Review

Clinical Epidemiology of Coronavirus Disease 2019: Defined on Current Research

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ABSTARCT

Coronavirus disease 2019 (COVID-19) is a new infectious respiratory disease that has caused the ongoing global pandemic. The primary purpose of this article is to describe evolving clinical epidemiology of COVID-19, including 1) infection and testing, 2) clinical spectrum including classification of clinical type, asymptomatic cases, severe cases and comorbidity, and clinical and immunological response, 3) regional variation in clinical presentation, 4) population distribution by age, sex, and occupation, and finally, 5) case-fatality. This content may provide important information on detailed clinical type and presentation of the disease, in which appropriate clinical outcomes can be derived for developing prevention strategies and clinical studies or trials that aim to test potential therapeutics or products for different patient populations.

Keywords: Clinical epidemiology; COVID-19; SARS-CoV2

OUTLINE

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel respiratory disease caused by severe acute respiratory syndrome-2 (SARS-CoV-2) discovered in 2019. The SARS-CoV-2 is an RNA virus and belongs to the beta coronavirus group, has high similarity (96%) with bat coronavirus in the genome and is 80% identical to the genome of SARS-CoV (1, 2). The new virus originated from a natural host and transformed to have a human-to-human transmission (3). While the exact source of the virus and the transmission mode from the natural host to humans have not been determined, the human-to-human transmission of SARS-CoV-2 has caused a worldwide public health emergency. Compared with other coronaviruses which cause the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), the SARS-CoV-2 virus exhibits not only higher infectivity and rapid transmission (**Box 1**) than the SARS-CoV and MERS-CoV, but also more severe clinical symptoms than the corona-viruses that cause seasonal influenza or common cold do(4). The high infectivity and a rapid transmission mode from person to person have posed a challenge in managing the initial outbreak to the epidemic. On March 11, 2020, when more than 20,000 confirmed cases and 1000 deaths

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were reported in Europe, the WHO announced a pandemic of COVID-19.

Understanding the epidemiology is fundamental for developing effective control and treatment strategies. However, it may take more time and require formal population-based studies (5) to define the epidemiology of COVID-19, which should involve both the viruses (including strains) and human hosts. As an acute infectious respiratory disease with direct person-to-person transmission, the development of COVID-19 requires an individual first to be exposed to the virus pathogen. Factors associated with the increased likelihood of exposure and the enhanced interaction between the pathogen and host genomes may facilitate the virus entering the hosts, and increase the risk of developing the disease. An individual's susceptibility to the SARS-CoV-2 virus is also determined by the host's innate immune system and adaptive immune response. The specific protective immunity or capacity for defending against the pathogen could vary and may be associated with that whether an individual has underlying chronic health conditions that may enhance or reduce an individual's ability to mount an effective immune response to the pathogen.

When the virus enters a host, an individual may experience one of several possible outcomes. First, some individuals who have viral testing positive may not develop symptoms (asymptomatic) but can spread the virus in a family or community and cause other people to be infected. The asymptomatic is a critical component for describing the disease's clinical spectrum (5), assessing infectivity and transmissibility (6), selecting public health strategies (7), and describing the epidemiology. Because asymptomatic patients are less likely to be noticed and identified promptly unless an active testing strategy is implemented, they may pose a dangerous threat to public health. Therefore, asymptomatic patients should be quarantined or treated with antiviral drugs to reduce viral load and prevent further transmission.

Box 1 some terminology of infectious epidemiology

Term	Definition
Infectivity	Infectivity is a pathogen's ability to establish infection at a horizontal level, i.e., from host to host in humans, not including maternal-fetal vertical transmission and humans to other hosts. It is determined by the pathogen's ability to enter, survival and replicate in the host. Infectivity is measured in population by the rate of infection after exposure to a confirmed source of infection, which is equivalent to incidence. In the case that a recurrent infection is rare in a short time for some pathogens (e.g., SARS-CoV-2), the infection rate is equivalent to prevalence of infection. Infectivity is determined by the rate of viral replication and the chance of exposure to the pathogen. It is estimated that the infectivity of SARS-CoV-2 is about 15 to 20% in the general population with little use of personal protection equipment, according to the statistics from the outbreaks such as on the Diamond Princess Cruise ship.
Transmission	Transmission is the ability to pass a pathogen that causes an infectious disease from an infected individual to other individuals or a group. It is usually by the following means: a) Airborne transmission, tiny dry and wet particles less than 5 micrometers (μm); b) Droplet transmission, small and usually wet particles large than 5μm; c) Direct physical contact (e.g., handshaking, other physical contacts); d) Indirect physical contact (e.g., contaminated surface); e) Fecal-oral transmission. Because of multiple means of transmission, the SARS-CoV-2 virus has a rapid transmission mode. So far, there has no evidence for maternal-fetal vertical transmission.
Transmissibility	Transmissibility is defined as the number of cases directly caused by one infected case in the absence of any deliberate intervention in disease transmission. It can be expressed as R_0=b*t; b, an infected individual makes an average of b infection-producing contacts per unit time in a certain infectious period t. R_0>1, outbreak will be expanded; R_0<1 will die out.

Characterizing the clinical manifestations of patients who require health care would help depict patients' clinical course with COVID-19. Currently, since there are no vaccines or effective pharmacological treatment for the disease, it is urgent to assess the need for health care and define its clinical epidemiology. Herein we describe the clinical epidemiology based on a review of clinical reports, mostly hospital-based case series, of the clinical types and features seen in patients with COVID-19, to understand distinct patient subpopulations and identify potential clinical outcomes. Besides asymptomatic patients, individuals infected with SARS-CoV-2 tend to have various clinical manifestations from mild to moderate, severe cases or critically ill, or death, which could vary with underlying health conditions and demographics. Information on the classification of clinical type and presentation would help plan health care services for subgroup patient populations and encourage etiological and clinical studies or trials that aim to test the efficacy and effectiveness of medical treatments and develop novel therapeutic applications.

1. INFECTION AND TESTING

Infection is defined as invasion and multiplication of microorganisms in the host's body tissues after exposure to a confirmed source of infections. When the foreign pathogen enters the host and invades the body's tissues, it colonizes and begins to replicate. Susceptible individuals may develop biological evidence of infection, which could be detected through related testing such as pathogen-related nucleic acid testing and genomic sequencing, and then have host-related responses such as the production of antibodies or physiological response (e.g., inflammation). Some individuals infected with a pathogen may develop a clinical illness, and may or may not have viral testing positives. Additionally, it is now established that some individuals who can test positive for SARS-CoV-2 nucleic acids do not develop symptoms (asymptomatic) or show only minimal symptoms but can still spread the virus and infect others. An early case report (8) showed that an individual with travel history to an epicenter might have become infected with SARS-COV-2, but developed no symptoms or fever; the computerized tomography (CT) test of chest and laboratory tests were normal, and the initial nucleic acid testing was negative. However, that person without symptoms likely caused five family members to be infected and confirmed cases with COVID-19. A recent study found that among individuals infected with SARS-CoV-2, the duration of viral shedding was quite similar between asymptomatic and symptomatic patients (9). Furthermore, a review of 16 reports indicates that asymptomatic patients could account for 40-96% of patients identified in the outbreaks of COVID-19 (10). The similar long duration of viral shedding and a high proportion of asymptomatic patients suggest that asymptomatic transmission is a critical concern for effective public health management.

1.1 Viral tests

Viral testing is an objective assessment used to confirm the presence of infection with the virus and to make a diagnosis of COVID-19. Reverse transcriptase polymerase-chain-reaction (RT-PCR) is a method to detect the genetic materials of a pathogen, including a virus, and it is the most widely used method for testing the presence of viral particles of SARS-CoV-2 in human biospecimens. All coronaviruses can only replicate and survive in living cells; therefore, the SARS-CoV-2 virus enters the cells of the mucosal membrane of the mouth and nose of the host and replicates there before moving down to the respiratory and gastrointestinal system. In general, viral testing requires samples of nasopharyngeal mucosa.

To use the RT-PCR technique, one must convert RNA into DNA (called reverse transcription), so DNA can be copied and amplified. The amplification is only on a specific part of transcribed viral DNA. In some guidelines (11, 12), the open reading frame 1ab (ORF1ab) or nucleocapsid protein (N) gene regions are included as testing targets. Others also choose the RNA dependent RNA polymerase (RdRP), N and E gene, in which E gene is used for screening to eliminate the bat SARS-related CoV, while RaRP and N gene were used to confirm the infection of SARS-CoV-2 (13). Viral testing positive is defined as the RT-PCR cycle threshold (CT) value of less than 37 or 40, which means higher viral loading may require fewer RT-PCR cycles to detect the viral components in a human biospecimen. Some biotechnology companies have also developed a qualitative rapid nucleic acid test (14).

Sequencing-based testing is another tool for viral testing. On June 10, 2020, Illumina announced receiving the United States Food and Drug Administration (FDA) emergency use authorization for its COVIDSeq test designed to target and amplify 98 segments of the full genome of SARS-CoV-2, instead of a few segments that the RT-PCR approach has usually focused. Therefore, the COVIDSeq test may increase the accuracy due to its target at the whole genome, leading to an increase in the testing sensitivity. More importantly, with the genome-wide sequencing test, abundant viral genomic data will be produced to facilitate population-based genomic research on the pathogen.

Viral nucleic acid testing can tell if an individual has an existing infection with SARS-CoV-2 and can quickly confirm cases of COVID-19. Due to limited capacity or large demands for testing, viral tests are sometimes performed only in people with (suspected) exposure to confirmed sources of infection or people who have already developed fever or respiratory symptoms. Testing based on this strategy may not reflect the actual infection rate in the general population or assess the full clinical spectrum of COVID-19 in the whole patient population.

However, viral nucleic acid testing may have a high rate of false-negative results (15, 16). False negatives may be caused by several factors such as the very load viral load at the early stage of infection, quality of test kits, type and quality of biospecimen taken, and assay errors. A fraction of patients may have lower respiratory tract infection, which might affect the viral testing if nasopharyngeal swap sample is used (17). Of note, the nucleic acid testing is on particles of the viral genome; it does not mean the virus *per se* is in the biospecimen. In most cases, the nucleic acid test cannot rule out a disease caused by other coronaviruses except those panels designed with specific procedures (13). Because of the limitation of the viral testing, history of exposure, clinical symptoms, computed tomography, or x-ray should also be considered to diagnose suspect COVID-19 (18).

1.2 Population-based infection rate

The estimate of the infection rate can be obtained from several outbreaks in which prevention measures were unlikely taken in advance. The first estimated infection rate was on the Diamond Princess Cruise ship after an index case with COVID-19 was identified (19). Passengers and crew members stayed in a closed environment and later were in quarantine together, so individuals on the cruise ship are assumed to have been exposed to the confirmed source of infection. It turned out that 19% (712/3711) of passengers and crew members tested positive for the SARS-CoV-2 viral RNA, of which 46% (331/712) were asymptomatic, according to the statistics of the United States Centers for Disease Control and Prevention. The infection rate was close to the estimates from the crew members of the USS Theodore Roosevelt (17%) and obstetric patients in New York (15%) but was lower than the estimates of 24 to 69% in the homeless shelters in Boston and Los Angeles, inmates in prison in four states of the US, and the elderly in a nursing home facility in Washington State (**Table 1**). The infection rates in the crew members of the Charles De Gaulle aircraft carrier (55%) and an Argentine cruise ship (59%) were relatively high.

Table 1 Infection rate after close exposure in different outbreaks (10, 19-22)

Author	Population	Place	Exposed	Case	%	Asymptomatic rate. (%)
Mizumoto et al	Adults	Diamond P, Japan	3711	712	19.2	46.5
US Navy	Crew member	USS Theodore Roosevelts	4954	856	17.3	60.0
Sutton, et al	Obstetric patients	New York, NY	214	33	15.4	87.9
Chou, et al	Homeless shelter	Los Angeles, CA	178	43	24.2	63.8
Arons, et al	Elderly	Nursing home, WA	89	57	64.0	*58.7
Baggett, et al	Homeless shelter	Boston, MA	408	147	36.0	87.8
So, et al	Inmates	AK, NC, VA, OH	4963	3277	69.8	96.0
France	Crew member	Charles De Gaulle aircraft	1760	1046	54.9	50.0
Ing et al	Cruise ship	Argentine, Argentina	217	128	59.0	81.3
Lu et al	Children	Wuhan, China	1391	171	12.3	22.8

*. Rate of presymptomatic patients, later majority developed symptoms; Diamond P, the Diamond Princess Cruise ship.

The prevalence of infection seemed lower in children exposed to a confirmed infection. In a population-based assessment of 1391 children (median age 6.7 years), Lu et al. (23) reported that 12.3% of children were infected with SARS-CoV-2 after being exposed to persons with confirmed or suspected COVID-19. Even though the exposure is likely more intensive, the children appears to have a lower infection rate than adults do in the outbreaks (17 to 69%).

In addition, the infection rate of SARS-CoV-2 seems much lower in the general populations. Community-based screenings for SARS-CoV-2 infection estimated the infection rate at 0.8% in Ireland, 1.7% and 1.8% in the residents in Indiana and San Francisco, CA, respectively (10). The infection rate in community residents was estimated at 1.2-2.6% in Italy (24).

1.3 Antibody tests

Antibody testing detects immunoglobins (antibodies) specifically to SARS-CoV-2 antigen in the body. In response to the invasion of viral antigen, the host first initiates the innate immune response (innate immune cells) and activates adaptive immune response (T-cell activation and B cell response) to fight infection through destroying the infected cells and antibodies (mainly by B cells) neutralizing the pathogens, which some antibodies may have long-term or lifelong protective immunity to a re-infection of the same pathogen. Serum antibodies (IgM, IgA, and IgG) tested against SARS-CoV (25) and SARS-CoV-2 (26-29) for evidence of early infection have been inconsistent. There have been about a hundred of manufacturers developing the variable serological tests (30). On April 18, 2020, FDA issues an umbrella emergency use authorization (EUA) for SARS-CoV-2 antibody test (lateral flow or enzyme-linked immunosorbent assay, ELISA test) (31). On July 21,2020, FDA issued a revocation of the umbrella EUA and may issue individual EUAs (31). There have been concerns raised about its clinical utility of the serological test (30, 32). Still, antibody test can be used for detecting infection with SARS-CoV-2 in recent or the past, through specifically looking for immunoglobin (Ig) G and IgM (28).

Population-based seroprevalence of antibody IgG and IgM positive status is valuable for public health strategies and helps describe the distribution of infection for study of risk factors. Therefore, a well-designed serological survey will be necessary for defining the epidemiology of COVID-19 after the pandemic. Xu et al. (33) published a survey in multiple selected samples in China on seroprevalence of IgG and IgM antibodies against the SARS-CoV-2 antigens. In confirmed patients with COVID-19 (n=242), seropositive rate reached 95% for IgG on day 16 and for IgM on day 20 after onset of symptoms. The seropositive IgG in patients with COVID-19 is consistent with that obtained in the patients in the US (34). Therefore, IgG can be at least used as a biomarker for confirming that a recent viral infection has occurred. In the same study, Xu et al. also performed immunoassays on antibodies in a few community-based samples (33). The seropositive IgG was the highest at 3.2 to 3.9% in healthcare workers, outpatients, and hotel staff workers. However, the IgM positives were relatively lower in most samples than the IgG, except for hemodialysis patients (1.9%) and community residents (0.3%), in which IgG and IgM positive rates were similar. Seropositive IgG has been reported at 1.79% in a community-based sample from the US (34).

Population-based seroprevalence surveys have recently provided some robust estimates of the infection rate in the pandemic of COVID-19. A nationwide seroprevalence survey conducted in Spain, one of the European most severely affected countries (35), on nearly 36,000 households (n=51958) across the country, provides the first estimate of seroprevalence from a large-scale randomly selected sample. The seroprevalence of IgG antibody was about 5% in the country as a whole, but with a considerable regional variability. In the central region around Madrid, where is the epicenter of COVID-19 in Spain, the seroprevalence was as high as 10-13%, while Barcelona had about 7% and other areas had 1-3%. Another study, monitoring for five consecutive weeks with randomly selected samples in Switzerland, reported a seroprevalence of IgG at 5-11% (36).

The low seropositive IgG and IgM may indicate a reduced level of exposure to the source of infection in the populations, probably due to proper preventive measures that have been taken. However, it may also indicate that a high proportion of people are still susceptible and that the community is at risk for a future outbreak unless or until a certain proportion of susceptible people have been vaccinated to produce effective “herd immunity”. It seems unlikely that the natural “herd immunity” will be achievable in modern society because of fast testing tools, personal protective equipment (PPE), and fast information sharing that enables adequate contact tracing leading to isolation and quarantine as needed.

2. CLINICAL SPECTRUM OF COVID-19

Heterogeneity of the clinical spectrum of COVID-19 must be understood in order to characterize its clinical epidemiology fully. Epidemiology is the study of the distribution of incidence and occurrence of a disease or an event in three dimensions (i.e., where, who and when) and various factors associated with the disease’s risk, so that preventive measures can be taken to reduce the risk for exposure. The estimates of epidemiological parameters can also be used for mathematical modeling that describes the mode and dynamics of transmission for an infectious disease. As a new disease, defining the epidemiology of COVID-19 will inevitably require more comprehensive research efforts using population-based representative samples. The number of exposure and infection is fundamental for estimating related epidemiological parameters, such as infectivity, incidence, and transmissibility.

Clinical epidemiology is the study of the distribution of clinical presentations and factors associated with clinical subtypes or outcomes in patient populations that enhance the understanding of clinical heterogeneity. Patients across the clinical spectrum serve as numerators for estimating some epidemiological parameters, but they are virtually the study populations for describing clinical epidemiology.

2.1 Classification of clinical type

The clinical type of COVID-19 can be classified into mild, moderate, severe, and critical. As a new disease, there are no long-established guidelines or accepted statistical and diagnostic criteria for COVID-19. The National Health Commission of China has released a trial version of a diagnosis and treatment protocol for coronavirus pneumonia (Trial Version 7), which has been revised multiple times as knowledge and evidence have been gained, and there are also proposed criteria for diagnosing COVID-19 in children (18, 37). In addition to viral testing positive and clinical symptoms, the clinical type is classified as a mild, moderate, severe, or critical case as follows (18):

a) Mild, clinical symptoms are mild, and there is no sign of pneumonia on imaging.
b) Moderate, an individual shows fever and clinical symptoms with radiological findings of pneumonia.
c) Severe, individual adults meet any of the following criteria: 1) Respiratory distress (>=30 breath per min); 2) Oxygen saturation below 93 % at rest; 3) Arterial partial pressure of oxygen (PaO2)/fraction inspired oxygen (FiO2) at or below 300 mmHg, which needs to be adjusted for altitude if individuals live at high altitude above 1000 meters. Infant and children have different diagnostic criteria (37).
d) Critical, cases meet any of the following criteria:1) respiratory failure and requiring medical ventilation; 2) shock; 3) with other organ failures that require to be in intensive care unit (ICU).

The clinical development of COVID-19 can be divided into several stages with multiple outcomes. Exposure to the pathogen is required for an individual to be infected with SARS-CoV-2. Strictly speaking, factors associated with the likelihood of exposure to the pathogen may determine the risk of COVID-19 in general populations. Usually, medical and healthcare professionals or people working in service sectors are at high risk of being infected with SARS-CoV-2, because of their increased likelihood of exposure to confirmed or potential sources of infections. Population-based surveys showed that healthcare workers, outpatients, and hotel staff workers have the highest seropositivity of IgG (33, 35).

2.2 Asymptomatic cases

An individual's immune system may modify the course of clinical development after infection with the pathogen. When susceptible people (i.e., without specific immunity) are infected with SARS-CoV-2, the host body may initiate the innate immune system and then activate the adaptive immune response to fight against the viral infection. This immune response may result in some people eradicating the viral pathogen and developing protective immunity without any symptoms. Such individuals who are infected but remain asymptomatic, are unlikely to be identified as cases unless a related test is performed, such as viral testing or a later, antibody seropositive. At present, a case of asymptomatic infection is defined as an individual with viral testing positive for SARS-CoV-2, but without any noted clinical symptoms and abnormalities of chest radiological imaging (37). In the early stage of infection with SARS-CoV-2, some people with viral testing positive are likely presymptomatic but may develop symptoms later. Therefore, a follow-up should be conducted for those presymptomatic people to determine if an individual is really an asymptomatic case.

Asymptomatic infection may account for a considerable proportion of the infection or cases with COVID-19. In the outbreak on the Diamond Princess Cruise ship, 46.69% of cases were asymptomatic (**Table 1)**. A review of 16 of 17 reports showed that asymptomatic patients might account for 40-90% of cases (10). These estimates were mostly based on the outbreaks in some special populations, in which some participants may be predominantly younger to middle-aged people such as crew members or in the military. In addition, some infected people may develop mild symptoms, but then soon recover with some routine or no medical treatment. According to the statistics of 44,672 confirmed cases in China, the mild or moderate cases may account for 80.9% of total confirmed cases (38), but it is not clear whether this estimation has included asymptomatic patients.

It should be noted that there are differences between asymptomatic and presymptomatic cases. As defined above, an asymptomatic case is an individual who has nucleic acid testing positive but without any symptoms. Presymptomatic cases are individuals who are the incubation period of the disease and without any symptoms at the time of viral testing but can develop symptoms in the late incubation period. In a point prevalence survey of residents in a nursing home facility (21), 27 of 46 individuals who were testing positive showed no symptoms, but 24 of 27 developed symptoms a few days later, thereby having only a 6.5% asymptomatic rate in the elderly residents. A community-based screening in China identified 178 individuals who were testing positive, and 60 were without any symptoms within 14 days of quarantine (9). However, continued observation found that 23 of 60 individuals developed symptoms, and 37 individuals remained asymptomatic. Some individuals might simply have a more extended incubation period to have an onset of symptoms. So, in this population-based screening of individuals with suspected exposure and quarantine, the asymptomatic rate has been estimated at 20% (37/178). This estimate is supported by a recent nation-wide survey in Spain that 22 to 36% of the seropositive cases were asymptomatic (35).

2.3 Severe cases and comorbidity

As noted previously, symptomatic cases can be classified into mild, moderate, severe, or critically ill. Some patients may first present for care with severe symptoms, leading to immediate hospitalization, and then being diagnosed with COVID-19 through viral testing. This pattern was seen in the early epidemic in many countries or regions where the viral testing capacity was limited, and testing was only performed for individuals with severe symptoms who were suspected of infection. In this setting, most of the identified patients were in severe or critical conditions. In other settings, infected individuals identified based on active viral testing in suspected people, who had close contact with conformed cases with COVID-19, may mostly be mild or moderate cases. China's national statistics estimated that 13.8% were severe and 4.7% were critical cases, while mild or moderate cases accounted for 80% of overall patients (38). Admittedly, these estimates might not have fully considered all asymptomatic patients, which were unknown in community since population-based wide-spread testing was not performed.

Individuals who developed severe and critical cases with COVID-19 predominantly have underlying chronic health conditions. In a clinical study of 1099 patients from a national sample in which severe cases were defined at hospital admission by the American Thoracic Society guideline for community-acquired pneumonia (39), severe cases had about 2- or 3-fold higher likelihood of presenting with diabetes, hypertension, coronary heart disease, 5-fold more likely to have chronic constructive pulmonary disease, but 75% less likely to have hepatitis B viral infection, compared with non-severe patients. Since these comorbidities of cardiovascular disease and hypertension are prevalent and associated with older age (40), the elderly who are infected with SARS-CoV-2 are likely to be severe or critically ill and may have a high rate of case-fatality (41). One must be aware that hospital-based patients are highly selected. Therefore, findings from a hospital-based observational study are likely confounded (42) or be subject to selection bias.

2.4 Clinical and immunological response

Individuals infected with SARS-COV-2 may have a variable degree of severity or not have a clinical response (i.e., clinical symptoms) but can have viral shedding and develop antibodies. The subtype of COVID-19 may have implications for the transmission of SARS-CoV-2. Compared with mild cases, severe cases with COVID-19 tend to have high viral load and a longer viral shedding (43). A recent study (9) showed that patients with viral testing positive and clinical symptoms had a median duration of viral shedding for 19 days (inter quarter range [IQR]:15-26), but 14 days (IQR:9-22 days) in asymptomatic patients. There were no significantly differences in the RT-PCR cycle threshold value in the two target genes tested (ORF1b and N). IgG antibody testing positivity was similar at 83.8% and 81.1% for symptomatic and asymptomatic patients, respectively, but the mean levels of IgG seemed higher in symptomatic patients both in the acute phase and the convalescent phase, which was defined as eight weeks after patients were discharged from the hospitals. More surprisingly, in the followed-up testing (80% response rate), more than 90% of patients had a decline in the level of IgG in the convalescent phase, compared with that in the acute phase. The IgG was expected to produce a long-term immunity to the viral pathogen. This finding is an additional evidence that a herd immunity strategy to combat COVID-19 might be dubious, let alone provides better prognostic outcomes (44); it may also provide information on the viability of developing a vaccine that produces long-term or lifelong immunity.

The study performed by Long et al. provides a systematic examination of cytokine biomarkers in two different types of patients (9). Eighteen serum cytokines were significantly elevated in the symptomatic patients compared with the asymptomatic. The top five cytokines include tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), macrophage colony-stimulating factor (M-CSF), growth-regulated oncogene-alpha (GRO-alpha), granulocyte colony-stimulating factor (G-CSF), and interleukin 6 (IL6), in which IL6 was proposed as an inflammatory marker for severe cases and a poor prognosis of COVID-19. However, compared with non-infected individuals, asymptomatic patients had elevated plasma levels of several other cytokines, including stem cell factor (SCF), IL-13, IL-12, and leukemia inhibitory factor (LIF).

Previous clinical studies of hospital-based patients indicated that the critically-ill patients tend to have increased white blood cells (e.g. neutrophils), lymphopenia, and changes in many other clinical parameters in laboratory tests such as elevated levels of C-reactive protein (39, 45). However, the clinical utility of these parameters is uncertain, since multiple regression analysis showed that they were not significantly associated with the severity or death after adjusted for other covariates. Older age remained significantly associated with critically ill or death (45), which was likely caused by underlying chronic conditions.

3. REGIONAL VARIATION IN CLINICAL PRESENTATION

3.1 Neurological manifestation

The clinical presentation of hospitalized patients seems heterogeneous. Park et al. (46) examined the difference in clinical symptoms and chest CT between patients from nine hospitals of China found that fever was the most frequent symptom (84.8%) but with a big difference (92%,n=338 vs.78%, n=286) in patients between Wuhan and outside Wuhan. Dyspnea was more common among patients in Wuhan than in patients outside human (21% vs. 3.8%). This regional difference was likely due to the overwhelming number of patients relative to the medical facility that may have delayed the hospitalizations in the epicenter of China. Additional heterogeneity in the clinical presentation seems to relate to various neurological manifestations, which acute cerebrovascular disorder, impaired consciousness, cranial nerve manifestation, and autoimmune diseases were often reported in the severe cases with COVID-19 (47).

SARS-CoV-2 might have implications for neurological manifestations. A review of 67 studies showed that SARS-CoV2 and other human coronaviruses are associated with multiple neurological disorders, including polyneuropathy, stroke, and encephalitis (48). Patients with COVID-19 tend to have headaches, myalgia, fatigue and dizziness, and chemosensory dysfunctions, suggesting that the nervous system is involved. It has been known that the viruses of SARS-CoV-2, SARS-CoV, and MERS share the receptor, ACE2, which facilitates the virus entering the host and is expressed in the brain renin-angiotensin system in transgenic mice (49). Mice with a deletion in the *Ace2* gene showed diverse phenotypes, including hypertension (50), likely suggesting that ACE2 may regulate blood pressure or disease involving the autonomous nervous system. It was also recently reported that genetic variants in ACE might modulate the antidepressant treatment response in patients with major depression (51).

3.2 Chemosensory dysfunction

Chemosensory dysfunction was prevalent in patients with milder to moderate COVID-19. In a few related studies (52-58), two larger-sized studies reported a consistently high rate of chemosensory dysfunction at about 80% in patients with mild or moderate COVID-19 in European countries (**Table 2).** However, one study showed that the combined disturbance of olfactory and gustatory function was about 79% (58), isolated olfactory and gustatory dysfunction was 8.9% and 12.1%, respectively (58). Mao et al. (56) examined the neurological manifestations of 214 patients in China and found that olfactory and gustatory dysfunction was 7.1% and 6.3%, respectively. This considerable difference in the chemosensory disturbance between populations may need a formal investigation with rigorous design. Recently, a seroprevalence survey on a national representative sample found that among 7273 individuals with anosmia in Spain, the seropositive rate was 15 to 19%, much higher than a 5% seropositive rate in the country as a while, supporting that chemosensory dysfunction is associated with the infection with SARS-CoV-2.

Table 2 Chemosensory dysfunction in patients with COVID-19 (52-58)

Author	Regions	Study type	n	Anosmia	Dysgeusia
Lechien JR (54)	Europe	Multicenter	417	85.6%	88.0%
Yan CH (53)	US	Single center	59	68%	71%
Luers JC (52)	Germany	Single center	73	74%	69%
Vaira LA(58)	Italy	Multicenter	256	79.3%	79.3%*
Passali GC (57)	Italy	Hospital	NA	25-29%	25-29%
Giacomelli A (55)	Italy	Single center	59	>33.9%	>33.9%
Mao L(56)	Asia	Single	214	7.1%	6.3%

*, for the dysfunction of both olfactory and gustatory, the isolated olfactory disorder was 8.6%, isolated gustatory disorder was 12.1%.

The pathogenesis of chemosensory dysfunction is not clear but might be associated with the receptors to which the viral pathogen SARS-COV-2 binds. *First*, ACE2 is one of the significant receptors for the viral binding. ACE2 inhibitors and angiotensin II blockers may have a side-effect of altered chemo-sensitivity (59, 60), but this side-effect typically disappears after drug discontinuation. Recent evidence shows that the loss of smell might be due to the key genes (ACE2 and TMPRSS2) expressed in non-neuronal support cells, stem cells, and perivascular cells (61). *Second*, SARS-CoV-2 uses sialic acids linked to host cell surface gangliosides (62), a molecule that is highly important in immunology and has been considered for possible therapeutics for neurodegenerative disorders (63). Sialic acid is a fundamental component of the salivary mucin that protects the glycoprotein, conveying gustatory molecules inside the taste pores. When the host is infected with SARS-CoV-2, sialic acid reduction may increase the gustatory threshold (60). Moreover, an In Silico study indicates that the Spike protein of SARS-COV-2 could use a dual strategy by binding ACE2 and the sialic acid receptors of the host cells in the upper airways (64), which might be a possible explanation for the observation of a high rate of disturbance in both olfactory and gustatory function in patients with COVID-19 (58).

In addition, inflammatory responses could contribute to the development of olfactory dysfunction in patients with

COVID-19. Individuals infected with SARS-CoV-2 might increase the production of proinflammatory cytokines in the nasal epithelium, and then undergo nasal olfactory epithelium destruction, which may lead to olfactory dysfunction. A recent study of three cases with anosmia COVID-19 and three healthy controls showed a trend that the IL-1B and TNF-a are elevated in the olfactory epithelium by infection with SARS-CoV-2 (65). However, a further investigation with a larger sample is needed.

3.3 Common symptoms

Clinical manifestation of symptoms can be used for making an early diagnosis of COVID-19, especially when there is limited viral testing availability. Early diagnosis can help initiate timely medical treatment of an individual and prompt preventive health measures to protect susceptible people. However, clinical manifestation varies greatly, depending on how or what the medical information is collected at presentation. Case records may include a systematic review of multiple systems of the human body in a patient, but the collection of detailed information on clinical symptoms often varies with studies. In the following section, we describe the related studies conducted in three significant epicenters of the COVID-19 pandemic, namely China and other Asian countries, the United States, and Europe, where related research is quite active; the selected reports were on clinical manifestations in their respective earliest cohorts of patients, and followed by one large-sample study in each region.

Asia

A study reported clinical presentations in the first 41 patients in Wuhan, China (66). Seventy-three percent of these patients were men, and the median age was 49 years. The most common symptoms at the onset of disease were fever (98%), cough (76%), myalgia or fatigue (44%), and sputum production (28%). About 55% of patients developed dyspnea within a median of eight days (IQR: 5-13), and 63% had lymphopenia. All patients had pneumonia with abnormal imaging on chest CT. Finally, 29% of patients developed acute respiratory distress syndrome (ARDS), 32% were in ICU, and 15% died. This case-fatality rate was relatively high in the first cohort, considering the majority of patients were middle-aged.

Additional clinical studies seemed to report consistent clinical symptoms in patients with COVID-19. One study was based on 214 patients in Wuhan, China (56), 88 severe and 126 non-severe cases, women accounted for 59%, and individuals aged above 50 years were 58%. Another study included 1099 patients in a national sample (39), with the majority being males and a mean age of 47. Both reports showed that fever and cough were the main symptoms (**Figure 1**). Additionally, patients from Wuhan showed more symptoms related to the nervous system (36%), and anorexia (32%), while in the national sample, the more prevalent symptoms were fatigue (38%) and sputum production (34%). In addition, Xu et al. (67) reported 62 patients from seven hospitals in Zhejiang. This cohort of patients seemed relatively younger, with a median age of 41 years, and only one patient was admitted to the ICU. The most common symptoms in this group were cough (81%), fever (77%), expectoration (56%), myalgia or fatigue (52%), and headache (32%). The median duration from exposure to onset of symptoms was four days. All these patients seemed to be relatively mild cases.

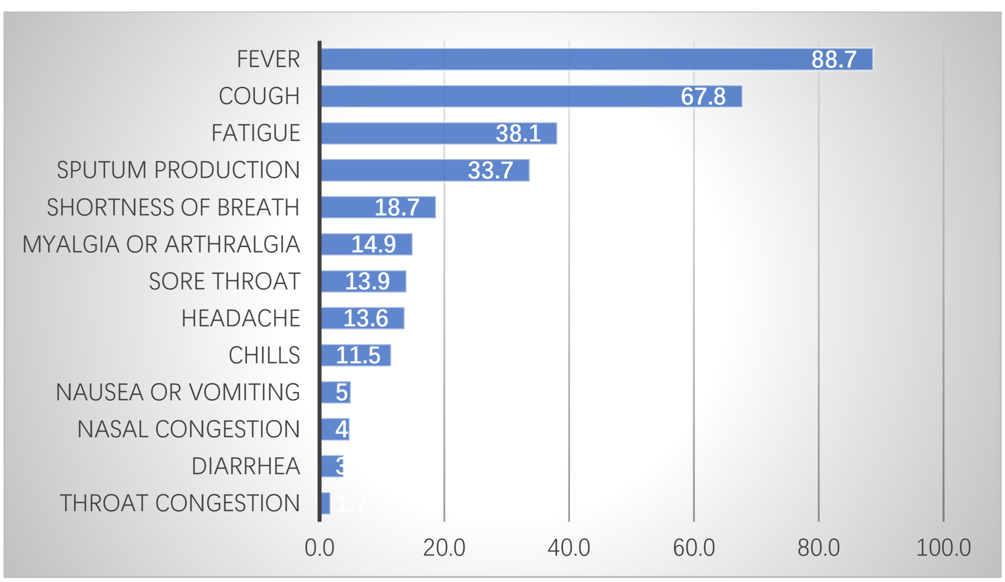

Figure 1 Clinical presentations of 1099 patients with COVID-19 in China (39, 56).

In southeast Asia, Pongpirul et al. reported the first 11 patients hospitalized in Thailand (68). Nine of 11 patients had a cough, malaise, sore throat in the first four days after admissions, and a few patients had a fever (>38 C) in the first two days. Guta et al. (69) reported the first 21 confirmed cases with COVID-19 in India. The mean age was 40 years, 62% were men, and 62% had travel history in the past 30 days, and two-thirds had traveled to Italy. The most common symptoms were fever (43%) and cough (43%), followed by sore throat, headache, and shortness of breath.

In northeast Asia, Korea reported 28 confirmed cases with COVID-19 in hospitalization (70), with a mean age of 40 years (min-max, 20-73 years), and 15 were men. The most common symptoms were cough (29%), sore throat (29%), fever (25%), and headache (25%). The symptomatic rate seemed lower in Korea, likely due to active viral testing strategies, which has been considered a model for other countries actively identifying individuals infected with SARS-CoV-2. Patients are therefore identified early, with milder and fewer symptoms. Kato et al. (71) reported the clinical presentations of 70 patients with COVID-19 in the outbreak on the Diamond Princess Cruise ship, including Japanese (46%), other Asian (34%) and European ancestry (20%), with a median age of 67 years, and 60% of patients had pneumonia (43/70). The common symptoms were fever (64%), cough (54%), fatigue (24%), shortness of breath (17%), and diarrhea (14%).

America

Patients with COVID-19 may show differences in clinical manifestations by age and severity. In the first 12 patients reported in the US (72), all had mild to moderately severe illness, the median age was 53 years, and 67% were men. The most common symptoms were cough (67%), fever (58%), fatigue (42%), and headache (25%). Another study reported 16 hospitalized elderly patients (73), with a median age of 67, and 75% were men. The common symptoms were history of fever (94%), dry cough (88%), dyspnea (81%), and fatigue (50%), which seemed more prevalent than that in the first cohort, likely because of older age.

A clinical study retrospectively analyzed a hospitalized case series of 1000 patients with COVID-19 in New York City (74). These patients were classified into three groups: first seen at the emergency department (n=150), in-hospital (but not in ICU, n=614), and ICU (n=236), with a median age of 63 years (IQR: 50 to 75 years) and 60% were men. This cohort of patients was ethnically diversified, including Hispanic or Latino (24.8%), others (21.6%), not specified (19.2%), Black or African American (18.1%), White (14.4%), and Asian (1.9%). The data shows (**Figure 2**) that cough and fever were the main symptoms (>70%), consistent across three groups of patients, but dyspnea was prevalent (73%) in patients who were in the ICU. Finally, 46% of patients in ICU care died and 14% of others died in hospital.

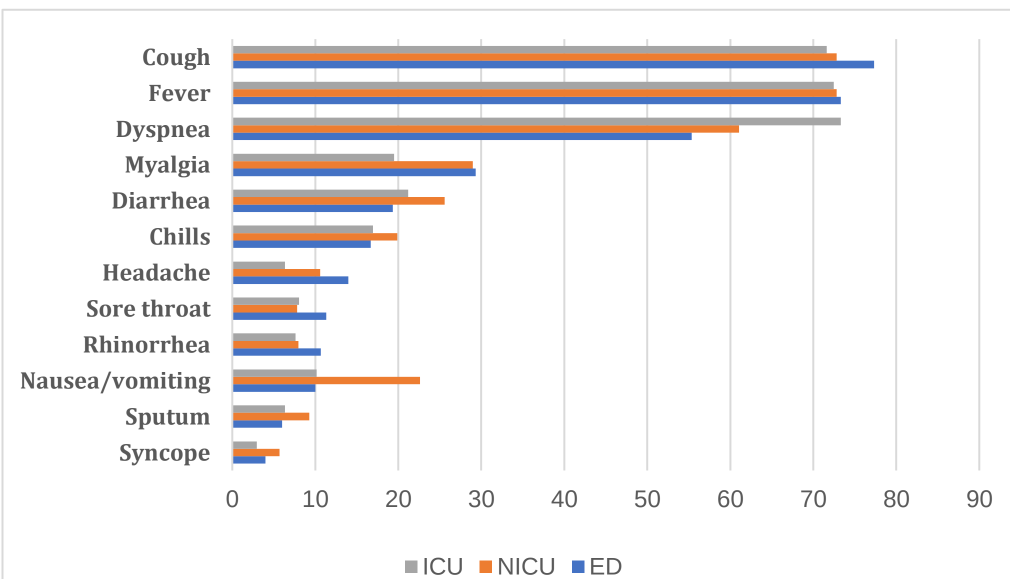

Figure 2 Clinical presentation of 1000 older patients with COVID-19 in New York City, USA

Europe

Two early reports in Europe showed similar clinical symptoms in older adults or the elderly based on each country's first cohort of patients. Colaneri et al. (75) reported the clinical presentations and outcomes of the first cohort of 46 patients with COVID-19 from a single hospital in Northern Italy at the beginning of the outbreak in Europe. Most of the sample were men (65%) and elderly patients (age >65 years) accounted for 54%. The common symptoms were fever (87%), cough (33%), and dyspnea (22%). Tomlins et al. reported the first cohort of 96 patients diagnosed with COVID-19 in the UK (76). The median age was 75 years (IQR: 59-82 years), and 63% were men. The common symptoms were cough (74%), fever (72%) and shortness of breath (43%), myalgia (14%). At the time of the report, 21% of patients died, 43% discharged, and 37% remained in the hospital for treatment.

Later, a large clinical study reported the clinical characteristics of 1420 patients with COVID-19 (40). The study samples covered patients with different groups of age, younger at 15-39 years (55.8%, n=793), middle-aged at 40-59 years (38.3%, n=551), and older at 60 years or above (n=76), and all were mild to moderate cases. The data was collected from 18 hospital centers in five countries in Europe. The clinical symptoms were different between age groups. Interestingly, in the younger age, the major symptoms were loss of smell, nasal obstruction, headache, and rhinorrhea, cough, and myalgia (**Figure 3**), whereas headache, loss of smell, myalgia, cough, and nasal obstruction were the major symptoms in the middle-aged. However, older patients mainly had a fever, loss of appetite, and cough, consistent with those patients with similar age in New York and the other first cohorts in Italy and the UK.

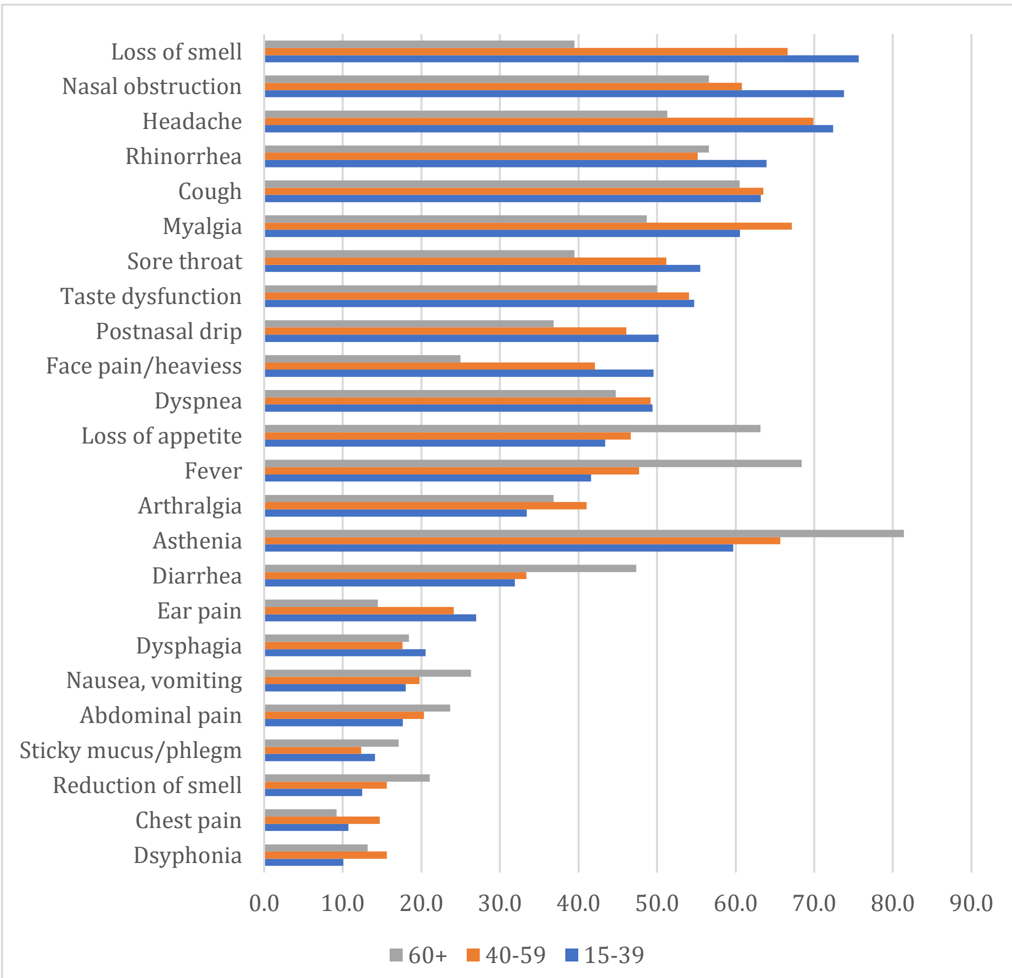

Figure 3 Clinical presentation of 1420 patients with COVID-19 by age in Europe.

Data Source: 18 hospital centers in five countries, including French (Paris, Marseille), Italian (Milan, Verona, Naples, Genova, Florence, and Forli), Spanish (Sevilla, Santiago de Compostela, San Sebastian), Belgian (Mons, Brussels, Charleroi, Saint Ghislain) and Geneva in Swiss.

In summary, the clinical symptoms of patients with COVID-19 vary with age, but in general, fever and cough were two consistent symptoms for older patients. Neurological symptoms are common, particularly in a younger age and those with mild to moderate severity. People with younger age or detected early may have relatively mild and fewer symptoms, predicting a better prognostic outcome. Older patients in the Europe and the US has 20% of death rate (40, 73).

4. POPULATION DISTRIBUTION

4.1 Pregnancy and pregnant women

Pneumonia caused by infectious agents is prevalent and a significant cause of death in pregnant women. During the 1918-1919 influenza pandemic, the case fatality rate was estimated at 27% in pregnant women and was even higher among those in the third trimester (77). Viral infections during the perinatal period are shown to harm the pregnancy outcome and fetal development (78). Wong et al. (79) reported on 12 pregnant women aged 27-44 years and infected with SARS-CoV virus in Hong Kong, consisting of five health workers and seven others in the community. The patients' diagnosis was confirmed with RT-PCR or antibody testing, and chest X-ray or CT evidence for pneumonia. All patients with SARS pneumonia had a fever and myalgia, and others presentations such as malaise (11/12), chills and rigors (11/12), cough (9/12), headache (6/12), lymphopenia (8/12). In addition, three patients (one in the first trimester and 2 in the third trimester) died, four of seven in the first trimester had a spontaneous miscarriage, and four of five women in the third trimester had a delivery through a cesarean section, two women recovered with a continuation of pregnancy but later developed intrauterine growth restriction.

During late gestational weeks, pregnant women infected with SARS-CoV-2 seem to develop fewer severe symptoms and have little evidence of intrauterine infections and maternal-fetal vertical transmission. Chen et al. (80) reported six pregnant patients with COVID-19 in Hubei, aged 25-31, at 38-41 gestational weeks, all patients were in the hospital for delivery and did not have a fever, but some developed a low-degree fever 24 hours after delivery. Five patients had chest imaging that featured ground-glass opacity. No other symptoms and complications were observed in pregnant women and newborns. Another report (81) of three pregnant women with COVID-19, in late gestational weeks in the hospital for delivery, also showed no abnormalities in both mothers and newborns, but one patient developed a low degree of fever before delivery and two after delivery. All three newborns tested negative for the SARS-CoV-2 infection. Also, Chen et al. (82) retrospectively reviewed nine hospitalized pregnant women with COVID-19, all had a cesarean section for delivery in their third trimester, and mothers and newborns did not exhibit any abnormalities; various bio-specimens from mothers and newborns tested for nucleic acids of SARS-CoV-2 showed no evidence for intrauterine vertical transmission. Other reports did not show any complications in pregnant women with COVID-19 and newborns, and all newborns tested negative (83, 84)

However, some pregnant women may develop symptoms and have preterm delivery after being infected with SARS-CoV-2. Savasi et al. (85) reported on 77 hospitalized pregnant women from 12 maternity hospitals in Italy, 14 of whom (18.18%) had severe diseases, and all had higher gestational body mass index and increased heart and respiratory rates. Two-third of 77 patients were in the third trimester, and 84% had symptoms; nine women (13%) had a preterm delivery, and all premature newborns were admitted to the neonatal ICU.

4.2 Infants and pediatric patients

While there is no evidence for maternal-fetal vertical transmission, infants are susceptible to SARS-CoV-2. Infants are likely to be infected through close contact with infected family members. Wei et al. (86) reported nine infants diagnosed with COVID-19 under one-year-old, five of the infants had at least two family members infected with SARS-CoV-2, four had a fever, two had upper respiratory symptoms, and one was asymptomatic. All infected infants were confirmed with at least two tests with positive. Kamali et al. (87) reported a 15-day-old neonate, reportedly, the youngest patient with COVID-19, with fever, lethargy, and respiratory distress without cough but had positive viral testing. All infected infants seemed to have recovered well.

Children accounted for a small proportion of patients with COVID-19, likely due to a reduced likelihood of exposure and not being frequently tested because they tend to be asymptomatic or have milder symptoms. Based on a nation-wide sample of 1011 patients with COVID-19, Guan et al. (88) reported that children under 14 years accounted 0.9% of overall patients. A national sample of 72,314 patients estimated that less than 1% of patients were under ten years of age (89). In the general transmission dynamics of infectious diseases, an infection may start in the community and be transmitted to infants or pre-school children through close contact with family members (90). An infected school-age child can likely spread the infection among other children or cause an outbreak in a school, which seems to have been less likely during the pandemic to date, few school outbreaks with COVID-19 has been reported. The proportion of cases with COVID-19 in children seems lower in China and Italy than those in Australia and Korea (91), likely due to the respective testing policies.

Population-based data suggest that children are less likely to develop COVID-19 after exposure to the pathogens. In a population-based assessment of 1390 children (median age 6.7 years), Lu et al. (23) found that 12.3% of children were infected with SARS-CoV-2 after exposure to persons with confirmed or suspected COVID-19 (**Table 1**). This infection rate in children was lower than the 19% on the Diamond Princess Cruise ship (19) and much lower than 64% in the nursing home facility in Washington State (92). Of note, children are generally likely to have more intensive exposure to infected family members than occurs between passengers on the cruise ship and a community of adult residents.

Of the 171 confirmed cases in children (23), the common symptoms were cough (48%), pharyngeal erythema (46%), and fever (41.5%) during illness; the common radiological findings were bilateral ground-glass opacity (32.7%). Three patients who required ICU care all had co-existing conditions including hydronephrosis, leukemia or intussusception. Additionally, six of 171 patients (3.5%) had lymphopenia, and among 39 (22.8%) asymptomatic cases, 27 children showed no abnormal in chest radiological imaging.

4.3 Asymptomatic and clinical severity in children

Children and adolescents with COVID-19 have less severe in inflammatory biomarkers and clinical manifestations than adults do. The asymptomatic rate is estimated about 30-50%. Bai et al. (93) reported 25 children tested positive for SARS-CoV-2, with a median age of 11 years (range:0.6 to 17 years), and all were secondary to a family cluster outbreak. Of all the children, eight (32%) were asymptomatic, four (16%) were very mild, 13 (52%) were moderate, and all showing abnormal chest CT imaging. The most common symptoms were cough (52%) and fever (24%), and majority of children had normal lab tests, such as white blood cell counts at hospital admission (21/25) and CD8+ T-lymphocyte counts (23/25). Qiu et al. (94) reported on 36 children with COVID-19, 17 (47%) were asymptomatic and 19 were symptomatic, mainly fever, cough, or diarrhea. It had been reported that many children infected with other coronaviruses such as SARS-CoV and MERS-CoV were asymptomatic (95).

Children with COVID-19 seem less likely to be severe or critical cases. Based on the nationally reported cases of 2143 children (731 confirmed and 1412 suspected) with COVID-19, Dong et al. (37) found that the proportion of combined severe and critical cases were at 2.9% in the confirmed cases and 7.4% in suspected cases, and patients from Hubei accounted for 31% and 53.3% of confirmed and suspected cases, respectively.

As described above, there have been a trial version of diagnostic criteria for COVID-19 (18), children might use a different diagnostic criterion. In this study (37), a suspected case with COVID-19 in children was determined when having any two of the following criteria: 1) fever or respiratory or digestive symptom or fatigue, 2) lab tests show white blood cell normal or decreased level of lymphocyte count or increased level of C-reactive proteins, and 3) abnormal x-ray imaging. A confirmed case was determined when viral testing positive for SARS-CoV-2, with either RT-PCR or genome sequencing in nasopharyngeal swab or blood sample.

Even when children are critically ill with COVID-19, the fatality rate seems to relatively low. Chao et al. (96) examined the clinical presentations and outcomes of treatment in critically-ill children tested positive for SARS-CoV-2 in a single tertiary children's hospitals in the US, including 67 patients (21 outpatients and 46 in-patients) who aged from one month to 21 years old. Of 13 patients with critically ill and admitted to the pediatric ICU, ten developed acute respiratory distress syndrome (ARDS), four were treated with hydroxychloroquine, six with remdesivir, six with methylprednisolone, and 11 with antibiotics. On day 14, one patient died, and three were still hospitalized, and all others discharged from the hospital.

4.4 Older adults

Older adults seem to have a high risk of developing COVID-19 after being exposed to a confirmed infection. After an index case confirmed at a nursing facility in King County of Washington State in the United States (92), 57 of 89 (64%) residents tested positive 23 days later (**Table 1**).

Older patients are more likely to become severely or critically ill after infection with SARS-CoV-2. Chen et al. (97) examined 203 adult patients and found that the elderly (age>65 years) with COVID-19 had a higher fatality at 34.5% (19/55) than 4.7% (7/148) seen in younger adults, likely because the older people had a higher prevalence of comorbidities with hypertension (38.2% vs. 14.9%), diabetes (21.8% vs. 2.7%), cardiovascular diseases (20% vs. 3.4%), and COPD (12.7% vs. 0.7%). Critical cases were 43.6%, far more common in the elderly than 6.8% in the younger adults. The elderly cases with COVID-19 tend to have abnormal lab tests, including total white blood cell counts above 10000 (18.2% vs. 2.7%), lymphocyte count less than 1000 (81.8% vs. 48.6%), and interleukin 6 more than 7 (40% vs. 14.9%). In France, as of March 15, 2020, people older than 75 years accounted for 20% of confirmed cases but 79% of the deaths (98).

4.5 Sex difference

Sex difference has been observed in the prognostic outcomes in patients with COVID-19. Meng et al. (99) reported a noted difference in death rate between males (11/86, 12.8%) and females (6/82, 7.3%) based on 168 consecutive severe patients, and there were also significant differences between males and females in the symptom of headache (7% vs. 19.5%), neutrophils/lymphocyte ratio (4.2 vs. 3.1), and mean level of C-reactive protein (59.5 vs. 28.7). According to the mortality surveillance system, males had a significantly higher excessive mortality in Italy across all age groups from younger to the elderly (100), especially in the north of Italy.

The immune response to SARS-CoV-2 are different by sex in patients with COVID-19. In patients with mild or moderate COVID-19 (101), males tend to have an elevated levels of plasma innate immune cytokines, chemokines, and monocytes, while female patients tend to mount a more robust T-cell activation. Males and females differ in their immune response to a foreign antigen or autoimmune response, which is mediated by differences in the innate and adaptive immune responses of males and females (102). It has been argued that the sex difference in the susceptibility to COVID-19 is likely caused by the sex difference in innate immunity, steroid hormones and genes related to immune response on X-chromosomes, which can explain that women infected with SARS-CoV-2 to have a lower level of viral load and inflammation, along with a higher level of activation in immune cells and antibody production (103).

In addition, a sex bias has been noted for disease susceptibility to the predecessor coronaviruses caused the disease of SARS and MERS (104). In an animal mouse model (105), male mice were shown to have an enhanced susceptibility to infection with severe acute respiratory syndrome coronavirus (SARS-CoV) than female mice, particularly at advanced age. The enhanced susceptibility is associated with increased virus titer, vascular leakage, and alveolar edema, which are concurrent with more accumulated inflammatory monocyte macrophages (IMM) and neutrophil in the lungs of male mice. Also, female mice treated with estrogen receptors antagonists had increased mortality upon infection with SARS-CoV, suggesting that estrogen signaling may have a protective effect on mice.

Of note, recent reports are showing that women are more likely to be infected than men are (106), because of a upregulated ACE2 caused by estrogen and some genes on chromosome X that are incompletely silenced. It is important to note that the sex difference was not observed in the seroprevalence that was based on a large national representative sample in Spain (35). Therefore, the observed sex differences in risk of death and infection need to be investigated with an enhanced rigor of the study, to rule out that the effects caused by potential confounding factors or selection bias, especially that both gender and sex may affect the chance of exposure and the underlying chronic health conditions unequally.

4.6 Occupation

Occupation may affect the risk of developing COVID-19 likely due to the chance of exposure. Healthcare and medical workers are at high risk of exposure to the infected people and therefore are at increased risk of acquiring infection with SARS-CoV-2. Two weeks after the first confirmed case with COVID-19 in the Netherlands, 127 cases were reported. However, nine of 127 cases were healthcare workers from two Dutch hospitals, and eight of them did not have any travel history (107). This evidence may have led to a cross-sectional survey conducted in these two teaching hospitals (107). Among 1353 of 9705 healthcare workers reported fever or respiratory symptoms, 86 (6.4%) were confirmed with COVID-19, but only three had histories of being exposed to an inpatient who was a confirmed case of COVID-19.

China reported 1688 healthcare workers with a confirmed diagnosis of COVID-19 (38). Most cases (60%) were in Wuhan, probably due to the overwhelming outbreak that occurred earlier. Severe and critical cases accounted for 38.9% of patients in Wuhan as of early January of 2020; the rate of severe and critical cases seem to reduce over time (**Table 3**). Liu et al. (108) reported 30 medical and health professionals with COVID-19 in one hospital, and the common symptoms were cough (83.33%), fever (76.7%), fatigue (70%), headache (53%), and dyspnea (47%).

Table 3 Confirmed and severe cases with COVID-19 in medical workers by three different locations (38).

	Wuhan			Hubei			China		
	N	SC	%	N	SC	%	N	SC	%
Jan 1-10	18	7	38.9	1	1	100.0	1	1	100.0
Jan 11-20	233	52	22.3	48	8	16.7	29	1	3.4
Jan 21-31	656	110	16.8	250	29	11.6	130	10	7.7
After Feb 1	173	22	12.7	95	3	3.2	54	3	5.6
Total	1080	191	17.7	394	41	10.4	214	15	7.0

Hubei, after excluding Wuhan; China, after excluding Hubei; N, Number of confirmed cases; SC, severe and critical cases.

Likely, other occupations in the public service sectors such as hotel workers may also be more likely to be exposed to a source of infection and may have a higher likelihood of developing COVID-19. In the US, the healthcare workers' infection rate was 7.3%, compared with 0.4% in non-healthcare workers (20). This is consistent with that in a recent national seroprevalence survey in Spain where healthcare workers had the highest infection rate at 10% (35), compared with 5% overall.

5. CASE FATALITY

Fatality can assess the severity and challenges that a disease may cause and the urgency for developing treatment strategies. The case fatality of COVID-19 is the proportion of the cumulative number of deaths over the number of cases identified or reported as of a specific time point. One must be cautious when comparing the fatality rate across countries, because several factors determine the fatality calculation. First, viral testing policy, new case identification, demographics (e.g., the proportion of the elderly, the prevalence of chronic health conditions), and public transportation system are important determinants of fatality. Second, the causes of death classification may be a factor in estimating the case-fatality rate, particularly, some people who died during the pandemic had significant underlying health conditions. In addition, the variation in fatality rate may depend on the country's strategies for prevention, healthcare system, capacity for medical care, and the overall capability of a region as a whole in response to the epidemic.

The case-fatality rate varies significantly around the world**.** As of June 7, 2020, 65 countries reported at least 6000 cases with COVID-19 (https://coronavirus.jhu.edu/). The countries with the highest fatality (**Table 4**) were Belgium (16.2%), France (15.3%), Italy (14.4%), United Kingdom (14.1%), Netherland (12.6%), Mexico (11.7%), Spain (11.2%) and Sweden (10.4%), notably all the countries except Mexico are in Europe, where is known to have an older population structure. The US reported a fatality rate of 5.5%, followed by China (5.51%), Japan (5.38%), Brazil (5.34%), Iran (4.8%), and Germany (4.78%). Different factors in each country may determine these comparatively low fatality rates.

Table 4 Number of confirmed cases, deaths, and fatality by country as of June 7, 2020

Rank	Country	Cases	Death	Fatality
1	Belgium	59,226	9,595	16.20
2	France	191,102	29,158	15.26
3	Italy	234,998	33,899	14.43
4	United Kingdom	287,621	40,625	14.12
5	Netherlands	47,780	6,032	12.62
6	Mexico	117,103	13,699	11.70
7	Spain	241,550	27,136	11.23
8	Sweden	44,730	4,659	10.42
9	Ecuador	43,120	3,621	8.40
10	Canada	97,176	7,877	8.11
11	Algeria	10,154	707	6.96
12	Ireland	25,201	1,679	6.66
13	Romania	20,479	1,333	6.51
14	Switzerland	30,965	1,921	6.20
15	Indonesia	31,186	1,851	5.94
16	Sudan	6,081	359	5.90
17	US	1,938,931	110,481	5.70
18	China	84,187	4,638	5.51
19	Japan	17,039	917	5.38
20	Brazil	672,846	35,930	5.34
21	Denmark	12,148	589	4.85
22	Iran	171,789	8,281	4.82
23	Germany	185,750	8,685	4.68
24	Finland	6,981	323	4.63
25	Philippines	21,895	1,003	4.58
26	Poland	26,561	1,157	4.36
27	Portugal	34,693	1,479	4.26
28	Honduras	6,155	250	4.06
29	Austria	16,902	672	3.98
30	Egypt	34,079	1,237	3.63
31	Moldova	9,700	341	3.52
32	Bolivia	13,358	454	3.40
33	Czechia	9,628	327	3.40
34	Guatemala	6,792	230	3.39
35	Colombia	38,149	1,265	3.32
36	Argentina	22,794	664	2.91
37	Ukraine	27,599	796	2.88
38	Nigeria	12,486	354	2.84
39	India	257,506	7,207	2.80
40	Iraq	12,366	346	2.80
41	Norway	8,547	238	2.78
42	Peru	196,515	5,465	2.78
43	Turkey	170,132	4,692	2.76
44	Dominican Republic	19,600	538	2.74
45	Cameroon	7,908	212	2.68
46	Morocco	8,224	208	2.53
47	Panama	16,004	386	2.41
48	Korea, South	11,776	273	2.32
49	Serbia	11,823	249	2.11
50	South Africa	48,285	998	2.07
51	Pakistan	98,943	2,002	2.02
52	Afghanistan	20,342	357	1.75
53	Israel	17,863	298	1.67
54	Armenia	13,130	200	1.52
55	Malaysia	8,322	117	1.41
56	Australia	7,260	102	1.40
57	Bangladesh	65,769	888	1.35
58	Russia	467,073	5,851	1.25
59	Chile	134,150	1,637	1.22
60	Azerbaijan	7,553	88	1.17
61	Kuwait	31,848	264	0.83
62	United Arab Emirates	38,808	276	0.71
63	Saudi Arabia	101,914	712	0.70
64	Belarus	48,630	269	0.55
65	Ghana	9,638	44	0.46
66	Oman	16,882	75	0.44
67	Kazakhstan	12,694	53	0.42
68	Bahrain	14,763	26	0.18
69	Qatar	68,790	54	0.08
70	Singapore	37,910	25	0.07

As older adults have a high risk of developing COVID-19, the population age structure would have a significant impact on the fatality by country. In the early stage, the fatality rate was reported at 2.3% in China, according to the

44,568 confirmed cases as of February 11, 2020. Italy reported a higher fatality of 7.2% in the early stage of the pandemic in that country as of March 17, 2020 (41). When examining the age-specific fatality, we can see that the age-specific case fatality under 70 was similar between China and Italy, but a significant difference in the elderly above 70 **(Figure 5**). The fatality on the Diamond Princess Cruise ship was 13.8% for individuals aged 80 to 89 (109).

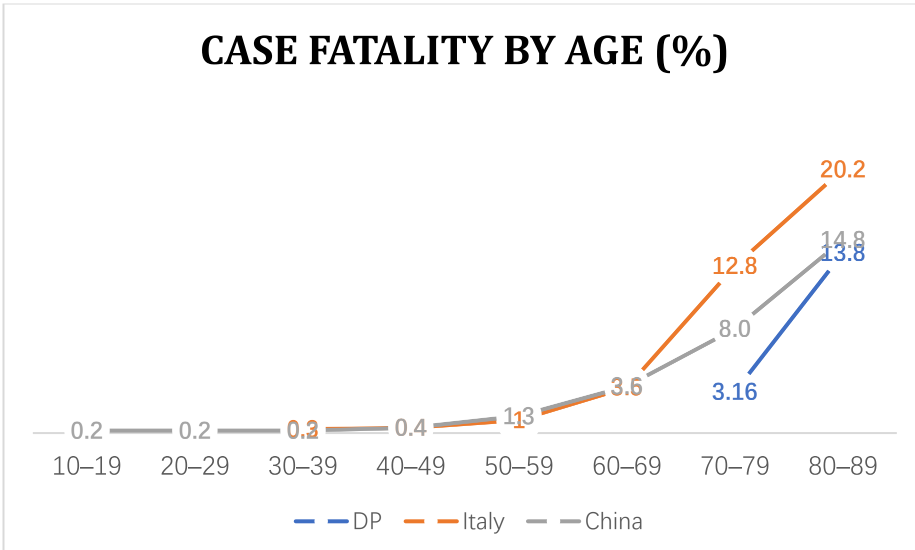

Figure 5. Case fatality of people on Diamond Princess Cruise ship, in Italy and China.

Note: the total number of cases were 301 in Diamond Princess cruse ship, 1625 from Italy as of Macrh 17, 2020, 1023, 1008 deaths from China as of February 11, 2020 (41, 109).

Comorbidities appear to increase the fatality rate in adults significantly. In China, the case-fatality rate was higher in individuals with cardiovascular disease (13.2%), diabetes (9.2%), hypertension (8.4%), chronic respiratory disease (8.2%), and cancer (7.6%), compared with those without chronic conditions (1.4%) (110). This may imply that chronic health conditions or advanced age may increase the fatality risk by about 4- to 9-fold. On this basis, 45% of adults in the US are estimated at an increased risk for COVID-19, which varies from 20% in age of 18 to 29 years to 80% in age of 80+ years due to the presence of chronic health conditions (111).

The case fatality is affected by underlying health conditions in patients with COVID-19, but it also may reflect the capacity and experience of the local health care system in response to the epidemic. According to the 44,672 confirmed cases by the China Centers for Disease Control and Prevention (38), the fatality rate was 2.9% (n=33,367) in patients from Hubei and 0.4% (n=11,305) in patients outside Hubei. Individuals with Wuhan-related exposure had a fatality rate of 2.8% compared with 1.2% in those without Wuhan-related exposure. The fatality rate has continuously declined over time of the epidemic (**Figure 6**). The fatality trend was consistent with that calculated based on all reported patients (n=82,719) and deaths (n=4632) in the country (112). Overall, the fatality rate was higher in Wuhan than in other areas of Hubei and non-Hubei, partly due to the limited capacity for prompt treatment of critical patients in the hospitals at the time when the medical facilities were overwhelmed.

CONCLUSION

This overview has focused on the clinical epidemiology of COVID-19. Because of limited information on population-based studies, some selected clinical studies are hospital-based case series and may not present full clinical spectrum of COVID-19. Besides lacking vaccines and effective therapeutics, the long-term consequence and potential complications caused by SARS-CoV-2 and related treatment remain unknown. A recent study (113), with a post-acute case assessment of 143 hospitalized patients (mean age of 56) with evidence of interstitial pneumonia in the majority (73%), found that 44% of patients reported reduced quality of life and that a considerable number of patients still reported the symptoms of fatigue (53%), dyspnea (44%), joint pain (27%), and chest pain (21%).

SARS-CoV-2 is known to impair multiple organs such as lung, heart, brain, liver, kidney, and coagulation system. In addition to the injuries in the lungs, individuals with COVID-19 can suffer from significant cardiovascular complications (114-116) including myocardial injury, myocarditis, ventricular arrhythmias, acute myocardial infarction, and venous and atrial thromboembolic events, which are very prevalent in hospitalized patients and those requiring ICU care (116).

The infection with SARS-COV-2 may have long-term consequences (117) because the inflammatory response may have broad implications for aging and neurodegenerative disorders. Coronaviruses display neurotropic and microinvasive pathologies (118), and such access to the central nervous system may have further implications for neurological disorders. All these complications may require additional treatment or rehabilitation for individuals who have been infected with SARS-CoV-2 and with severe cases. Undoubtedly further basic, clinical, and public health studies are required to provide effective treatment and prevention.

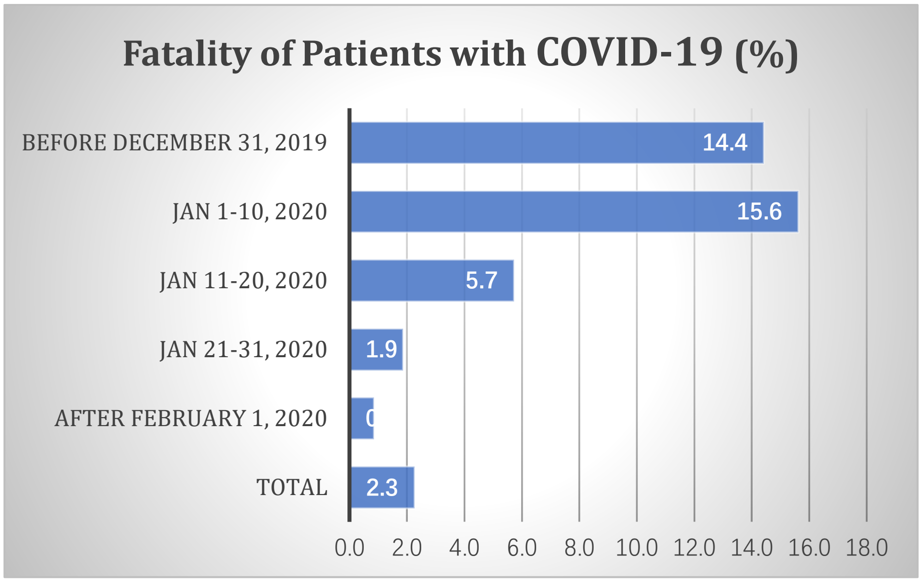

Figure 6. Case fatality of patients with COVID-19 in the early stage of epidemic in China. *Data Source*: Total 44568 cases and 1008 death from China CDC weekly (38).

CONFLICT OF INTERESTS

The authors have no conflict of interests regarding the publication of this article.

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