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Review Article

Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths

Chih-Cheng Lai [a], Yen Hung Liu [b], Cheng-Yi Wang [b], Ya-Hui Wang [c], Shun-Chung Hsueh [d], Muh-Yen Yen [e,f], Wen-Chien Ko [g], Po-Ren Hsueh [h,i,*]

[a] *Department of Internal Medicine, Kaohsiung Veterans General Hospital, Tainan Branch, Tainan, Taiwan*
[b] *Department of Internal Medicine, Cardinal Tien Hospital and School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan*
[c] *Medical Research Center, Cardinal Tien Hospital and School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan*
[d] *Department of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[e] *Section of Infectious Diseases, Taipei City Hospital, Taipei, Taiwan*
[f] *Department of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan*
[g] *Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[h] *Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[i] *Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*

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Abstract Since the emergence of coronavirus disease 2019 (COVID-19) (formerly known as the 2019 novel coronavirus [2019-nCoV]) in Wuhan, China in December 2019, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), more than 75,000 cases have been reported in 32 countries/regions, resulting in more than 2000 deaths worldwide. Despite the fact that most COVID-19 cases and mortalities were reported in China, the WHO has declared this outbreak as the sixth public health emergency of international concern. The COVID-19 can present as an asymptomatic carrier state, acute respiratory disease, and pneumonia. Adults represent the population with the highest infection rate; however, neonates,

* Corresponding author. Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, Number 7, Chung-Shan South Road, Taipei, 100, Taiwan.
E-mail address: hsporen@ntu.edu.tw (P.-R. Hsueh).

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Acute respiratory disease;
Wuhan pneumonia

children, and elderly patients can also be infected by SARS-CoV-2. In addition, nosocomial infection of hospitalized patients and healthcare workers, and viral transmission from asymptomatic carriers are possible. The most common finding on chest imaging among patients with pneumonia was ground-glass opacity with bilateral involvement. Severe cases are more likely to be older patients with underlying comorbidities compared to mild cases. Indeed, age and disease severity may be correlated with the outcomes of COVID-19. To date, effective treatment is lacking; however, clinical trials investigating the efficacy of several agents, including remdesivir and chloroquine, are underway in China. Currently, effective infection control intervention is the only way to prevent the spread of SARS-CoV-2.

Introduction

In December 2019, an outbreak of pneumonia due to unknown cause occurred in Wuhan, China and rapidly spread throughout the country within 1 month. The pathogen of this disease was confirmed as a novel coronavirus by molecular methods and was initially named as 2019 novel coronavirus (2019-nCoV); however, the World Health Organization (WHO) announced a new name on February 11, 2020 for the epidemic disease: Corona Virus Disease (COVID-19). To date, COVID-19 has affected people in more than 28 countries/regions, including Taiwan, and has become a global threat.[1–4] In addition, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses has renamed the virus, which was provisionally named 2019-nCoV, as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) based on phylogeny, taxonomy, and established practice.[5] Prior to this, on January 30, 2020, the WHO declared the COVID-19 outbreak as the sixth public health emergency of international concern; therefore, this outbreak constitutes a public health risk through the international spread of disease and requires a coordinated international response. Increased dissemination of information through use of the internet is associated with increased transmission of information from all geographical regions and across disciplines regarding recognition of SARS-CoV-2 and COVID-19[6]; nevertheless, important factors associated with COVID-19, specifically age and sex distribution, incubation period, clinical features, and optimal treatment, remain uncertain. Therefore, herein, we performed a literature review, focusing on the epidemiological characteristics and clinical manifestations of COVID-19, including asymptomatic carrier state, acute respiratory disease (ARD), and pneumonia.

Severity of COVID-19

COVID-19 was defined as the respiratory disease caused by SARS-CoV-2 that emerged in China in 2019 (https://www.who.int/westernpacific/emergencies/covid-19). The clinical manifestations of COVID-19 are protean, which include asymptomatic carrier, ARD, and pneumonia of varying degrees of severity. First, asymptomatic cases were diagnosed based on positive viral nucleic acid test results, but without any COVID-19 symptoms, such as fever, gastrointestinal, or respiratory symptoms, and no significant abnormalities on chest radiograph[7,8] However, the transmission of COVID-19 through asymptomatic carriers via person-to-person contact was observed in many reports.[4,7,9,10] Second, patients with ARD defined as laboratory-confirmed COVID-19 cases had respiratory symptoms; however, chest computed tomography (CT) did not reveal signs of pneumonia.[11] Third, patients with pneumonia defined as COVID-19 cases had both respiratory symptoms and pneumonia on chest radiograph. This category includes severe pneumonia — either respiratory rate $\geq$30/minute, $SpO_2 \leq 93\%$, or $PaO_2/FiO_2 \leq 300$ mmHg, and a critical condition, characterized by respiratory failure requiring mechanical ventilation, shock, or other organ failure requiring ICU management.[8]

Epidemiology

As of February 21, 2020, data from the WHO revealed altogether 76,769 cases of COVID-19.[1] Thirty-two countries or regions have reported confirmed cases, including mainland China, Japan, Singapore, Hong Kong Special Administrative Region (SAR), Thailand, South Korea, Taiwan, Australia, Malaysia, Germany, Vietnam, the United States, Macao SAR, the United Arab Emirates, Canada, France, the Philippines, the United Kingdom, Italy, India, Russia, Finland, Sweden, Sri Lanka, Cambodia, Nepal, Spain, Belgium, Iran, Egypt, Israel, and Lebanon. In addition, 643 cases were found in international conveyance — Diamond Princess. China has the largest number of patients with COVID-19 (n = 75,543), followed by South Korea (n = 204), Japan (n = 93), and Singapore (n = 85). To date, the reported number of deaths is 2247 and only 11 occurred outside of mainland China, including two each in Hong Kong Special administrative regions (SAR), Iran, and Diamond Princess, and one each in Taiwan, South Korea, Japan, Philippines, and France. However, asymptomatic patients or patients with mild COVID-19 symptoms may not seek health care, nor receive diagnosis, which leads to underestimation of the burden of COVID-19.

Age and sex

Initially, most reported COVID-19 cases in Wuhan were adult patients; however, all of these cases had pneumonia.[12–14] Their median or mean ages were 55.5, 49.0, and

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56 years in three separate studies.[12–14] A similar finding was observed in two recent non-peer-reviewed studies: one study with 1099 patients from 552 hospitals in 31 provinces in China, in which the median age was 47.0 years, and 55.1% of the patients were between the ages of 15–49 years; and a second study that included 4021 confirmed cases in 30 provinces of China, in which the mean age was 49 years and 50.7% of patients were between the ages of 20–50 years.[11,15] Both these studies included ARD and pneumonia cases.[11,15] Similarly, the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team in China reported that 66.7% (n = 29,798) of 44,672 cases of COVID-19 of varying degrees of severity were between 20 and 60 years of age.[8] In Korea, Ryu et al. found that the initial 15 cases were aged between 25 and 62 years.[16] Regarding elderly patients infected with SARS-CoV-2, one study showed that 14.6% (6 in 41) of patients were aged ≥65 years,[13] while another study showed that 15.2% (15 in 99) patients were aged ≥70 years, among pneumonia cases.[12] In addition, two non-peer-reviewed studies showed only 153 (15.1%) patients were elderly patients aged ≥65 years,[11] and 407 (10.1%) patients were aged >70 years.[15] According to the recent China CDC report,[8] 12.0% (n = 5326) of patients were aged ≥70 years. Regarding children with COVID-19, nine (0.9%) patients aged 0–14 years were found in only one study,[11] while 14 (0.35%) patients were aged ≤10 years in another study.[15] The largest study in China showed that 0.9% (n = 416) of patients were aged <10 years.[8] Further, Wei et al. reported that nine infants under 1 year of age were infected with SARS-CoV-2 in China.[8] Regarding patient sex ratio, male sex comprised more than half of the cases in most COVID-19 studies[11–14] and the proportion of males ranged from 51.4% to 73.2%.[8,11–14,16]

Initially, approximately half of the cases had Huanan seafood market exposure and animal-to-human transmission was suspected.[12,13] However, fewer cases had exposure to this seafood market and an increasing number of cases demonstrated human-to-human transmission.[11,17] Fortunately, no evidence was found for intrauterine infection caused by vertical transmission in women who contracted COVID-19 pneumonia in late pregnancy.[18] In addition to family cluster infections due to human-to-human transmission,[19] nosocomial spread of SARS-CoV-2 is a serious concern. Indeed, one study in a Zhongnan hospital of the Wuhan University showed 29.0% (n = 40) were medical staff and 12.3% (n = 17) contracted COVID-19 during hospitalization.[14] Two other studies showed that 2.1% (n = 23) and 3.8% (n = 1716) of patients were health workers.[8,11]

Risk factors

Although the risk factors of COVID-19 remain unclear, many studies reported that a significant proportion of patients had underlying conditions.[8,11–14] For patients with SARS-CoV pneumonia, Chen et al. showed that 50.5% (n = 51) of patients had chronic medical illness, namely cardiovascular and cerebrovascular diseases (40.4%).[12] Among 1099 patients with SARS-CoV-2 ARD, Guan et al. showed that 23.2% (n = 255) of patients had at least one coexisting disorder, and hypertension was the most common underlying disease (14.9%), followed by diabetes mellitus (7.4%).[11] Another large study on COVID-19 cases of varying degrees of severity also showed that hypertension was the most common underlying disease (n = 2,683, 12.8%), followed by diabetes mellitus (n = 1,102, 5.3%), and cardiovascular disease (n = 873, 4.2%).[8] Moreover, patients with severe COVID-19 were more likely to have comorbidities than those with non-severe diseases (37.6% vs. 20.5%, $p < 0.001$).[11] A similar trend was observed in another study of 138 hospitalized patients with SARS-CoV-2 pneumonia, in which 46.4% (n = 64) of patients had comorbidities and the intensive care unit (ICU) patients were more likely to have underlying diseases compared to non-ICU patients (72.2% vs. 37.3%, $p < 0.001$).[14]

In summary, these studies disclosed several significant findings. First, although most patients with COVID-19 were middle-aged adults, elderly patients and children also contracted COVID-19. Second, there is a higher prevalence of men with COVID-19 than that of women; however, further studies are warranted to confirm this finding. Third, health care workers and hospitalized patients could be infected by SARS-CoV-2 in the hospital setting. Finally, at least 20% of COVID-19 cases had underlying diseases, and more severe cases were more likely to have comorbidities than non-severe cases.

Incubation period

It is essential to know the incubation period, the time elapsing between the moment of exposure to an infectious agent and the appearance of signs and symptoms of the disease, for infection control and guidance for the duration of isolation. Initially, Li et al. used the data on exposure among 10 confirmed cases in Wuhan to estimate the mean incubation period, which was 5.2 days (95% confidence interval [CI], 4.1–7.0); the 95th percentile of the distribution was 12.5 days (95% CI, 9.2–18).[20] One estimation based on 125 patients with clearly defined exposure periods in China indicated that the median incubation period was 4.75 (interquartile range: 3.0–7.2) days.[15] Using the travel history and symptom onset of 88 confirmed cases that were detected outside of Wuhan in the early outbreak phase, Backer et al. estimated that the mean incubation period was 6.4 days (95% credible interval: 5.6–7.7), ranging from 2.1 to 11.1 days (2.5th to 97.5th percentile).[21] However, Guan et al., using a large sample for estimation, suggested that the median incubation period was only 3.0 days, but could be as long as 24 days.[11] Overall, these estimates will be refined as more data become available. Detailed epidemiological information based on a larger sample of patients infected with COVID-19 is needed to determine the infectious period of SARS-CoV-2, as well as to determine whether transmission can occur from asymptomatic individuals during the incubation period.

Clinical manifestations

Previous reports revealed that there are asymptomatic patients infected with SARS-CoV-2.[7,8,22] These patients can spread the virus and may represent a population that can

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be easily neglected in epidemic prevention. Therefore, it is important to identify asymptomatic patients with COVID-19. Since these patients are asymptomatic, careful monitoring of the natural course of the disease and contact history may only identify them. Based on the current data, we do not know whether these patients are only asymptomatic initially after contracting the disease or if they are asymptomatic throughout the course of the disease.

Among a pooled analysis of 970 patients with ARD (Table 1) based on two studies with detail clinical characteristics,[11,23] males comprised more than half of the patients and the mean age was 45 years. Hypertension was the most common underlying disease, followed by diabetes mellitus. Approximately two-thirds of patients had cough, but only 44.7% patients had fever. In addition, sputum production was observed in one-third of patients and sore throat was found in 14.0% of patients. Only fewer than 5% of patients had gastrointestinal symptoms, such as diarrhea, nausea, and vomiting. Meanwhile, 32.4% of patients required oxygen therapy, but none required mechanical ventilation. Only one patient with ARD died and the mortality rate was 0.1%.

Table 1 Demographic data, underlying medical conditions, clinical manifestations, and laboratory findings of patients with acute respiratory disease caused by SARS-CoV-2.

	Liu et al.[23] (n = 44)	Guan et al.[11] (n = 926)
Sex		
Male	21 (47.7)	540 (58.3)
Female	23 (52.3)	386 (41.7)
Age, year	39.8 (17.1)	45.3 (17.3)
Smoking	2 (4.5)	120 (13.0)
Comorbidities		
Hypertension	6 (13.6)	123 (13.3)
Diabetes mellitus	2 (4.5)	53 (5.7)
COPD	2 (4.5)	6 (0.6)
Chronic liver disease	NA	22 (2.4)
Chronic kidney disease	NA	5 (0.5)
Malignancy	NA	7 (0.8)
Presentation		
Fever	43 (97.7)	391 (42.2)
Cough	25 (56.8)	622 (67.2)
Myalgia/fatigue	23 (52.3)	133 (14.4)
Headache	18 (40.9)	124 (13.4)
Sputum production	16 (36.4)	306 (33.0)
Sore throat	6 (13.6)	130 (14.0)
Chills	6 (13.6)	99 (10.7)
Diarrhea	5 (11.4)	31 (3.3)
Dyspnea	4 (9.1)	139 (15.0)
Nausea or vomiting	3 (6.8)	43 (4.6)
White blood cell, $\times 10^9$/L	4.2 (1.4)	4.9 (1.6)
Neutrophil	2.6 (1.1)	NA
Lymphocyte	1.1 (0.4)	1.1 (0.5)
Treatment		
Oxygen therapy	10 (22.7)	304 (32.8)
Ventilator	0 (0.0)	0 (0.0)
Renal replacement therapy	0 (0.0)	0 (0.0)
ECMO	0 (0.0)	0 (0.0)
Antibiotic therapy	12 (27.3)	493 (53.2)
Antiviral therapy	23 (52.3)	313 (33.8)
Outcome		
Discharged	3 (6.8)	50 (5.4)
Remained hospitalized	41 (93.2)	875 (94.5)
Died	0 (0.0)	1 (0.1)

Data are n (%), n/N (%), and mean (SD).
COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; NA, not available.

Among a pooled analysis of 468 patients with pneumonia (Table 2) based on five studies with detailed description of clinical features of the disease,[11–14,23] male sex comprised 60.3% of patients and the mean age was 53 years. Approximately one-fifth of patients reported smoking history. Hypertension was the most common underlying disease (20.5%), followed by diabetes mellitus (14.4%). Additionally, 76.3% of patients had fever and 70.5% of patients presented cough. Furthermore, dyspnea and sputum production were observed in approximately one-third of patients. Moreover, 8% and 6% of patients had nausea/vomiting or diarrhea, respectively. In all, 70.9% of patients required oxygen therapy, and 28.8% required mechanical ventilation. Moreover, 5.1% and 3.1% of patients required renal replacement therapy and extracorporeal membrane oxygenation, respectively. The overall mortality was 8.2% (n = 37); however, 313 (66.9%) patients remained hospitalized.

Furthermore, patients with pneumonia were older, with a higher prevalence of smoking history, more underlying diseases, and were more likely to have fever, myalgia/fatigue, dyspnea, headache, and nausea/vomiting compared to patients with ARD (all $p < 0.05$) (Table 3). In addition, pneumonia cases presented a higher white blood cell count and neutrophil count, but had a reduced leukocyte count compared to ARD cases. Serum procalcitonin levels of $\geq$0.5 ng/mL were found in 6.1% (6/99),[12] 7.7% (3/39),[13] to 13.7% (16/117),[11] among SARS-CoV-2 pneumonia patients reported from three studies.[11–13] Moreover, patients with pneumonia were more likely to require oxygenation therapy, mechanical ventilator, renal replacement, and extracorporeal membrane oxygenation, and received more antibiotics and antiviral therapy than patients with ARD. Finally, pneumonia was associated with a higher mortality rate than ARD ($p < 0.0001$).

Image

Based on the findings of 1099 ARD cases of COVID, only 14.7% (n = 162) of patients had an abnormal chest radiograph.[11] In contrast, 840 (76.4%) patients had abnormal and diverse chest CT images, in which ground-glass opacity (GGO) was the most common abnormality (n = 550, 65.5%), followed by local patchy shadowing (n = 409, 48.7%), and interstitial abnormalities (n = 143, 17.0%). In addition, 505 (50.1%) had bilateral involvement.[11] The predominance of GGO and bilateral involvement in chest CT is consistent with previous studies.[24–26] In contrast, other types of abnormalities, such as cavitation, pleural effusion, and lymphadenopathy, were not found.[24,27] As the disease progressed, follow-up CT showed enlargement and

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Table 2 Demographic data, underlying medical conditions, clinical manifestations, and laboratory findings of patients with pneumonia caused by SARS-CoV-2.

	Huang et al.[13] (n = 41)	Chen et al.[12] (n = 99)	Wang et al.[14] (n = 138)	Liu et al.[23] (n = 17)	Guan et al.[11] (n = 173)
Sex					
Male	30 (73.2)	67 (67.7)	75 (54.3)	10 (58.8)	100 (57.8)
Female	11 (26.8)	32 (32.3)	63 (45.7)	7 (41.2)	73 (42.2)
Age, year	49.3 (13.0)	52.7 (46.7)	55.3 (19.9)	54.3 (29.9)	52.3 (19.2)
Smoking	3 (7.3)	NA	NA	2 (11.8)	38 (22.0)
Comorbidities					
Diabetes mellitus	8 (19.5)	NA	14 (10.1)	3 (17.6)	28 (16.2)
Hypertension	6 (14.6)	NA	43 (31.2)	6 (35.3)	41 (23.7)
COPD	1 (2.4)	1 (1.0)	4 (2.9)	3 (17.6)	6 (3.5)
Chronic kidney disease	NA	NA	4 (2.9)	NA	3 (1.7)
Chronic liver disease	1 (2.4)	NA	NA	NA	1 (0.6)
Malignancy	1 (2.4)	1 (1.0)	10 (7.2)	NA	3 (1.7)
Presentation					
Fever	40 (97.6)	82 (82.8)	136 (98.6)	17 (100.0)	82 (47.4)
Cough	31 (75.6)	81 (81.8)	82 (59.4)	14 (82.4)	122 (70.5)
Sore throat	NA	5 (5.1)	24 (17.4)	4 (23.5)	23 (13.3)
Dyspnea	22 (53.7)	31 (31.3)	43 (31.2)	6 (35.3)	65 (37.6)
Myalgia/fatigue	18 (43.9)	11 (11.1)	96 (69.6)	12 (70.6)	99 (57.2)
Sputum production	11 (26.8)	NA	37 (26.8)	11 (64.7)	61 (35.3)
Headache	3 (7.3)	8 (8.1)	9 (6.5)	3 (17.6)	26 (15.0)
Diarrhea	1 (2.4)	2 (2.0)	14 (10.1)	1 (5.9)	10 (5.8)
Nausea or vomiting	NA	1 (1.0)	19 (13.8)	2 (11.8)	12 (6.9)
White blood cell, $\times 10^9$/L	6.9 (4.9)	7.5 (3.6)	4.7 (2.2)	4.6 (1.5)	4.3 (2.5)
Neutrophil	5.7 (4.3)	5.5 (3.7)	3.3 (2.2)	3.3 (2.0)	NA
Lymphocyte	0.8 (0.4)	0.9 (0.5)	0.8 (0.4)	0.9 (0.3)	0.8 (0.3)
Treatment					
Oxygen therapy	27 (65.9)	75 (75.8)	106 (76.8)	10 (58.8)	114 (65.9)
Ventilator	14 (34.1)	17 (17.2)	32 (23.2)	5 (29.4)	67 (38.7)
Renal replacement therapy	3 (7.3)	9 (9.1)	2 (1.4)	NA	9 (5.2)
ECMO	2 (4.9)	3 (3.0)	4 (2.9)	NA	5 (2.9)
Antibiotic therapy	41 (100.0)	70 (70.7)	NA	14 (82.)	139 (80.3)
Antiviral therapy	39 (95.1)	75 (75.8)	124 (89.9)	11 (64.7)	80 (46.2)
Outcome					
Discharged	28 (68.3)	31 (31.3)	47 (34.1)	0 (0.0)	5 (2.9)
Remained hospitalized	7 (17.1)	57 (57.6)	85 (61.6)	10 (58.)	154 (89.0)
Died	6 (14.6)	11 (11.1)	6 (4.3)	NA	14 (8.1)

Data are n (%), n/N (%), and mean (SD).
COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; NA, not available.

consolidation of single GGO, an enlarged fibrous stripe, and solid nodules. In contrast, a small fibrous stripe, as well as the resolution of GGO, may be associated with improvement in the patient's condition.[28,29]

Treatment

Several reports suggest the following as potential drug candidates, although the clinical effectiveness of these drugs have not yet been evidenced for COVID-19: lopinavir/ritonavir (Kaletra®), nucleoside analogs, neuraminidase inhibitors, remdesivir, umifenovir (arbidol), DNA synthesis inhibitors (such as tenofovir disoproxil, and lamivudine), chloroquine, ACE2-based peptides, 3C-like protease (3CLpro) inhibitors, novel vinylsulfone protease inhibitor, teicoplanin, and Chinese traditional medicine (such as ShuFengJieDu or Lianhuaqingwen capsules).[30–39] The effectiveness of remdesivir is more evident in the literature to date; indeed, it appears to be the most promising drug for COVID-19. In fact, an *in vitro* study demonstrated that the 50% effective concentration (EC_{50}) of remdesivir against nCoV-2019/BetaCoV/Wuhan/WIV04/2019 in Vero E6 cells was 0.77 μM, and the 90% effective concentration (EC_{90}) was 1.76 μM.[31] However, only one case in the US showed a clinical response to remdesivir, although the viral load appeared to decline at the time of initiating remdesivir (cycle threshold from 18–20 to 23–24).[33] Subsequently, two large clinical trials, NCT04252664 (https://clinicaltrials.gov/ct2/show/NCT04252664) for mild/moderate COVID-19 and NCT04257656 (https://clinicaltrials.gov/ct2/show/NCT04257656) for severe

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Table 3 Comparison among demographic data, underlying medical conditions, clinical manifestations, and laboratory findings of patients with acute respiratory disease and pneumonia caused by SARS-CoV-2.

	Acute respiratory disease, N = 970	Pneumonia, N = 468	*p* value
Sex			0.3824
Male	561 (57.8)	282 (60.3)	
Female	409 (42.2)	186 (39.7)	
Age, years	45.1 (17.3)	53.1 (27.6)	**<0.0001**
Smoking	122 (12.6)	43/231 (18.6)	**0.0166**
Comorbidities			
Hypertension	129 (13.3)	96/369 (26.0)	**<0.0001**
Diabetes mellitus	55 (5.7)	53/369 (14.4)	**<0.0001**
Chronic liver disease	22/926 (2.4)	2/214 (0.9)	0.2883
COPD	8 (0.8)	15 (3.2)	**0.0007**
Chronic kidney disease	5/926 (0.5)	7/311 (2.3)	**0.0143**
Malignancy	7/926 (0.8)	15/451 (3.3)	**0.0004**
Presentation			
Fever	434 (44.7)	357 (76.3)	**<0.0001**
Cough	647 (66.7)	330 (70.5)	0.1467
Sputum production	322 (33.2)	120/369 (32.5)	0.8143
Myalgia/fatigue	156 (16.1)	236 (50.4)	**<0.0001**
Dyspnea	143 (14.7)	167 (35.7)	**<0.0001**
Headache	142 (14.6)	49 (10.5)	**0.0291**
Sore throat	136 (14.0)	56/427 (13.1)	0.6506
Nausea or vomiting	46 (4.7)	34/427 (8.0)	**0.0170**
Diarrhea	36 (3.7)	28 (6.0)	0.0503
White blood cell, $\times 10^9$/L	4.9 (1.6)	5.3 (3.2)	**0.0109**
Neutrophil	2.6 (1.1)/44	4.4 (3.3)/295	**<0.0001**
Lymphocyte	1.1 (0.5)	0.8 (0.4)	**<0.0001**
Treatment			
Oxygen therapy	314 (32.4)	332 (70.9)	**<0.0001**
Ventilator	0 (0.0)	135 (28.8)	**<0.0001**
Renal replacement therapy	0 (0.0)	23/451 (5.1)	**<0.0001**
ECMO	0 (0.0)	14/451 (3.1)	**<0.0001**
Antibiotic therapy	505 (52.1)	264/330 (80.0)	**<0.0001**
Antiviral therapy	336 (34.6)	229 (48.9)	**<0.0001**
Outcome			
Discharged	53 (5.5)	111 (23.7)	**<0.0001**
Remained hospitalized	916 (94.4)	313 (66.5)	**<0.0001**
Died	1 (0.1)	37/451 (8.2)	**<0.0001**

Data are n (%), n/N (%), and mean (SD).
COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; NA, not available.
Bold indicates $p < 0.05$.

COVID-18, were initiated in China, with an estimated end date in early April 2020. In these two trials, the 10-day regimen of remdesivir was 100 mg once daily for 9 days after the loading of 200 mg on day 1.[34] Chloroquine is another promising drug.[35,36] An *in vitro* study on the time-of-addition assay in Vero E6 cells demonstrated that chloroquine functioned at both entry and at post-entry stages of COVID-19, and the EC90 value of chloroquine against the 2019-nCoV was 6.90 μM.[31] In addition, passive immunization therapy and the use of interferon could theoretically be helpful, but to date there is no evidence to validate this hypothesis.

Systemic corticosteroid was administered in 18.6%–44.9% patients in order to control the inflammatory response caused by SARS-CoV-2 in 4 initial large studies.[11–14] However, corticosteroid therapy could be associated with delayed MERS-CoV RNA clearance (adjusted hazard ratio, 0.35; 95% CI, 0.17–0.72; $p = 0.005$) for critically ill patients with MERS,[40] and early corticosteroid treatment could be associated with higher subsequent plasma RNA load of SARS-CoV for adults with SARS.[41] Moreover, corticosteroid-associated psychosis and diabetes were observed in the treatment of SARS.[42,43] Thus, clinical use of corticosteroids in the treatment of COVID-19 was not recommended in the interim, unless indicated for another reason.[44,45]

Outcomes

According to WHO reports, the overall mortality rate for COVID-19 was 2.9% (2247 in 76,769),[1] however, the mortality rate varied among studies. Initial studies reported that the mortality rate associated with SARS-CoV-2 pneumonia ranged from 11%[12] to 15%,[13] but later studies revealed that the mortality rate was between 1.4%[11] and 4.3%.[14] The differences in the results among different studies could be due to the study population, as well as the differences among the studies in terms of disease severity. In addition, these results need further clarification, since a majority of the reported mortality was all-cause mortality, not COVID-attributed mortality; also, the outcome measurement was incomplete because many patients remained hospitalized before publication of the results.

Several prognostic factors of COVID-19 were also reported in these studies. In one study using the MulBSTA score system,[46] which includes six indices, namely multilocular infiltration, lymphopenia, bacterial co-infection, smoking history, hypertension, and age, revealed that these indices were poor prognostic factors.[12] Another study showed similar findings, and specifically the indicators of disease severity, including oxygenation, respiratory rate, leukocyte/lymphocyte count, and the chest imaging findings, were associated with a poor clinical outcome.[11] Moreover, a substantially elevated case-fatality rate included the following patient characteristics: male sex, ≥60 years of age, baseline diagnosis of severe pneumonia, and delay in diagnosis.[15] Similarly, the China CDC reported that patients aged ≥80 years had the highest case fatality rate, 14.8%, among different age groups, and the case

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fatality rate of patients in which disease severity was critical was 49.0%.[8] Together, these findings suggest that old age and increased disease severity could predict a poor outcome.

In this stage of lack of effective drugs, the implementation of infection control interventions and traffic control bundle to effectively limit droplet, contact, and fomite transmission is the only way to slow the spread of the SARS-CoV-2. These infection control interventions include early identification of cases and their contacts, avoiding close contact with people with airway symptoms, appropriate hand washing, and enhanced standard infection prevention, and control practices in the healthcare setting.[47,48]

Uncertain issues

Although information on COVID-19 has increased rapidly since the emergence of SARS-CoV-2, many issues remain unresolved. First, the clinical manifestation of COVID-19 ranges from the asymptomatic carrier state to severe pneumonia; however, most early reports only showed the findings of SARS-CoV-2 pneumonia, in which the ratio of male patients was much larger than that of female patients, there were no pediatric cases, and the mortality rate was high.[12–14] Subsequent to the publication of the studies of patients with only ARD or mild pneumonia, we found the ratio of male-to-female patients decreased, children or neonates could contract COVID-19, and the mortality rate declined compared to that of previous reports.[8,11] However, whether children were less susceptible to SARS-CoV-2, or their presentation was mostly asymptomatic or difficult to detect, remains unclear.[49] In addition, most studies, especially those with a large patient population, were conducted in China, and the study of asymptomatic carriers was limited. More studies are needed to clarify the epidemiologic characteristics of COVID-19 and to identify the risk and prognostic factors of patients infected with SARS-CoV-2. Second, Zou et al. reported that the viral load detected in asymptomatic patients was similar to that found in symptomatic patients; however, the viral loads from patients with severe diseases were higher than those in patients with mild-to-moderate presentations. Moreover, higher viral loads were detected in the nose than in the throat.[50] As there is a concern of virus spread due to severe cough induced by performing a throat swab, nasal swab may be a relatively safe and sensitive alternative to collect the respiratory specimen of patients with COVID-19. However, this study involved a population of only 18 patients, including one asymptomatic patient.[49] In addition, every test has its own limitation and sensitivity/specificity; however, the studies investigating the performance of current diagnostic methods of SARS-CoV-2 among different COVID-19 populations, including asymptomatic carriers, ARD, and pneumonia, are lacking. The false positive and negative rates of each diagnostic tool among patients with COVID-19 presenting varying degrees of severity of the disease remain unknown. This type of information is important for screening patients with COVID-19 and to aid isolation and infection control strategies. Finally, since SARS-CoV-2 can be detected in the asymptomatic individual, the prophylactic or pre-emptive use of effective anti-viral agents to reduce the viral load and decrease the risk of virus spread from asymptomatic carriers may help to control the spread of COVID-19.

Conclusions

This review provides updated information about COVID-19. SARS-CoV-2 can affect patients of all ages. COVID-19 can present as asymptomatic carriage, ARD, and pneumonia. Severe cases are more likely to be older and to have increased underlying comorbidities compared to mild cases. Age and disease severity can be correlated with the outcomes of COVID-19. To date, effective treatment for SARS-CoV-2 is lacking; however, two trials investigating the clinical efficacy of remdesivir are underway in China. Currently, effective infection control intervention is the only way to prevent the spread of SARS-CoV-2.

Declaration of competing interest

The author declares no conflict of interests.

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