pharmaceutical interventions stand as the central means in COVID-19 management [139]. Infection control policies with rigorous contact tracing and case isolation have been highly effective in stopping the spread of the outbreak [140]. China's successful public health measures in controlling the disease have driven most countries to mirror such interventions. Starting January 23, 2020, the Chinese authorities implemented a series of measures to halt the newly emerging coronavirus spread, including city lockdowns, transport restriction, social distancing, home confinement, centralized quarantine, and universal symptom survey. These interventions improved the control of the COVID-19 outbreak [15]. Measures to reduce transmission with a particular focus on protecting health care providers and elderly include case identification and isolation, monitoring of contacts, environmental disinfection, and personal protective equipment, with no current substitute for social isolation [141]. If daily testing of a large portion of the population is not achievable for economic or logistic reasons, mass-based social isolation becomes the only effective containment method [142].

These strict measures might be difficult to sustain. More direct and lower-cost interventions include regular hand washing, good respiratory hygiene, minimal touching of mucosal surfaces (eyes, nose, and mouth), and maintaining a one-meter distance between people [143, 145, 146]. SARS-CoV-2 can be transmitted by direct contact with an infected person, mainly through respiratory droplets, or by indirect contact with surfaces used by the latter [147, 149]. Strict precautions should be adopted while handling bodily secretions such as urine, sputum, or stools of COVID-19 patients and sewage from hospitals [150]. Since transmission through fomites is possible, the virus stability on different surfaces was studied; it can remain for 72 hours on plastic and stainless steel, less than 24 hours on cardboard, and less than 4 hours on copper [151]. Hence, hand washing is indispensable to reduce the risk. These recommendations might seem simple, but effective practices are far from reality. In a study of 3,749 individuals, only about 5% applied a proper handwashing technique, hence the necessity of raising awareness and reinforcing good technique [152].

Surgical masks prevent the spread of droplets from sneezing or coughing to the surrounding environment. So far, only social distancing coupled with mass-masking appears to be temporarily effective [153]. Although the WHO does not advise healthy individuals to wear face masks in community settings due to lack of evidence, the absence of evidence of effectiveness does not mean evidence of ineffectiveness, especially when facing a novel virus with limited alternative control measures [153, 154]. If everyone wears a mask in public, asymptomatic shedding may be prevented, and stigmatization is reduced [20, 155-157]. Mass-masking panic has prevailed regardless of recommendations. Individuals are wearing masks for self-protection, unintentionally, protecting others through source control [153]. The N95 masks are currently recommended for healthcare workers conducting aerosol-generating procedures, while surgical masks are reserved when managing suspected or confirmed cases [154]. A study showed that air samples at an approximate 4-meter radius from patients are positive for the virus, but this finding was not replicated in other studies [151, 158, 159]. Despite inconclusive evidence, healthcare workers recommend using the N95 or FFP2 (Filtering facepiece 2) particulate-filtering respirators in aerosol-generating procedures [154].

Whether animals transmit the virus to humans has been an important question, especially with the virus being zoonotic in origin [160]. Studies showed that pigs, chickens, and ducks were not

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susceptible to SARS-CoV-2. Dogs had a low viral susceptibility and did not support viral replication, and ferrets carried the virus in the upper respiratory tract. However, there was no transmission between them, and cats exhibited airborne transmission between them, but human-cat-human transmission potential needs further investigation [161]. To date, the risk of animals spreading COVID-19 is considered low. Health authorities recommend treating pets as human family members and reducing their interaction with people or animals outside the household. Positive home isolation cases must also be isolated from household pets, which could act as contaminated surfaces [162].

As the world is fighting both an epidemic and an infodemic, global and local public health authorities should provide accurate information and correct misinformation to guide the public on dealing with this novel infection. This will also reduce public panic about COVID-19 and ensure people are informed to act appropriately. The WHO risk communication team has launched an information platform called WHO Information Network for Epidemics (EPI-WIN) for these purposes [163].

The importance of wearing a face mask in public has been addressed and recommended repeatedly. Changes in daily COVID-19 growth rates have been monitored on a county level in the US, where face mask use was mandated in public. Results showed a statistically significant decline in the growth rate of COVID-19, where a decrease in daily rate by 0.9, 1.1, 1.4, 1.7, and 2.0% within 1-5, 6-10, 11-15, 16-20, and 21+ days of implementation of the facemask-wearing policy. On the other hand, no significant results were seen in the daily COVID-19 growth rate when employees were solely wearing masks. Those results further validate the role face masks wearing, as a community, plays in mitigating the spread of COVID-19 [164].

2) Vaccination

Researchers are rapidly developing a vaccine against SARS-CoV-2 amidst the pandemic. The advanced understanding of genomics and structural biology has paved the way for enhanced vaccine development. Previous experience with urgent outbreaks response has highlighted the requirement of new vaccine platform technologies readily adaptable to a novel emerging “Disease X,” such as COVID-19 [165]. The main SARS-CoV-2 vaccine types under development include DNA, RNA, protein subunit, inactivated, nonreplicating vector, replicating viral vector, and live attenuated technologies [166]. However, vaccine production is a long and expensive process calling for multiple candidates over several years before licensing [167]. Developing a vaccine fast enough entails a modification in the typical linear sequence of steps, which poses additional challenges such as performing steps in parallel at an elevated financial risk. For instance, the candidates proceeding rapidly beyond phase 2 trials are ramping up production to commercial levels before establishing safety and immunogenicity [168].

Deoxyribonucleic acid (DNA) and RNA based platforms followed by those for recombinant-subunit vaccines confer a tremendous potential for speed because they use synthetic procedures and can benefit from next-generation sequencing and reverse genetics [168]. The first phase 1 trial was conducted in China with a nonreplicating vector-based vaccine. This candidate is a recombinant adenovirus type 5 vectored COVID-19 vaccine expressing the spike glycoprotein of SARS-CoV-2, which is a promising immunogen for protection. It was found to be tolerable and immunogenic in healthy adults with a peak in humoral response at day 28 and a specific T-cell response at day 14 post-vaccination. It would be given in a single dose, and since its platform is licensed, it possesses a large-scale manufacturing capacity. Hence, proceeding with its clinical development and evaluation is warranted [169]. Other trials are also showing promising results, but none is yet available for licensing and use in the community.

B) Pharmaceutical Interventions

Since discovering the first cases of COVID-19, efforts to find the best antiviral therapy began. An efficient approach to drug therapy is to start with previously discovered compounds that might have worked on similar viral species. Those drugs are run over several viral cultures, testing the Median Effective Concentration (EC50) and the 50% cell cytotoxic concentration (CC50) of each. Out of a long list of drugs, remdesivir and hydroxychloroquine initially showed potential benefits due to their wide therapeutic window [158, 170]. Remdesivir, an adenosine analog,

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showed promising activity against RNA viruses. It incorporates into the nascent viral RNA chains and results in premature termination of viral replication [170, 171]. Hydroxychloroquine is a disease-modifying antirheumatic agent. It is commonly used for several conditions, including rheumatoid arthritis, systemic and discoid lupus erythematosus, and juvenile idiopathic arthritis. Chloroquine, the antimalarial drug, has also been used to treat other infections such as human immunodeficiency virus (HIV) and had potential effects against the avian influenza A virus (H5N1) [29]. Chloroquine increases endosomal pH required for virus and cell fusion and interferes with the glycosylation of cellular receptors of SARS-CoV, therefore blocking virus infection of the cell. The drug exhibited antiviral activity at both the entry and post-entry stages of SARS-CoV-2 [29, 170, 172].

1) Hydroxychloroquine

Based on promising in vitro studies, a trial of hydroxychloroquine (HCQ) on patients with confirmed COVID-19 was conducted. The study included 36 patients, of which 20 received HCQ and 16 acted as a control group. Among the patients who received HCQ, six patients also received azithromycin to prevent a superimposed bacterial infection. The study showed that HCQ efficiently results in viral clearance within 3-6 days when compared to control groups and suggested that there may be a synergistic effect when combining HCQ and azithromycin; the investigators warned against the potential risk of this combination, particularly that of severe QT prolongation [173]. This study was limited by the small sample, the lack of randomization, and the lack of follow up.

Another trial, a double-blinded and multicenter randomized controlled trial (RCT) that involved a total of 128 patients, with 67 receiving HCQ, showed that HCQ is associated with an increased mean corrected QT interval and a greater length of stay. However, this study was also limited by the small sample size, and the authors concluded that larger RCTs are needed [174].

Although some observational studies had shown a benefit with the use of HCQ, 7 RCTs have so far denied any benefit. However, more than 250 studies are registered to evaluate the effects of HCQ in COVID-19 patients [175].

A systematic review of 12 clinical studies reviewing the role of HCQ in COVID-19 patients showed that most of the research studies had had significant limitations when it comes to their methodology, as can be noticed from the previous examples. It also concluded that the efficacy and safety of HCQ in COVID-19 is still not satisfactory and that the combination of HCQ with azithromycin may have deleterious adverse events. Randomized controlled trials are still needed to determine whether HCQ, with or without azithromycin, has a role in COVID-19 [176]. The most recent IDSA recommendation regarding the treatment of hospitalized patients with hydroxychloroquine, with or without azithromycin, remains limited to the context of a clinical trial [177]. This makes us question how many more studies would we need to abandon HCQ? [175].

2) Remdesivir

Even though SARS-CoV and SARS-CoV-2 share not more than 82% RNA sequence identity, a 96% sequence identity in their RNA-dependent RNA polymerase has been noted [178]. This led researchers to start using drugs that were used to target RdRp proteins of SARS-CoV. The IDSA has released compassionate use of remdesivir following many studies. A simple example of its use was demonstrated in Washington, USA, where the first COVID-19 pneumonia case was treated with IV remdesivir, and clinical improvement was noted. The investigators also noted a progressive decline of the viral load in the nasopharyngeal swabs [178].

Another study also demonstrated the compassionate use of remdesivir in COVID-19 patients. The study enrolled patients who had a positive SARS-CoV-2 RT-PCR from a respiratory tract swab and pneumonia confirmed by imaging, who were on mechanical ventilation or had an oxygen saturation SaO2 < 94% or a National Early Warning Score 2 (NEWS2) equal or more than 4. They received an intravenous (IV) loading dose of 200 mg of remdesivir, followed by an IV dose of 100 mg/day for a total of 10 days. The patients were allowed to continue any existing treatment, including hydroxychloroquine but discontinued lopinavir/ritonavir treatments. Patients were divided between ICU (18 patients) and Infectious Disease Ward (IDW, 17 patients). At day 10 of treatment, 4 (22.2%) of the ICU patients showed an improvement in

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hospitalization status, 10 (55.5%) remained on invasive ventilation, and 4 (22.2%) died. At day 28 of follow-up, 38.9% of the ICU patients improved, and 16.7% remained on mechanical ventilation, whereas 44.4% died. On the other hand, on day 10 of treatment, six patients (35.3%) had improved in the IDW group, two were still hospitalized. However, they did not require high-flow therapy of mechanical ventilation, but ten still required high-flow therapy or mechanical ventilation. On day 28, in the IDW group, 88.2% had improvement in the hospitalization status, and only one patient still required high flow therapy or mechanical ventilation. Those results may show the better efficacy of remdesivir in non-critical conditions if initiated early enough [179].

A randomized, double-blinded, placebo-controlled, multicenter clinical trial of remdesivir in adults with severe COVID-19 was conducted in 10 hospitals in Wuhan, China. Patients were men and non-pregnant women >18 years of age, with a positive RT-PCR for SARS-CoV-2, pneumonia confirmed by imaging, and decreased oxygenation. IV remdesivir was administered (200 mg loading dose, and then 100 mg daily for a total of 10 days), or the same volume of IV placebo. Results analysis showed similar 28-day mortality between the two groups. Patients who had taken remdesivir within ten days of symptoms onset had a numerically lower mortality rate than the placebo group, but not statistically significant. Patients who had a late use of remdesivir had numerically higher mortality than placebo, with no statistical significance. The duration of invasive mechanical ventilation was numerically lower in the remdesivir group, but not statistically significant. The authors noted no significant difference between the two groups regarding the hospital length of stay, length of oxygen support, days from randomization to discharge, and to death. Both groups had a decrease in viral load with no significant difference. 102 of 155 patients (66%) in the remdesivir group reported adverse events compared to 50 of 78 patients (64%) in the control group. As mentioned in earlier papers, adverse events in the remdesivir group included gastrointestinal disturbances, anemia, hypokalemia, hypoalbuminemia, thrombocytopenia, and increased total bilirubin. All deaths during the investigation period were considered unrelated to the intervention. This study concluded that IV remdesivir did not significantly improve mortality rates or time to clinical improvement of viral clearance when compared to placebo. However, the study population was less ill than those used in compassionate use studies. That being said, the authors could not disregard the clinically meaningful differences and numerical reductions in some clinical parameters [180]. However, this study was underpowered to provide conclusive information because it has been stopped earlier because of the reduction of the number of COVID-19 cases in China [179]. More clinical trials are on the way to investigate the role of remdesivir in mild to moderate cases of COVID-19.

More recently, the U.S National Institute of Allergy and Infectious Diseases (NIAID) initiated a phase II trial of remdesivir to evaluate the medication's efficacy and safety in hospitalized patients with COVID-19. The randomized, double-blind, controlled trial involved 1059 patients divided 1:1 into treatment and control groups. The treatment group received a 200 mg loading dose of remdesivir on the first day of treatment, followed by 100 mg per day for nine days. Preliminary results showed that the remdesivir group had a shorter recovery time (11 days [95% CI 9-12]) as compared to placebo (15 days [95% CI 13-19]). [181]

Gilead Sciences, Chinese Health Authorities, the Institut National de la Santé et de la Recherche Médicale also have ongoing studies evaluating remdesivir. Remdesivir has been approved by the U.S. Food and Drug Administration (FDA) as an emergency use for treating hospitalized patients with severe COVID-19. Based on the NIAID trial and other ongoing trials, the Japanese Ministry of Health has also approved the use of remdesivir [182].

Based on the Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19, recommendations have been placed regarding the usage of remdesivir. The panel suggests using remdesivir in hospitalized patients with severe COVID-19 over no antiviral treatment and suggests five days of Remdesivir rather than ten days for patients with severe COVID-19 on supplemental oxygen but not intubated or on ECMO where ten days of treatment is needed [177].

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3) Ivermectin

Ivermectin is a broad-spectrum antiparasitic drug that has been in the microbiologic industries for a long time. Due to older studies linking the mechanism of infection of SARS-CoV with ivermectin, in vitro studies using ivermectin have been conducted on SARS-CoV-2 viral cultures. Upon adding 5 μM of ivermectin to cell cultures infected with SARS-CoV2 for 0.1 and 2 hours, a 93% reduction in viral RNA was observed in the supernatant of samples treated with ivermectin compared to the vehicle dimethyl sulfoxide (DMSO) after 24 hours. Cell-associated viral RNA similarly had a 99.8% reduction. At 48 hours of treatment, there was a 5000 folds reduction in viral RNA in the ivermectin treated group compared to DMSO. However, no further reduction was noted at 72 hours. The results demonstrated an antiviral action of ivermectin against SARS-CoV2. Also, ivermectin has a good safety profile for human use, making it a potential candidate for COVID-19 treatment if further studies and trials succeeded in demonstrating its benefit [183].

4) Colchicine

A study by *Deftereos et al.* looked at colchicine versus standard care on cardiac and inflammatory biomarkers. Clinical outcomes in patients hospitalized with COVID-19 showed no significant difference between the control group and the group receiving colchicine for high-sensitivity cardiac troponin and C-reactive protein levels. However, patients who received colchicine had a significantly improved time to clinical deterioration, which was assessed by 2 points on a 7-grade scale clinical status scale, ranging from the ability to resume everyday life to the patient's death. Hence the use of colchicine showed a significant clinical benefit [184].

5) Corticosteroids

The effect of dexamethasone on hospitalized COVID-19 patients' mortality was assessed in an open-label randomized clinical trial. The RECOVERY collaborative group study assigned one group of patients to receive dexamethasone and the other to receive usual care. Results showed that for patients in the dexamethasone group, death incidence was lower than that of patients receiving usual care. The incidence of death at 28 days among patients receiving dexamethasone on invasive mechanical or patients receiving oxygen without invasive mechanical ventilation was significantly lower than patients on usual care (Rate Ratio [RR] 0.64 (0.51-0.81); 0.82 (0.72-0.94), respectively). However, no difference was recorded between the control and the experimental group in 28-day mortality for those not receiving respiratory support (RR 1.19 (0.91-1.55)). Moreover, the dexamethasone group reported shorter hospitalizations than the control group [185]. A meta-analysis of 7 randomized clinical trials, conducted by the WHO, also showed a decrease in all-cause mortality at 28 days in patients receiving systemic corticosteroids vs. usual care or placebo [186].

As for corticosteroids, the IDSA recommends Dexamethasone 6 mg IV or orally (PO) for ten days or its equivalent for hospitalized patients with severe COVID-19 rather than no glucocorticoids. However, in the case of hypoxemia, the IDSA recommends against the use of glucocorticoids [177].

6) Tocilizumab

A large number of T cells and mononuclear macrophages activation has been described as the immune system's response to COVID-19. This has been majorly linked to a significant interleukin-6 (IL-6) level mitigating the cytokine storm and the severe inflammatory response. The IL-6 blockade's role was assessed with tocilizumab, a recombinant humanized anti-human IL-6 receptor monoclonal antibody. A systematic review of the efficacy of tocilizumab in COVID-19 showed that the addition of the drug to the standard of care reduced mortality and the need for mechanical ventilation in severe cases [187]. The limited research on the topic requires randomized clinical trials and has led IDSA to recommend tocilizumab usage only in the context of clinical trials [177].

7) Lopinavir-Ritonavir

The use of combination drugs Lopinavir-Ritonavir as a treatment trial for coronavirus goes back to 2003. Researchers found that Lopinavir and Ritonavir, which are HIV type 1

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aspartate protease inhibitors, have an inhibitory mechanism against SARS-COV. An open-label RCT of Lopinavir- Ritonavir in hospitalized adults with COVID -19 was conducted by CoA B. et al. (2020). The research study included 199 hospitalized patients with COVID-19, 94 received Lopinavir- Ritonavir treatment regimen, and 100 patients received the standard treatment. Depending on the patient's status, the standard treatment consisted of supplemental oxygen, non-invasive or invasive ventilation, antibiotics, vasopressor support, renal replacement therapy, and extracorporeal membrane oxygenation (ECMO). Systemic glucocorticoids were added to 33% of the patients in the Lopinavir-Ritonavir group and 37% of the control group patients. However, the trial results did not favor the use of Lopinavir-Ritonavir as a treatment regimen. When used within 12 days after the onset of symptoms, there was no shorter time towards clinical improvement. The mortality at 28 days did not show any difference between standard treatment and the Lopinavir-Ritonavir regimen. Furthermore, the treatment regimen under study showed more gastrointestinal severe side effects, and 13.8% of patients under this treatment had to stop the regimen early on because of side effects. In conclusion, the Lopinavir-Ritonavir trial didn't show any benefit for adult hospitalized patients with COVID-19 pending future studies to confirm this result [188]. A systematic benefit-risk assessment of lopinavir-ritonavir was conducted and included seven papers, which showed no conclusive benefit for using this drug compared to the standard of care. There was a decrease in ARDS in one study, but we need further studies to establish this combination's benefit-risk profile [189].

8) Ascorbic acid

Clinical trials were conducted to study the effect of vitamin C (Ascorbic acid) in Covid-19 treatment. Vitamin C has antioxidant properties that can prevent the accumulation and activation of neutrophils and eliminate alveolar fluid. Furthermore, it can shorten the common cold's duration and decrease the cytokine surge, which plays an essential role in sepsis secondary to respiratory infection. This explains its inclusion as a potential drug against Covid-19. A prospective RCT was performed on 140 participants who tested positive for COVID-19. The study classified the patients as having serious and critical severe acute respiratory infection (SARI). The experimental group received 12 g of vitamin C via the infusion pump twice a day for seven days, with a speed of 12mL/h. This clinical trial results are not released yet; however, promising results are expected. Further research studies are warranted to support the use of vitamin C in severe cases of COVID-19 [190].

9) Traditional Chinese Medicine

According to Yang Y. & Islam et al. (2020), Traditional Chinese Medicine (TCM) is an essential used therapy in the treatment of COVID-19 patients. TCM was used in the SARS-CoV pandemic back in 2002. Compelling evidence shows the beneficial implications of TCM in the treatment and prevention of SARS-CoV. Its use in 2002 resulted in a dramatic decrease in fatalities in Beijing, Hong Kong, and Singapore. Evidence shows that the use of Chinese herbal extract *Sang Ju Yin* plus *Yu Ping Feng San* decreased the chance of infection by modulating T cells and enhancing host defense capacity against SARS-CoV in hospital workers and laboratory technicians.

Furthermore, a study published in The Lancet tested *glycyrrhizin*, a principal active constituent of licorice root, a frequently used Chinese herb, and results supported its use in SARS-CoV, as it potently inhibits the replication of clinical isolates of SARS virus. The Chinese government highly values TCM, and they implemented them as part of the COVID-19 treatment regimen. Astragalus membranaceus, Glycyrrhizae uralensis, Saposhnikoviae divaricata, Rhizoma Atractylodis Macrocephalae, Lonicerae Japonicae Flos, Fructus forsythia, Atractylodis Rhizoma, Radix platycodonis, Agastache rugosa, and Cyrtomium fortune J. Sm were the ten most commonly used Chinese herbs in the treatment of COVID-19 [191].

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10) Monoclonal Antibodies

At the moment, clinical trials of monoclonal antibodies against SARS-CoV-2 are enrolling. A couple of phase 3, randomized, double-blinded placebo-controlled trials are investigating the effect of those neutralizing antibodies in the prevention of infection and hence ultimately end the pandemic. Additional information about both trials can be found on clinicaltrials.gov using the identifiers NCT04497987 and NCT04452318 [192].

11) Convalescent Plasma

Most studies on the use of convalescent plasma CCP in COVID-19 for the severely and critically ill patients have been observational and non-randomized trials. Those studies had patients receiving additional interventions, including antiviral, antibiotics, steroids, and other drugs, in addition to the CCP. This has made the specific role of CCP unclear. Mortality was lower among patients who received CCP within three days of diagnosis. In a Chinese study, patients with CCP infusion showed more frequent and faster clinical improvement. Studies have been encouraging, but so far, the evidence for CCP efficacy is still inconclusive [193]. Available data suggest that if benefits exist from CCP infusions, the infusion must be given early in the disease and with a high titer of neutralizing antibodies [177].

VII. Response to COVID-19

Soon after the rapid rise of COVID-19 cases, the Chinese government has rapidly implemented severe measures in a short time that proved their efficacy and alleviated the burden of the disease progressively, transferring the epicenter to other regions. Compared with the 2003 outbreak, the SARS-CoV-2 has a higher infectivity rate and incubation period, making the pathogen more challenging to contain. The state announced a travel ban on the 23rd of January 2020 and forced a quarantine on more than 45 million people [195]. Additionally, all transportations were closed and public places such as shopping centers, parks, schools, cinemas, etc. Rapidly, two hospitals were approved to take care of infected patients, the Huo Shen Shan Hospital and Lei Shen Shan Hospital, whose constructions were completed on February 2 and 6. This measure not only provided a specialized center for treating COVID-19 but helped reduce the burden on other hospitals and prevent the lack of medical resources [196]. All supplies, including food and medical ones, were provided to Wuhan's residents [133].

After China, the largest pool of COVID-19 patients happened in February 2020, the majority being attributed to the Diamond Princess, a cruise ship that departed from Japan. Initially, the ship's response was to isolate all passengers after a case of COVID-19 entered the boat. Then, authorities aimed at quarantining everyone. Several other cruise ships such as the Grand Princess were isolated as well, as cases of SARS-CoV-2 infected passengers emerged on board. More than seven hundred passengers in total tested positive [197]. Therefore, limiting cruise ships during the pandemic is a reasonable approach due to the closed environment favoring the virus's rapid spread.

The disease's epicenter shifted after its debut in China to European countries and, more specifically, Italy, that faced a massive disease burden. With a shortage of healthcare personnel and resources, around 1000 patients required ventilatory support in the Lombardy region [198]. The lack of healthcare practitioners obliged the state to increase the recruitment of new medical staff, including retired doctors and non-graduated students [199]. The Italian healthcare system was suffering from a chronic financial problem due to a cut down of the state's financing, which left the country in weak response towards the disease [200]. Moreover, the fragmentation of the national healthcare system leaving local authorities in charge of health services left the state with a fragile strategy. In just one month, cases reached 41035 after the first recorded case on the 21st of February 2020 [137].

Till now, the COVID-19 epicenter remains the United-States, with 9,689,999 cases and 238,617 deaths on November 3, 2020, the highest numbers of all countries [2]. The response of the government amidst the

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pandemic was slow and somehow variable across the states. The federalist healthcare system that divides power among local officials has led to this uneven response [201]. Some states, including Kentucky, Tennessee, Connecticut, and Massachusetts, did not initiate a stay-at-home order but instead advised the residents to do so [201]. However, with a highly transmissible virus that crosses every boundary, a nationwide, unified response is required. Additionally, early information concerning the virus might have misled officials and caused some confusion [203]. More importantly, the stock market, fearing that the disease would affect their business, made some pressure to spread calm and prevent a negative effect on the workflow [138].

These responses came in contrast to that of Taiwan that has proven its efficiency in battling COVID-19. The latter showed a quick response after having experienced the SARS outbreak before. With emergent management and reassurance and providing clear information to the public, the country showed an example to others [204].

Throughout the pandemic, healthcare workers were on the frontline and at high-risk for infection. Hospitals managed the situation in different ways. A study in Cleveland Clinic, Ohio, showed that routine testing of patients on admission could decrease the delayed diagnosis of COVID-19 and concluded that retesting of initially negative patients may also be warranted because of the relatively high rate of false negatives [205]. In fact, false negatives have been reported to range from 2% and up to 29% [206]. Therefore, implementing such practices and others has been essential in decreasing the spread of the disease among healthcare workers and reducing their risk of infection.

Limitations

Like other narrative reviews, this work's limitation lies in the method used to find and select publications, which entails that we may have missed essential articles. Another limitation was that we had to include some non-peer-reviewed studies when we judged them of high importance and quality. Furthermore, a complete assessment of the situation is not feasible before the pandemic is over, as there are ongoing studies. New information will likely add to the literature, building on the content of this review shortly. While much information provided in this narrative review will continue to be accurate, others will further develop as more studies are published, and new conclusions will be made. Nonetheless, this article provides a valuable extensive overview of what is known so far about COVID-19.

Conclusion

It is undeniable that the novel SARS-CoV-2 reshaped our world. The vast number of publications regarding COVID-19 has made it hard for the scientific community to track and understand this disease and its implications on our lives. The studies and trials regarding disease management have further complicated decision-making, especially with the absence of conclusive evidence on pharmaceutical interventions and the contradicting results from published research. With the continuous flux of information, it is essential to be careful and critical when analyzing new data, with an eye for gaps and limitations. This article provided a synthesis of some of the most relevant literature that has been published so far regarding COVID-19. It has been divided into clear subsections to be simple and easy to navigate by the scientific community.

With no licensed vaccines or antivirals against COVID-19, and with strict measures becoming harder to sustain, continuous awareness on simple interventions such as regular hand washing and maintaining a one-meter distance between people must continue to be emphasized. When the pandemic is over, we hope the world will invest in developing an efficient response system shall another pandemic arise, as we were indeed not ready for this one.

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