Covid-19: The Biggest Threat of the 21st Century: In Respectful Memory of the Warriors All Over the World

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Abstract

Since the first case was diagnosed in China, the new coronavirus infection (COVID-19) has become the number one issue in the world and it seems to remain trend-topic for a long time. Until 17 April, it affected 210 countries, infected over 2 million people and caused approximately 150000 deaths. Although the course of the disease ranges from asymptomatic state to severe ARDS; the majority of patients reveal only mild symptoms. Though adults are the most commonly affected group; it can also be seen in newborns and elderly patients. Unfortunately, elderly patients are the most vulnerable group with higher mortality. Elderly patients, smokers and patients with comorbid conditions are most affected by the disease. In certain diagnostical tool is the real-time reverse transcription-polymerase chain reaction (real-time RT-PCR) test. However, it can be resulted in false-negative results and in this case the computed thorax tomography (CT) is one of the most important tools with high sensitivity. Besides the supportive treatment, most commonly used agents are immunomodulatory drugs such as plaquenil and azitromycin, and anti-virals including oseltamivir, ritonavir-lopinavir, favipiravir. Until a vaccine or a specific therapy invented, the most important intervention to control the disease is to fight against transmission. This is a real war and the doctors are the soldiers.

KEYWORDS: COVID-19, ground glass opacity, polymerase chain reaction, pandemic

Received: April 18, 2020   *Accepted:* July 6, 2020

INTRODUCTION

The novel coronavirus (CoV), officially named severe acute respiratory syndrome (SARS) CoV 2 (SARS-CoV-2), fell into the world's agenda like a bomb and reminded us of a long-forgotten entity: pandemic. Historically, the word pandemic consists of "pan," which means "all" and "demos," which means "people." Pandemic defines an outbreak of a disease that affects an exceptionally high proportion of the population.

Pandemics are large-scale outbreaks of infectious diseases that can significantly increase morbidity and mortality over a wide geographic area and cause economic, social, and political disruption. Evidence suggests that the likelihood of pandemics has increased over the past century because of increased global travel and integration, urbanization, changes in land use, and greater exploitation of the natural environment [1].

Although we know that most of the epidemic diseases affecting humankind have originated through the transmission of microorganism from animals to humans, some mechanisms such as in today's corona virus disease (COVID-19) pandemic are not well defined in terms of transmission.

For an animal virus to become a specialized human virus, it needs to go through many complicated and not yet fully understood processes. It must evolve into a pathogen capable of infecting humans and maintaining long-term human-to-human transmission without the need for reintroducing from the original animal host [2].

The pandemics, which have repeated frequently throughout history, have brought about remarkable economic, social, political, and scientific results. For example, the Athenian plaque was powerful enough to finish a war (430 BC), the Antonine plague (165-180 AD) accelerated the fall of the Eastern Roman Empire, and the Plague of Justinian (541-542 AD) killed 40% of Constantinople's population [3]. Starting in China, following the trade routes and reaching Italy, the plague named Black Death (14th century) caused an estimated 200 million deaths and has left the most famous concept regarding the pandemic to the present day, quarantine [4].

One of the most devastating pandemics was the Spanish flu. In the first decades of the 20th century, it was the first real global pandemic and the first one that occurred in the setting of modern medicine, with specialties such as infectious diseases and epidemiology and studying the nature of the illness and the course of the pandemic as it unfolded. It is also, as of this time, the last real global pandemic with devastating consequences for societies across the globe [3].

Now we are facing a new disastrous pandemic that affects the whole world: COVID-19.

What is Coronavirus?
Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses with a nucleocapsid of helical symmetry. These viruses are divided into four groups called alpha, beta, gamma, and delta 5]. Although some alphacoronaviruses (NL63) can cause infection in humans, the most pathogenic group is betacoronaviruses, and the majority of viruses typically cause common cold symptoms.

In the past two decades, the world has experienced two different outbreaks called SARS caused by SARS-CoV and Middle East respiratory syndrome (MERS) caused by MERS-CoV. Genomic analysis revealed that the cause of COVID-19 is a betacoronavirus, just like its close relatives. The new virus (formerly known as the novel coronavirus) resembles SARS-CoV much more rather than MERS-CoV because both SARS-CoV and the new coronavirus use angiotensin-receptor-2 (ACE2) receptor to enter a cell [6]. Therefore, the virus was renamed as SARS-CoV-2 by The Coronavirus Study Group of International Committee on Taxonomy of Viruses [7].

Epidemiology
On 31 December 2019, after the Chinese doctors reported a pneumonia-like disease with unknown etiology, a new agenda emerged that resulted in the forgetting about all economic problems, political conflicts, and wars all over the world. In the beginning, although the rest of the world seemed to watch these developments like a film produced in China, the virus quickly spread to 210 countries all over the world, including Turkey, in a short time, and the World Health Organization (WHO) declared COVID-19 as a pandemic. The novel coronavirus later got its official name, SARS-CoV-2; peaked in early February; and began to slow down in China. However, by then it had infected over 2 million people and caused 150,000 deaths till April 17, 2020

MAIN POINTS

- COVID -19 as a disaster of the 21st century seems harm all of as for a while more.
- Though it can affect all ages, the elderly are the most vulnerable group.
- Computed tomography and reverse transcriptase PCR are most useful diagnostic tools.
- Despite many of drugs has been speculated as a treatment agent, we have still no effective modality.
- Ongoing vaccine studies look promising for the future.

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[8]. Whereas the exact transmission route has not been fully understood, clustering of cases around a seafood market where live animals were sold made us think that the origin of the disease could be live animals, especially bats. Nevertheless, after human-to-human transmission through respiratory droplets and touching contaminated surfaces was first described in the USA [9], the virus started playing the lead role in a new pandemic.

Symptoms
The most common symptoms of COVID-19 are fever (temperature ≥37.3°C), fatigue, and non-productive cough. Some patients may experience headache, nasal congestion, sore throat, and diarrhea. Besides these relatively mild manifestations, a group may be entirely asymptomatic.

A retrospective cohort study presented the following details: laboratory-confirmed COVID-19 was seen in 191 adults, and definite clinical outcome (death or discharge) revealed that the most common symptoms on admission were fever (94%) and cough (79%) followed by sputum production (23%) and fatigue (23%). Diarrhea (5%) and nausea or vomiting (4%) were less common [10].

Risk Factors
According to the available information and clinical expertise, older adults and people of any age who have serious underlying medical conditions might be at higher risk of severe illness from COVID-19. Zhou et al. [10] confirmed that increased age was associated with death in patients with COVID-19, and the median age of the 191 patients was 56 (18-87).

Prevalence and severity of the disease may vary among individuals in terms of age, smoking history, and expression of ACE-2 receptor [11]. It seems there is a sex predisposition in terms of being infected by SARS-CoV-2. In the latest report of 1.099 patients with COVID-19 from 552 hospitals in 30 provinces in China, 58% of the patients were men [12]. This sex predisposition might be associated with a much higher smoking rate in men than in women in China (288 million men vs. 12.6 million women were smokers in 2018) [11].

Comorbidities were present in nearly half of the patients, with hypertension being the most common comorbidity, followed by diabetes and coronary heart disease [13, 14]. In a retrospective study, covering 201 patients, published by Chaomin Wu et al. [15], 66 patients had comorbidities, including hypertension (n=39, 19.4%), diabetes (n=22, 10.9%), liver disease (n=7, 3.5%), nervous system disease (n=7, 3.5%), chronic lung disease (n=5, 2.5%), chronic kidney disease (n=2, 1%), and tumors (n=1 0.5%).

Lighter et al. [16] found that obesity is a risk factor for critical care in patients aged <60 years. Patients with a body mass index (BMI) above 35 were 3.6 times more likely to be transferred to critical care than patients with a BMI below 30 [16].

These results suggest that age, obesity, and comorbidities may be risk factors for critical patients. The diseases such as hypertension, diabetes, respiratory system disease, and cardiovascular diseases may be linked to the pathogenesis of COVID-19.

Clinical Manifestations

The clinical course of COVID-19 ranges from asymptomatic infection to acute respiratory distress syndrome (ARDS) [17]. According to our current knowledge, the majority of patients with COVID-19 have uncomplicated or mild illness (81%), 14% develop severe illness, and nearly 5% require treatment in the intensive care unit (ICU) [14].

There is no definitive information about the number of individuals who are asymptomatic. Patients may be entirely asymptomatic throughout the illness or have some complaints afterward. A study containing data of approximately 72,000 patients from China showed that 30 of 1,012 patients (3%) were asymptomatic on admission, but only 14 (1.4%) remained asymptomatic during the 24-day follow-up [14]. Dong et al. [17] showed that almost 13% of reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 in patients, and infection in children were asymptomatic.

The mild or uncomplicated illness generally present with symptoms of an upper respiratory tract infection, including dry cough, mild fever, nasal congestion, sore throat, headache, muscle pain, and malaise [18]. Most patients do not complain about serious symptoms such as dyspnea, and active radiological findings in case of these patients are absent as well; prognosis and recovery are usually excellent at this stage. In the case of mild illness, hospitalization may not be required, but isolation should be prioritized [19].

According to clinical management of Severe Acute Respiratory Infection (SARI), COVID-19 related pneumonia was classified into two types: pneumonia and severe pneumonia [19)]. COVID-19 related pneumonia causes fever, respiratory symptoms, and radiological findings of pneumonia. The respiratory rate is below 30/minute, and there is no need for supplemental oxygen [19]. In contrast, in case of severe pneumonia, there is fever or suspected respiratory infection with one of the following: respiratory distress with respiratory rate>30 breaths/minute, severe respiratory distress, and oxygen saturation at rest ≤93% on room air [19]. We know that patients with severe pneumonia are significantly older (>65 years) and have comorbidities such as hypertension, diabetes, and cardiovascular and cerebrovascular diseases [14, 18]. Besides, older patients and those with comorbidities may present with mild symptoms but have a high risk of impairment and should be closely monitored [14, 18]. Yang et al. [20] reported that 52 of 710 confirmed patients with pneumonia (7.3%) had severe pneumonia. The median duration from onset of symptoms to radiological confirmation of pneumonia was 5 (IQR 3-7) days, and ICU admission was for 9.5 (7.0-12.5) days. ARDS has been reported in 35 (67%) patients, of whom 26 (81%) died [20].

COVID-19 related ARDS is defined when these four findings are present:

I) respiratory distress that occurs or worsens within one week;
II) bilaterally opacities, not fully explained by volume overload, lobar or lung collapse, or nodules in chest imaging;
III) respiratory failure, which cannot be explained by heart failure or excessive volume; and
IV) Partial pressure of oxygen/fraction of inspired oxygen≤300 mmHg (with positive end expiratory pressure or continuous positive airway pressure ≥5 cm H2O or non-ventilated) [19].

Different studies reported that the need for invasive mechanical ventilation varies from 30% (Wuhan, China) to 71% (Washington State, USA) and even to 88% (Lombardy, Italy) in patients in ICU [14, 21]. Moreover, it was reported that the frequency of mortality was between 16% and 78% among patients admitted to ICU [21]. According to Chinese data, all deaths occurred in patients with critical illness, and the fatality rate in these patients was 49%. In the same study, the overall fatality rate was found to be 2%-4% [14].

The term critical illness also includes thrombotic events, cytokine release syndrome, neurologic complications, shock, and multi-organ failure. Venous thromboembolism (VTE), most of which are pulmonary embolism (PE), is a significant problem, especially for patients in the ICU. Several clinical and post-mortem studies demonstrated that thromboembolic events are prevalent despite prophylaxis [22-24].

A study reported from Wuhan, where the pandemic broke out, revealed that 36.4% of the patients have neurologic manifestations. Although anosmia, taste disturbance, and muscle symptoms are more common, severe neurologic involvement concerns the central nervous system. They reported that severe neurologic events, including acute cerebrovascular accident, ischemic stroke, and cerebral hemorrhage, are associated with severe infection [25].

Cytokine release syndrome is characterized by high fever and elevated inflammatory markers and cytokines as a result of overworking of the immune system, which is also associated with disease severity and high mortality [26, 27].

Other relatively common complications are acute kidney injury (AKI), cardiac events, including acute coronary syndrome, arrhythmia, and sudden death. Although the real cause is not yet known, it may be due to the direct effect of the virus, side effects of the drugs, elevated cytokine release, or hypotension. AKI can be seen in up to 37% of patients and is an indicator for critical disease [28, 29]. Cardiac complications, including acute coronary syndrome, disease or drug-related arrhythmia, and acute cor pulmonale (may be due to pulmonary embolism), are also related to critical illness [30, 31].

Protection

To prevent and control infectious diseases that spread quickly, such as COVID-19, first the elimination of the source of infection should be targeted, followed by policies that cut off the route of transmission and protection of especially subgroups of the population who are more susceptible to infections [32]. SARS-CoV-2 is transmitted mainly by respiratory droplets and by contact with contaminated surfaces, which implies that personal protective measures are crucial to stop the spread of infection [33].

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Table 1. Comparison of 21th century's Coronavirus Infections

Demographics	COVID-19 (17th April)	MERS-2012	SARS-2002
Date started	December 2019	June 2012	November 2002
Starting point	Wuhan, China	Jeddah, Saudi Arabia	Guangdong, China
Number of affected countries	210	27	26
Confirmed patients	2.248.863	2.494	8.096
ICU requirement	N/A	N/A	15%-20%
Healthcare worker	N/A	476 (19.1%)	1.706 (21%)
deaths	154.145	858	774
Mortality rate	6.85%	34.4%	9.6%

N/A: Not applicable
References: https://www.who.int/emergencies/mers-cov/en/
https://www.who.int/csr/sars/country/table2004_04_21/en/
https://www.worldometers.info/coronavirus/#countries

Table 2. Clinical features

	China (Wuhan), Zhou et al. [10] (n=191)	Singapore, Young et al. [76] (n=18)	United Kingdom, Easom et al. [77] (n=68)	Italy, COVID-19-Surv.Gr. [78] (n=3,200)	South Korea, Kong et al. [79] (n=28)
Fever	94%	72%	40%	76%	32.1%
Cough	79%	83%	78%	40%	17.9%
Shortness of breath	NR	11%	25%	73%	NR
Diarrhea	5%	17%	NR	8%	NR
Myalgia	15%	NR	16%	1%	14.3%
Sputum	23%	NR	NR	NR	17.9%
Fatigue	23%	NR	NR	NR	10.7%
Nausea	4%	NR	NR	NR	NR
Rhinorrhea	NR	6%	29%	NR	NR
Sore Throat	NR	61%	57%	NR	32.1%

NR, not reported

Personal measures: According to the Centers for Disease Control and Prevention guidelines, handwashing with soap and water for 20 seconds or hand sanitizing and cleaning surfaces with at least 60% alcohol containing sanitizers are critical to inactivate viruses such as SARS-CoV-2 that has a protective coat made of lipids [34]. It is also essential to keep hands away from the nose, eyes, and mouth, the main routes for the viruses to enter the body. People should avoid sharing towels, clothes, drinks, or food and should not hug, shake hands, or have close contact with others. Because co-infections with other viruses such as influenza can occur, it is also vital for susceptible groups to be regularly vaccinated each year. These measures are essential not only for symptomatic patients but for everyone who can be asymptomatic but transmit the disease [34].

General measures: To slow down the spread of disease despite personal measures, governments and hospitals have to undertake some general measures. Isolation is a useful measure when an individual is sick, and according to the symptoms, the individual is isolated at home or a hospital ward. On the other hand, quarantine is used for individuals who are not sick but have been exposed to patients with infection and are followed daily by health professionals, usually by phone regarding body temperature or other signs or symptoms. Social distancing (at least 1.8 m) is another measure to limit close contact of healthy people who can be asymptomatic but can still spread the virus. Limitating travel and even banning to go outside are some examples of strict policies undertaken by some countries [34].

Face masks: Studies have shown that viral shedding can occur even in exhaled breath. The use of face masks plays an important role in reducing the detection of viral RNA in both aerosols and respiratory droplets [35]. Because of inadequate resources, the general protocol is to recommend surgical face masks for the symptomatic patients to reduce the contamination and to healthcare workers or caregivers who look after infected patients. Cloth masks are adequate for the general population [36]. Surgical masks are disposable and designed to provide a barrier to splashes and droplets impacting wearer's nose, mouth, and respiratory tract that would be used for various procedures in the community and hospital settings. While providing patient care, gloves, eye

protection, and gown are also recommended. Although surgical masks are a barrier for large droplets, they are inefficient against small droplets and thus are not recommended for aerosol-generating procedures. Respirators or Filtering facepiece (FFP2) or (N95) masks have a minimum of 94% filtration percentage, whereas FFP3 masks are the most filtering masks with a minimum filtration percentage of 99% and maximum 2% leakage to the inside, and thus, they can protect against very fine particles such as asbestos. FFP2 and especially FFP3 masks are highly recommended for the healthcare workers while performing aerosol-generating procedures such as intubation/extubation, bronchoscopy, non-invasive ventilation, and high flow nasal oxygen to the patients with COVID-19. Respirators might be disposable or re-used, according to the manufacturer.

Vaccines: A vaccine would be the most effective measure to protect against COVID-19, especially in susceptible populations. Unfortunately, there is still no vaccine for the SARS-CoV-2 virus yet. There are many ongoing studies that are trying to find an appropriate vaccine. Clinical trials are multi-step studies that try to determine whether a vaccine generates an immune response or not. Researchers are working to have a vaccine ready in 18 months [37]. Vaccines are mainly divided into two: specific and non-specific. Specific vaccines (around 100 have been tested around the world) target mainly the spike protein throughwhich the virus binds the ACE2 receptors. These vaccines consist of the following: 1) virus (either inactivated or weakened), 2) viral vector (replicating or non-replicating), 3) nucleic acid (DNA, RNA), and 4) protein-based particles (protein subunit or virus-like particles) [37].

On the other hand, non-specific vaccines such as Bacillus Calmette-Guérin (BCG) and oral polio vaccine have also been tested. The BCG vaccine induces metabolic and epigenetic changes that enhance the innate immune response to subsequent infections, a process termed as trained immunity [38]. The BCG vaccine might reduce viremia after SARS-COV-2 exposure, and two randomized controlled trials are underway (NCT04327206, NCT04328441) [38].

Healthcare Workers
As the number of patients increased, the outbreak infected many healthcare workers (HCW) working at the frontline. A total of 1.716 HCWs had confirmed cases in China, representing 3.8% of all cases, according to an article published at the end of February [14]. The prior report says an estimated 3.000 HCWs have been infected in China and at least 22 have died [39]. Another report investigating the association of public health intervention with the epidemiology of the COVID-19 outbreak in Wuhan found that the daily rate of cases in local HCWs was higher than that in the general population over the whole period [40]. The latest reports from Italy show that more than 2,600 HCW have been infected and more than 60 have died [41]. Not every country has reported on the percentages regarding the HCWs with infection and the HCW death rates, thus we do not have the exact numbers for now. The burden and severity of COVID-19 results in the development of burn-out syndromes and increases anxiety, depression, insomnia, and distress [42]. A paper focusing on HCW's needs during the outbreak listed eight sources of anxiety; inadequacy of personnel protective equipment, risk of infecting family members, not having access to test, uncertainty over their and their family's future if they develop the disease, childcare issue at the time of their working hours, inability to support their own and their family's needs, appointment to a new place, and the inability to access the newest information [42]. A cross-sectional survey-based study measuring the mental health status of 1.257 HCW working in equipped wards for patients with COVID-19 from 34 hospitals in China stated that being a woman and having an intermediate professional title was associated with severe symptoms of depression, anxiety, and distress [43]. A study pointed out the telemedicine approach using smartphones or webcam-enabled computers for forward triage that allows the medical staff to refer moderate to high-risk patients to nurse triage system but also to schedule video visits for both homecare patients' follow-up and for the sicker patients to be placed directly into the COVID ward without admitting to the emergency room and thus minimizing the exposure of HCW and other patients [44].

Our priority should be the protection of HCW working on the frontline because if HCWs get infected, it becomes impossible to overcome the disease despite all our equipment. The health care force, including physicians, nurses, pharmacists, non-medically trained assisting personnel, and security staff of the hospital need to be listened to, cared for, and supported to restore their energy.
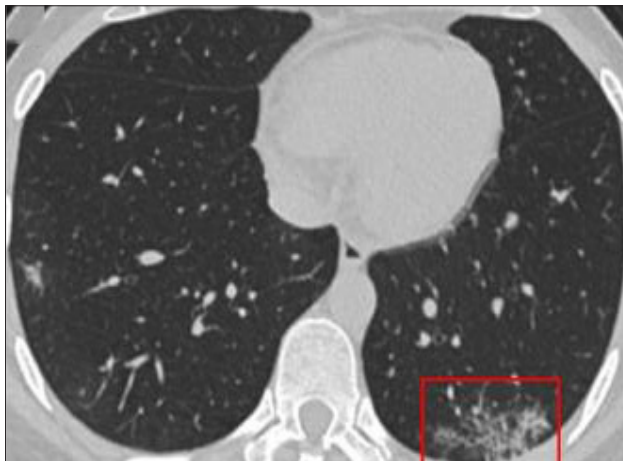
Diagnosis

Molecular Techniques and Serology
RT-PCR, a molecular test, is recommended for the detection of COVID-19 infection. The viral load increases in the upper and lower airways within a week after the symptoms appear. The recommended initial testing is collecting sample from the upper respiratory tract via a nasopharyngeal specimen , oropharyngeal specimen, a nasal mid-turbinate swab, nasal swab (anterior nares), or nasopharyngeal wash specimen [45]. Although there is insufficient evidence about which sample is ideal, the Infectious Diseases Society of America recommends using nasal samples over oral samples owing to higher positivity rates (66% and 34%, respectively). Despite higher positivity rates, lower respiratory tract samples such as expectorated sputum, tracheal aspirate, and bronchoalveolar lavage are suggested to be reserved for hospitalized patients because of the risk of transmission [46, 47]. Wang et al. [46] stated that bronchoalveolar lavage has the highest positivity at 93% followed by sputum (72%), nasal swabs (63%), fibro-bronchoscopic brush biopsy (46%), and pharyngeal swabs (32%).
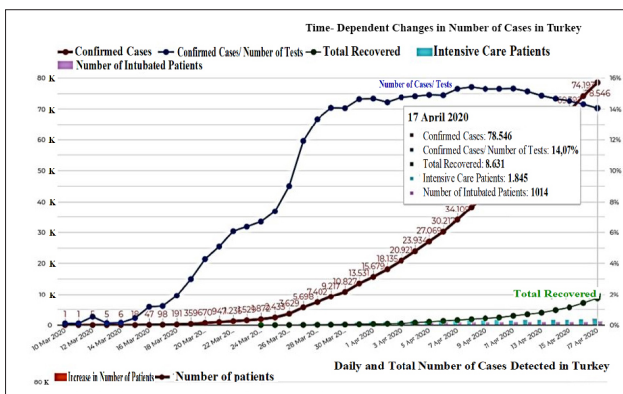
Factors such as a person's experience, taking the sample with the correct technique and transport, and the stage of the disease can affect the RT-PCR test result. The reliability of RT-PCR is higher in sputum or bronchoalveolar lavage. Respiratory Syncytial Virus and Influenzae viruses should also be eliminated in patients. When SARS-CoV-2 pandemic emerged, immunoassay methods were developed for the rapid diagnosis of antigen and antibody. Lateral flow immu-
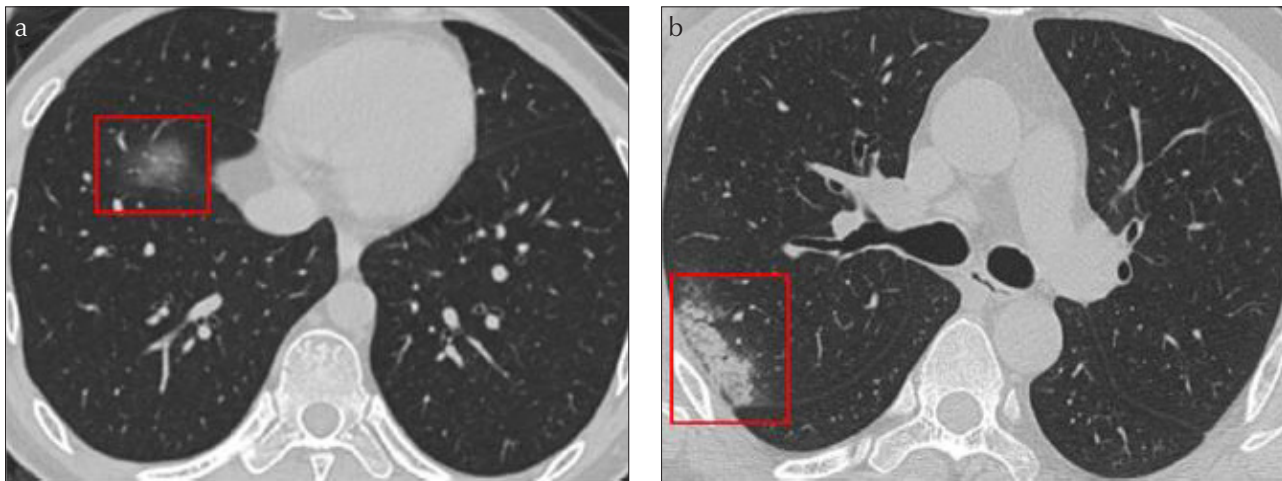
Figure 1. a, b. (a) GGO in the right lower lobe (red frame). (b) Consolidation in the right lobe subpleural area (red frame). GGO, ground-glass opacities

Figure 2. Reticular pattern in the left lower subpleural area (red frame)

Figure 3. Statistics of Turkey

noassay methods can detect SARS-CoV-2 IgM and IgG antibodies. However, IgM responses are not specific, and IgG occurs weeks later; therefore, they are not useful in the management of acute infection. They may play a role in determining the immunity of healthcare staff or in detecting late COVID-19 cases [48]. Deep sequencing molecular methods such as next-generation sequencing and metagenomic next-generation sequencing can detect SARS-CoV-2 mutations, but their use in diagnosis is still not recommended. Point-of-care molecular diagnostic tests, which are simpler and give results in as early as one hour, can also be used. Antigen detection tests are tests with low sensitivity in excluding the disease. Studies on advanced prototypes are ongoing. Monoclonal antibodies are being developed, which will be the basis of rapid antigen screening tests [49].

Radiology

Thorcic computerized tomography (CT) is helpful in the diagnosis and differential diagnosis of COVID-19 pneumonia. It mainly plays an important role at the time of diagnosis of the asymptomatic or RT-PCR negative patients. It could be useful in assessing the severity of disease at the time of diagnosis. However, routine CT scanning is not recommended by several radiology associations. Typical radiological findings of COVID-19 pneumonia are multifocal ground-glass opacities (GGOs), which show peripheral distribution and patchy consolidations. Involvement is mostly observed in lower lobes or posterior segments. When GGOs are high in number and density and widely distributed, the infection is assessed to be more severe [50]. Whereas round-shaped opacities, crazy-paving patterns (GGO with superimposed inter- and intralobular septal thickening), and peripheral consolidations are more common; pulmonary nodules, cavitation, pleural effusion, and lymphadenopathy are rare [50, 51]. In COVID-19 pneumonia, differences were observed in the distribution and prevalence of GGOs and peripherally located consolidations on the basis of the severity of disease and whether the disease is in the early or late phase (Figure 1. a,b). Typical findings of COVID-19 include diffuse, multifocal, and segmental consolidations located in the subpleural areas or around the bronchovascular tree. Following GGO and consolidation, reticular pattern seen together with interlobular septal thickening, which is thought to be caused by interstitial lymphocyte infiltration, are among the most common CT findings (Figure 2) [52].

Laboratory Findings

The most common laboratory finding is lymphopenia (35%-90% of patients) followed by leukopenia and leukocytosis [26, 31, 53]. It seems that hemoglobin and thrombocyte counts are usually within normal limits [26, 54]. Higher neutrophil/lymphocyte ratio (NLR) is associated with severe dis-

ease, and NLR>3.13 can be used as an early marker for admission to ICU [55].

Elevated lactate dehydrogenase, serum aminotransferase, and ferritin levels are common among patients with COVID-19. Patients often have normal serum procalcitonin levels on admission even if they have had pneumonia. Elevated D-dimer, prothrombin time, and troponin levels are more common in ICU patients than in non-ICU patients, and they have also been associated with increased mortality [26, 53, 54, 56]. Other markers associated with increased mortality are pro-inflammatory cytokines such as IL-1, IL-2, and IL-6, and treatments targeting associated pathways can be used in critically ill patients [26, 57].

Treatment
Thus far, there is no effective treatment for COVID-19. Current clinical management includes infection prevention, control measures, and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated. Several potential drug candidates, including chloroquine (CQ), hydroxychloroquine (HCQ), azithromycin, lopinavir/ritonavir, favipiravir, neuraminidase inhibitors, remdesivir, umifenovir (Arbidol), ribavirin, interferon, convalescent plasma, steroids, and tocilizumab have been administered to patients.

General Measures and Supportive Care
Patients with mild disease do not require hospitalization, but isolation is necessary to contain virus transmission. Symptomatic treatment such as anti-pyretics must be commenced. Patients with mild COVID-19 should be counseled about signs and symptoms of complicated disease and monitored closely. If they develop any of the severe symptoms, they must be immediately hospitalized [1]. Patients with pneumonia and/or SARI must be hospitalized and be given supplemental oxygen therapy [58].

Low molecular weight heparins (LMWH) are suggested in the treatment of hospitalized adult patients with COVID-19 on the basis of the prognostic importance of coagulopathy (elevated levels of D-dimer) and post-mortem studies that revealed thrombotic microangiopathy in patients with COVID-19 [59]. The International Society on Thrombosis and Haemostasis recently recommended that all hospitalized patients with COVID-19, even those not in the ICU, should receive standard prophylactic anti-coagulation with LMWH in the absence of any contraindications. There are some controversial issues about the treatment of hospitalized patients with COVID-19. Current WHO recommendations advise against routine use of prednisolone in the management of COVID-19. However, case reports still exist of complex patients managed with steroids in low doses. Vitamin C has been suggested as a treatment option for COVID-19 based on a prospective randomized trial of intravenous vitamin C in patients with sepsis and ARDS. In that trial, there was no difference in the sequential organ failure assessment score and 28-day mortality between the vitamin C and placebo groups [60].

Specific Treatment Against SARS-CoV-2

1. Anti-malarials
CQ and HCQ (anti-malarial agents) showed potential broad-spectrum antiviral activities by increasing endosomal pH required for virus/cell fusion and interfering with the glycosylation of cellular receptors of SARS-CoVs. It is also speculated that the known immunomodulant effect of HCQ may enhance the antiviral effect. Both CQ and HCQ demonstrated marked efficacy in clinical and radiological regression, negative conversion and shortening of the disease period, and have acceptable safety in treating COVID-19 associated pneumonia in multicenter clinical trials conducted in China [61]. The National Health Commission of China recommended using CQ or HCQ in the treatment of patients with COVID-19 with several precautions, including the development of QT interval prolongation or bradycardia and appearance of visual and/or mental disturbance/deterioration. The American Thoracic Society suggested HCQ (or CQ) for hospitalized patients with COVID-19 who have evidence of pneumonia on a case-by-case basis in some conditions [62]. Food and Drug Administration (FDA) issued an "Emergency Use Authorization" advisory to allow the use of HCQ or CQ for treatment of hospitalized adults and adolescents (weight ≥50 kg) with COVID-19 for whom a clinical trial is not available or participation is not feasible. More recently, two major observational studies from the USA have failed to confirm the clinical benefit of HCQ in treating patients with COVID-19 [63, 64]. With HCQ, a more rapid negative conversion of the virus could not be demonstrated in a randomized controlled study. At the same time, adverse events were more frequent in HCQ recipients than in non-recipients [65].

2. Antivirals
Lopinavir, a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, has in vitro inhibitory activity against SARS-CoV and MERS-CoV. Ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome P450. In a trial conducted to evaluate the efficacy of lopinavir-ritonavir combination in hospitalized patients with COVID-19, treatment with lopinavir-ritonavir was not associated with clinical improvement, reduced mortality, or reduced viral RNA levels. Lopinavir-ritonavir combination led to a median time to clinical improvement gain of one day. Gastrointestinal side effects were more common in the treatment arm, and therapy was ceased early in 14% of the patients [66]. Favipiravir is a new type of RNA-dependent RNA polymerase inhibitor. In addition to its anti-influenza virus activity, favipiravir is capable of blocking the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses, and therefore, it may have potential antiviral action on SARS-CoV-2, which is an RNA virus. It was shown that favipiravir had more potent antiviral action than lopinavir-ritonavir and also had significantly fewer adverse effects than the lopinavir-ritonavir group [67]. Remdesivir is a nucleoside analog, a broad-spectrum antiviral, and has in vitro activity against SARS-CoV-2 and in vitro and in vivo activity against related beta-coronaviruses. A series of 53 patients received remdesivir, 68% of whom were reported to have clinical improvement, and the mortality rate was reported to be 13% [68]. The first randomized controlled trial published regarding the use of remdesivir did not support this agent's clinical benefit [69]. In contrast, the first results of another randomized controlled clinical trial showed that remdesivir shortens the time to recovery compared with placebo [70].

3. Other Agents

Teicoplanin could be administered for the treatment of SARS-CoV-2 infection. The spike glycoprotein (S protein) is the leading mediator of viral entry, followed by further cleavage of S protein in endocytic vesicles mediating by cathepsin L. Teicoplanin blocks virus entry by specifically inhibiting the activity of cathepsin L. In a study, it was demonstrated that teicoplanin could inhibit the entry of HIV-1-2019-nCoV-S pseudoviruses [71]. Ivermectin is a commonly used anti-parasitic drug recently shown in Australia to have in vitro activity against COVID-19. A single dose in vitro was able to reduce viral replication within 24-48 hours [72].

4. Immunomodulators

Clinical features consistent with a cytokine release syndrome with elevated IL-6 levels have been described in patients with severe COVID-19. A small case series of patients with relatively severe COVID-19 in China revealed good outcomes with the IL-6 receptor inhibitor tocilizumab [73]. In another series where tocilizumab was administered to patients with severe COVID-19, all patients were reported to have survived, and no serious side effects were seen [74]. There is no evident data except case reports, but clinical trials evaluating its efficacy are still ongoing. Tocilizumab should be kept for critically ill patients rather than mild or moderate cases. This agent must be considered in patients with bilateral, diffuse lung disease and elevated IL-6 levels, especially where levels of inflammatory mediators are rising continuously.

5. Convalescent plasma

A case series described the administration of plasma from donors who had recovered entirely from COVID-19 to five patients with severe COVID-19 on mechanical ventilation and persistently high viral titers despite investigational antiviral treatment [75]. The patients had decreased nasopharyngeal viral load, decreased disease severity score, and improved oxygenation by 12 days after transfusion; however, these findings do not establish a causal effect. FDA has issued guidance for administering or studying the use of convalescent plasma for treatment of patients with COVID-19.

The Situation in Turkey

It has been more than a month since the first COVID-19 case was reported on 11 March 2020 in Turkey. The first death was reported four days after the first case. That scary scenario seems to have peaked, and now the detection rate of the positive cases is decreasing despite the increasing number of tests performed. We believe that Turkey is dealing with the situation in average conditions. What makes the scenario different is our economic power and health utilities. Turkish health resources seem to deal with the situation adequately, considering the mortality rate, which is 2.25% currently. However, we are very anxious that these statistics may not reflect the real situation of all patients with COVID-19 who tested negative in PCR but have symptoms or x-ray findings suggestive of the disease. Although the PCR positivity rate is about 60%, we believe that we have higher false negative results in Turkey. The preventive measures taken in Turkey started early; however, they seem inappropriate in several circumstances, such as preventing social gathering. HCWs

may be more affected by the crisis, although we do not know the current number of PCR positive cases till April 18, 2020). Finally, as doctors dealing with patients with COVID-19 in the frontline, our number one priority is to feel safe and protected. We would also like to be better informed scientifically about this new threat.

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