



## REVIEW

# Clinical features of COVID-19 and SARS epidemics. A literature review

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## Keywords

COVID-19 • SARS-CoV-2 • SARS-CoV • SARS • Clinical features

## Summary

SARS-CoV-2, responsible for the current pandemic, is a novel strain of the Coronaviridae family, which has infected humans as a result of the leap to a new species. It causes an atypical pneumonia similar to that caused by SARS-CoV in 2003. SARS-CoV-2 has currently infected more than 9,200,000 people and caused almost 480,000 deaths worldwide. Although SARS-CoV-2 and SARS-CoV have similar phylogenetic and pathogenetic characteristics, they show important differences in clinical manifestations.

We have reviewed the recent literature comparing the characteristics of the two epidemics and highlight their peculiar aspects. An analysis of all signs and symptoms of 3,365 SARS patients

and 23,280 COVID-19 patients as well as of the comorbidities has been carried out. A total of 17 and 75 studies regarding patients with SARS and COVID-19, respectively, were included in the analysis. The analysis revealed an overlap of some symptoms between the two infections. Unlike SARS patients, COVID-19 patients have developed respiratory, neurological and gastrointestinal symptoms, and, in a limited number of subjects, symptoms involving organs such as skin and subcutaneous tissue, kidneys, cardiovascular system, liver and eyes.

This analysis was conducted in order to direct towards an early identification of the infection, a suitable diagnostic procedure and the adoption of appropriate containment measures.

## Introduction

The Coronavirus Disease 2019 (COVID-19) outbreak represents a serious public health problem that is straining health systems around the world.

As of June 25<sup>th</sup>, 2020, as many as 9,296,202 cases of COVID-19 have been confirmed and 479,133 patients have died globally, according to the World Health Organization (WHO) [1].

In addition to confirmed cases, there are also suspected cases of COVID-19 which should be promptly tested where possible in order to immediately implement isolation measures and trace contacts. In a context of uncertainty, since the infection is caused by a new and still little understood virus for which no vaccines or specific medications are currently available, the recognition of clinical signs and symptoms as well as clinical features in affected subjects is of vital importance. Severe Acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is the latest known virus that has spread worldwide. Viruses, particularly RNA viruses, have high mutation rates and are characterized by a particularly high virulence and transmissibility and can cause more or less severe infections. To date, SARS-CoV-2 appears to be highly virulent and easily transmissible, it can affect many organs of the body and manifest in many ways [2]. Applying the lessons learned from past epidemics can help us to better address the new challenges. The previ-

ous Coronavirus (CoV) epidemic that hit the world population was Severe Acute Respiratory Syndrome (SARS) in 2003 which manifested as an atypical pneumonia with reported symptoms including fever, dry cough, dyspnea, diarrhea and sore throat [3]. The modes of transmission and the clinical features of the two infections initially seemed to be superimposable. Both infections are transmitted through respiratory droplets or secretions and by close person-to-person contact [4]. In some cases, COVID-19 patients do not show the typical signs of respiratory infections but have unusual symptoms or only very mild symptoms [5].

Furthermore, the presence of underlying health conditions increases the risk of developing severe illness [6]. Therefore, early recognition of suspected cases through the evaluation of clinical and symptomatic characteristics should represent the first tool that can direct towards the most appropriate diagnostic and therapeutic strategies and that can help interrupt the chains of transmission of the virus.

This review is a comparative analysis of the characteristics of the SARS and COVID-19 epidemics and summarizes in detail the clinical signs and symptoms as well as the comorbidities of subjects with SARS and COVID-19, analyzed in studies published worldwide to date.

## Virological characteristics

This century has been characterized by the presence of several zoonotic coronavirus epidemics spread from southern China, which have infected humans as a result of genetic recombination that have allowed to make the leap to a new species [7]. Phylogenetic analysis revealed that SARS-CoV-2, like Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), belongs to the genus *Betacoronavirus* of the *Coronaviridae* family, exhibiting about 79% sequence identity with SARS-CoV and sharing the same receptor-binding domain (RBD) structure [8]. The complete genome sequence contains 29,751 bp for SARS-CoV [9] and 29,811 bp for SARS-CoV-2 [10]. The mutation rate in the SARS-CoV genome is similar to that of other coronaviruses and moderate compared to other RNA viruses [11], unlike that of SARS-CoV-2 which appears to have a higher evolutionary rate estimated (mean  $2.15 \times 10^{-6}$  subs/site/day corresponding to  $7.8 \times 10^{-4}$  subs/site/year) (Tab. I) [12].

## Epidemiological characteristics

The first cases of atypical pneumonia of unknown etiology of SARS were reported on November 16<sup>th</sup>, 2002 in Guangdong Province, China and then spread mainly among household contacts and healthcare workers [13]. It was only after 300 people became infected and 5 died, on February 11<sup>th</sup>, 2003, that the Chinese Ministry of Health informed the WHO of an outbreak of acute respiratory syndrome [14]. At the end of February 2003, the infection was transmitted to Hong Kong by an infected doctor and in a few months the infection spread to other countries of the world mainly through intercontinental flights. The epidemic spread rapidly to Hong Kong, Taiwan, Singapore and Hanoi, mostly related to the movement of people during the Chinese New Year holiday season [15].

The number of reported cases increased exponentially, prompting the WHO to issue a global alert about the disease on March 13, 2003 (Tab. I) [14].

The outbreak was contained in July 2003 with a total of 8,098 cases and 774 deaths in 32 countries, with an estimated overall case fatality rate (CFR) estimate of 9.6%. In mainland China, the country where the epidemic started and where the greatest number of cases was reported, there were 5,327 infected people and 349 deaths [16].

A number of hospitals in various regions of China were designated to treat SARS patients only. The outbreak came under control and the number of new cases gradually declined. On June 24<sup>th</sup>, 2003, Beijing was removed from the WHO's list of areas with recent local transmission of SARS [15].

The country most affected after China was Hong Kong with 1,755 cases and a mortality rate of 17%. The most affected country outside Asia was Canada with 251 cases and 43 deaths. The European region was slightly affected, with 33 total cases and one death in France. In Italy, only 4 cases

Tab. I. Summary of virological and epidemiological characteristics of SARS-CoV and SARS-CoV-2 infections.

Characteristics	SARS-CoV	SARS-CoV-2
First occurrence	Nov. 16, 2002 in Foshan, Guangdong	Dec. 07, 2019 in Wuhan, Hubei
Global alert declaration (WHO)	March 13, 2003	Jan 30, 2020
Pandemic declaration (WHO)	-	March 11 <sup>th</sup> , 2020
Genome	RNA	RNA
Length, bp	29,751	29,811
Mutation rate RNA	$0.80-2.38 \times 10^{-3}$ subs/site/year	$7.8 \times 10^{-4}$ subs/site/year
	Moderate	High
Mode of transmission	Respiratory droplet	Respiratory droplet
	Contact	Contact
	-	Fecal-oral (?)
	-	Airborne (?)
Incubation period (median)	4.0 days (95% CI: 3.6-4.4)	5.1 days (95% CI: 4.5-5.8)
R0	2-4	1.4-7.23
Asymptomatic rate	2.3-13%	5-8%
Case fatality rate	9.6%	5.1%

SARS-CoV: severe acute respiratory syndrome; SARS-CoV-2: coronavirus disease-2019; bp: base pairs; R0: basic reproduction number; CI: confidence interval.

have been observed [17]. The epidemic was declared ended on July 5<sup>th</sup>, 2003 [14].

Another global epidemic is currently underway which started on December 7<sup>th</sup>, 2019, the day when the first positive COVID-19 case was detected.

The first cases of pneumonia of unknown origin were found in China, connected to those who frequent the wholesale market of seafood and wet animals located in Wuhan, in the province of Hubei, assuming also in this case a zoonotic source [18]. A new coronavirus, named SARS-CoV-2, was isolated from the epithelium of these patients. It then spread, through person-to-person transmission in family homes and hospitals, outside Hubei Province in China to many countries across the world. The family of the causative agent of this outbreak as well as the country where this epidemic started are the same as those of SARS [19].

The announcement of this epidemic was provided by the Wuhan government to the WHO on January 3<sup>rd</sup>, 2020, after the involvement of 27 persons and no deaths [20]. Following a rapid spread in China and around the world, on January 30, 2020, the International Health Regulations Emergency Committee of the WHO declared the outbreak a Public Health Emergency of International Concern (PHEIC) [21].

About 40 days after the declaration of the global emergency, with over 118,000 cases in 114 countries and territories worldwide and 4,291 deaths, on 11 March 2020, WHO announced the state of pandemic (Tab. I). The last time the WHO used the label was on June 11, 2009 for the H1N1 flu, known as "swine flu", which spread across the world, whereas the 2002-2004 SARS outbreak was never declared a pandemic.

Since the end of December 2019 and as of June 25<sup>th</sup>, 2020, the infection has been detected in all countries causing more

than 9,200,000 confirmed cases and almost 480,000 deaths, with an overall CFR estimate of 5.1% (Tab. I).

At present, in China there are 85,119 confirmed cases and 4,647 deaths. The virus initially spread exponentially in China and in the Western Pacific Region, exceeding 100,000 cases. In the last few months, the situation seems to have stabilized in China and in other Asian countries after weeks of rigid control measures. In the last month, new cases have emerged, causing fear of a second epidemic wave.

The European Region has exceeded 2,600,000 infections, reaching nearly 200,000 deaths, and is currently the most affected Region with a higher lethality rate (7.5%). America has over 4,600,000 infections and 230,000 deaths, followed by the Eastern Mediterranean Region with almost 970,000 confirmed cases and 22,000 deaths.

The countries worst affected in terms of number of infected people are the United States of America (USA) and the Brazil with 2,329,463 and 1,145,906 cases, respectively, followed by the Russian Federation, the United Kingdom, Peru e Chile with 613,994, 306,866, 260,810 and 254,416 cases, respectively [1]. The country with the highest number of COVID-19 deaths is the USA where 120,955 have lost their lives, with an average lethality of 5.2%. Belgium and United Kingdom are currently the worst affected countries in terms of the case fatality rate (15.9 and 14.0%, respectively) [1].

## Transmission

Both viruses are transmitted from human to human via droplets generated by coughing and sneezing, through exposure to fomites and through direct contact of mucous membranes (eyes, nose and mouth).

Whether the infection can be transmitted by the oral or conjunctival routes has not yet been demonstrated. However, SARS-CoV2 has been detected in tears [22], similar to SARS-CoV [23]. Although there is a low prevalence of SARS-CoV-2 in the tear fluid of patients, it cannot be excluded that the infection could be transmitted via the eyes [24].

The role of fecal-oral transmission for SARS-CoV is still unknown. Although some coronaviruses are known to be spread by the fecal-oral route [25], there is currently no evidence that this mode of transmission plays a key role in SARS [3]. There is still limited knowledge regarding fecal-oral transmission of SARS-CoV2, although Chen Y et al. have demonstrated the presence of SARS-CoV-2 RNA in the feces of COVID-19 patients suggesting that, in addition to respiratory and body contact, fecal-oral transmission is a potential route for SARS CoV-2 infection [26]. In a meta-analysis, SARS-CoV-2 RNA was detected in 48.1% of the stool samples derived from a cohort of patients with COVID-19 and persisted even after respiratory samples were negative (Tab. I) [27].

In spite of the fact that the data on intrauterine vertical transmission are scarce, there is little, if any, clinical or serologic evidence suggestive of SARS-CoV and SARS-CoV-2 transmission from pregnant mothers to newborn

infants [28, 29]. Contact with infected droplets on a surface can be a source of infection, too [3, 30]. Van Doremalen et al. found that SARS-CoV-2 can remain viable and infectious in aerosols for 3 hours and on surfaces up to days. The stability of this virus is similar to that of SARS-CoV [30]. This study has also shown that the virus is most stable on plastic and stainless steel with viable virus detected up to 72 hours in the absence of any intervention. Viruses lose their infectivity after exposure to common disinfectants such as Clorox, 75% ethanol and fixatives such as formaldehyde and paraformaldehyde [31, 32]. Careful attention should also be paid to asymptomatic cases whose role in viral transmission is still controversial. During the SARS epidemic, some studies reported the absence of asymptomatic cases, while, where reported, the incidence of asymptomatic cases corresponded to 13% of all SARS-positive cases [33]. The rate of asymptomatic or mild infections of COVID-19 ranges between 5 and 78% (Tab. I) [34, 35]. Asymptomatic SARS infection was associated with lower SARS antibody titers and the transmission from asymptomatic patients appeared to play no or only a minor role [33].

SARS-CoV viral load in upper respiratory tract secretions was low in the first 5 days of illness, then increased progressively and peaked early in the second week, which helped reduce more effectively the infection transmission in the first days of illness [36].

In a study, Zou L et al. showed that the viral RNA levels in people with COVID-19 appear to be higher soon after symptom onset compared with later in the illness [37], which suggests that transmission is more likely to occur at an earlier stage of infection even when symptoms are relatively mild. The high rate of asymptomatic infections is often the result of a long incubation period. The median incubation period for COVID-19 is estimated to be 5.1 days, (95% CI: 4.5 to 5.8) [38], slightly longer than for SARS-CoV (4.0 days, 95% CI: 3.6-4.4) (Tab. I) [39]. The incubation period for SARS in children and adolescents was 2-10 days, with a mean of 6.4 days (95% CI: 5.2-7.7) [39]. The average incubation period for COVID-19 in children is 6.5 days (95% CI: 4,6-8,4), with a range from 2 to 10 days [40]. The interval during which an individual with COVID-19 is infectious is still uncertain.

The transmissibility of SARS was determined by a basic reproduction number ( $R_0$ ) of approximately 3, with values oscillating between 2 and 4, consistent with a disease spread by direct contact or larger virus-laden droplets that travel only a few meters rather than by lighter airborne particles [3, 41]. Some studies have estimated the mean  $R_0$  for COVID-19 to range from 1.4 to 7.23 (Tab. I) [2].  $R_0$  is used when there is a dynamic infectious disease and the population is not vaccinated, and it is usually estimated on the basis of the growth rate of the number of cases. The estimated values of  $R_0$  were lower in the early phase of the epidemic. They subsequently increased during the other phases of the epidemic and then returned to the initial levels [42].

Therefore, COVID-19 can be considered as a highly transmissible disease compared with SARS. Epidemiological factors, such as the ability to recognize



the infection at an early stage, the measures of social distancing adopted, the access to public health resources can cause considerable variations of this parameter.

## Pathogenesis and clinical features

SARS-CoV and SARS-CoV2 cause severe acute respiratory syndrome and appear to have the same pathogenesis. Both viruses use the angiotensin-converting enzyme 2 (ACE2) as cell receptor to gain entry into the human cells. The infection is triggered by the binding of the virus spike protein to ACE2 and causes both upper and lower respiratory tract infections [43, 44].

Based on past studies on SARS-CoV, both viruses bind to epithelial cells in the nasal cavity and start replicating. The viruses then propagate and migrate down the respiratory tract along the conducting airways, also becoming clinically manifest [45]. A study reports that SARS CoV-2 has higher affinity for binding than SARS CoV and this contributes to its more efficient infection of humans [46]. About 20% of the infected patients develop severe disease. The virus reaches the gas exchange units of the lung causing a progressive respiratory failure due to alveolar damage, resulting in apoptosis and even cell death [44, 47]. ACE2 receptors are present in the lung alveolar cells, but are also expressed in numerous other organs, in the enterocytes of the small intestine, as well as in the heart, kidney, bile duct, liver, esophagus and testicle, and in arterial and venous endothelial cells and arterial smooth muscle cells. This tissue distribution of ACE2 correlates with the sites of infection and with the pathology [43].

## Signs and symptoms

SARS is characterized as a viral pneumonia with rapid respiratory deterioration [48]. COVID-19 has many clinical features similar to those of SARS but COVID-19 infection presents with a wide spectrum of severity and often with non-specific symptoms. About 80% of patients experience no signs or mild symptoms of disease, 14% have severe clinical manifestations and only 5% critical conditions. Older age and presence of comorbidities appear to be important factors associated with clinical severity of disease [4].

We analyzed the clinical characteristics reported in patients with SARS-CoV and SARS-CoV-2. A total of 17 and 75 studies regarding patients with SARS and COVID-19, respectively, were included in the analysis. Overall, 3,365 patients with SARS-CoV and 38,318 patients with SARS-CoV-2 were analyzed.

The results are detailed in Table II. In the first part of the Table, signs and symptoms of 3,365 SARS patients and 23,280 COVID-19 patients were considered. This analysis revealed an overlap of some symptoms between the two infections. SARS-CoV2 infection presents a greater variety of symptoms and involves several organ systems. SARS-CoV affects a few organs and a limited

number of symptoms are present in a high percentage of the infected subjects. In particular, the most common clinical manifestations were systemic [fever (87.90%), chills (53.52%), and malaise (49.18%)]. In addition, respiratory symptoms [cough (58.31%)], neurological symptoms [headache (44.40%)], and musculoskeletal and connective symptoms [myalgia (40.62%)] were detected. SARS-CoV2, on the other hand, preferentially infects the cells of the respiratory tract, but it also has high affinity for other organs. Therefore, symptomatic patients present a greater variety of symptoms affecting many organs but in a smaller number of subjects. Typical symptoms are respiratory among which cough is the most frequent (62.50%). Other frequent symptoms are: fever (58.9%), myalgia/arthralgia (35.62%), headache (32.48%), shortness of breath/dyspnea (27.46%), and diarrhea (18.52%). Unlike SARS patients, COVID-19 patients have developed numerous other respiratory, neurological and gastrointestinal symptoms, and, in a limited number of subjects, symptoms involving organs such as skin and subcutaneous tissue, kidneys, cardiovascular system, liver and eyes.

## Comorbidities

Seventeen studies have been included in the analysis of comorbidities and risk factors for a total of 3,365 patients with SARS-CoV.

In the 3,365 SARS patients analyzed, the most common comorbidities, present in a very low percentage of subjects, were diabetes (0.21%), cardiovascular disease (0.12%), COPD and chronic liver disease, both present in 0.09% of subjects. A total of 72 studies and 26,650 patients with COVID-19 have also been analyzed. The results showed the most prevalent comorbidities were hypertension (21.00%) and diabetes (15.37%), followed by cardiovascular disease (11.28%). The data also showed numerous COVID-19 infected subjects with hyperlipidemia (10.20%) or obesity (9.77%). Furthermore, diseases of the respiratory system such as COPD and asthma were present in 2.57 and 2.26% of patients, respectively. Chronic kidney disease was also found in 2.02% of patients.

Smoking habits have been reported in 2.75% of patients. There are numerous differences in the prevalence of comorbidities among the studies analyzed. In one recent study conducted, the authors presented the comorbidities of 5,700 patients hospitalized for COVID-19 in the New York City area. The most common comorbidities were hypertension (3,026; 56.6%), obesity (1,737; 41.7%) and diabetes (1,808; 33.8 %) [49]. The data are significantly different from those obtained in other studies from various areas of the world.

Guan WL et al. analyzed the clinical characteristics of more than 1,000 patients from mainland China. The most common comorbidities were hypertension in 15% of patients and diabetes in only 7.4% of patients. No other comorbidities were observed in over 2.5% of the COVID-19 patients analyzed [50].

Tab. II. Clinical features of patients with SARS-CoV and SARS-CoV-2 infections.

Characteristics	N. of studies	SARS-CoV % (95% CI)	N. of studies	SARS-CoV-2 % (95% CI)
<b>Patients, n.</b>	17	3,365	71	23,280
<b>Gender</b>				
Male, n. (%)	17	1,360 (40.4)	67	6,530 (55.8)
Female, n. (%)	17	2,005 (59.6)	67	5,179 (44.2)
<b>Age group</b>				
Children (<18 ys), n. (%)	4	92 (2.7)	15	807 (3.5)
Adults/Older, n. (%)	14	3,273 (97.3)	55	22,374 (96.5)
<b>Systemic/General symptoms</b>				
Fever	17	87.90 (86.80-89.01)	71	58.9 (58.23-59.49)
Fatigue/Malaise	17	49.18 (47.49-50.87)	71	8.91 (8.54-9.27)
Chills	17	53.52 (51.84-55.21)	71	0.96 (0.84-1.09)
Influenza-like	17	30.61 (29.05-32.17)	71	-
Night sweats	17	11.80 (10.71-12.89)	71	-
<b>Respiratory, thoracic and mediastinal symptoms</b>				
Cough	17	58.31 (56.64-59.97)	71	62.50 (61.87-63.12)
Shortness of breath/Dyspnea	17	26.48 (24.99-27.97)	71	27.46 (26.89-28.03)
Sputum production	17	26.54 (25.05-28.03)	71	7.32 (6.99-7.65)
Rhinorrhea/Runny nose	17	2.97 (2.40-3.55)	71	4.90 (4.62-5.18)
Sore throat	17	21.63 (20.24-23.03)	71	3.69 (3.45-3.94)
Acute respiratory distress	17	-	71	0.77 (0.41-0.88)
Nasal congestion/Stuffiness	17	-	71	0.55 (0.46-0.65)
Chest pain	17	1.84 (1.39-2.30)	71	0.34 (0.26-0.41)
Pharyngeal erythema	17	-	71	0.34 (0.26-0.41)
Chest distress	17	-	71	0.31 (0.24-0.38)
Haemoptysis	17	0.68 (0.41-0.96)	71	0.30 (0.23-0.37)
Tachypnea	17	1.58 (1.15-2.00)	71	0.22 (0.16-0.28)
Voice hoarse	17	-	71	0.06 (0.03-0.10)
Coryza	17	15.75 (14.52-16.98)	71	0.03 (0.01-0.05)
Oropharyngeal pain	17	-	71	0.004 (0.00-0.01)
Rhonchi	17	1.10 (0.75-1.45)	71	-
Percussion dullness	17	0.21 (0.05-0.36)	71	-
Pleurisy	17	0.09 (0.00-0.19)	71	-
Wheezing	17	0.03 (0.00-0.09)	71	-
<b>Cardiovascular symptoms</b>				
Cardiac injury	17	-	71	0.12 (0.07-0.16)
Palpitation	17	2.91 (2.34-3.48)	71	0.12 (0.08-0.17)
Tachycardia	17	1.96 (1.49-2.34)	71	0.03 (0.01-0.06)
Shock	17	-	71	0.02 (0.00-0.04)
<b>Gastrointestinal symptoms</b>				
Diarrhea	17	19.82 (18.47-21.17)	71	18.52 (18.12-19.12)
Abdominal pain	17	5.65 (4.87-6.43)	71	6.51 (6.19-6.82)
Vomiting	17	9.30 (8.32-10.28)	71	5.00 (4.72-5.28)
Nausea	17	13.16 (12.02-14.31)	71	4.63 (4.36-4.90)
Anorexia	17	24.07 (22.63-25.52)	71	1.40 (1.25-1.56)
Dehydration	17	-	71	0.03 (0.01-0.05)
<b>Neurological symptoms</b>				
Headache	17	44.40 (42.72-46.08)	71	32.48 (31.88-33.08)
Ageusia	17	-	71	1.89 (1.72-2.07)
Dizziness	17	20.48 (19.11-21.84)	71	0.37 (0.30-0.45)



Anosmia	17	-	71	0.34 (0.26-0.41)
Impaired consciousness	17	-	71	0.27 (0.20-0.33)
Agitation	17	-	71	0.17 (0.12-0.23)
Corticospinal tract signs	17	-	71	0.17 (0.11-0.22)
Dysexecutive syndrome	17	-	71	0.06 (0.03-0.09)
Perfusion abnormalities	17	-	71	0.05 (0.02-0.08)
Acute cerebrovascular disease	17	-	71	0.04 (0.01-0.06)
Guillain-Barré syndrome (GBS)	17	-	71	0.03 (0.01-0.05)
Leptomeningeal enhancement	17	-	71	0.03 (0.01-0.06)
Nerve pain	17	-	71	0.02 (0.00-0.04)
Seizure	17	0.03 (0.00-0.09)	71	0.01 (0.00-0.03)
Ataxia	17	-	71	0.004 (0.00-0.013)
Miller Fisher Syndrome	17	-	71	0.004 (0.00-0.013)
Polyneuritis cranialis	17	-	71	0.004 (0.00-0.013)
Anxiety	17	0.03 (0.00-0.09)	71	-
<b>Kidney symptoms</b>				
Dialysis	17	-	71	0.15 (0.10-0.21)
Kidney injury	17	-	71	0.11 (0.07-0.15)
<b>Musculoskeletal and connective symptoms</b>				
Myalgia/arthralgia	17	40.62 (38.96-42.28)	71	35.62 (35.00-36.23)
Hypodynamia	17	-	71	0.25 (0.19-0.32)
Back discomfort	17	-	71	0.01 (0.00-0.03)
Rigor	17	19.17 (17.84-20.50)	71	-
Neck pain	17	0.09 (0.00-0.19)	71	-
<b>Skin and subcutaneous tissue symptoms</b>				
Itch	17	-	71	0.91 (0.79-1.04)
Maculopapular rash	17	-	71	0.76 (0.64-0.87)
Urticaria	17	-	71	0.33 (0.25-0.40)
Pseudo-chilblains	17	-	71	0.30 (0.23-0.38)
Chickenpox-like vesicles	17	-	71	0.15 (0.10-0.20)
Pain	17	-	71	0.14 (0.09-0.19)
Livedo/necrosis	17	-	71	0.09 (0.05-0.13)
Erythematous rash	17	-	71	0.07 (0.04-0.25)
Burning	17	-	71	0.09 (0.06-0.13)
Rash	17	00.3 (0.00-0.09)	71	0.02 (0.00-0.04)
Cyanosis	17	-	71	0.004 (0.00-0.013)
<b>Eye symptoms</b>				
Conjunctival congestion	17	-	71	0.05 (0.02-0.08)
Vision impairment	17	-	71	0.01 (0.00-0.03)
<b>Hepatic symptoms</b>				
Liver injury	17	-	71	0.37 (0.29-0.45)

**Comorbidities and risk factor**

Characteristics	N. of studies	SARS-CoV % (95% CI)	N. of studies	SARS-CoV-2 % (95% CI)
Patients, n.	17	3,365	72	26,650
<b>Gender</b>				
Male, n. (%)	17	1,360 (40.4)	68	15,163 (58.3)

Female, n. (%)	17	2,005 (59.6)	68	10,860 (41.7)
Cardiovascular diseases	17	0.12 (0.00-0.24)	72	11.28 (10.90-11.66)
Hypertension	17	0.03 (0.00-0.09)	72	21.00 (20.51-21.49)
Cardiac arrhythmia	17	-	72	1.14 (1.01-1.27)
Coronary artery disease	17	-	72	6.43 (6.13-6.72)
Congestive heart failure	17	-	72	2.29 (2.11-2.47)
Cerebrovascular disease	17	0.03 (0.00-0.09)	72	0.89 (0.78-1.01)
Respiratory system diseases	17	-	72	0.58 (0.49-0.67)
Asthma	17	-	72	2.26 (2.08-2.44)
COPD	17	0.09 (0.00-0.19)	72	2.57 (2.38-2.76)
Chronic lung disease	17	-	72	0.81 (0.71-0.92)
Nervous system disease	17	-	72	0.36 (0.29-0.43)
Chronic kidney disease	17	0.06 (0.00-0.14)	72	2.02 (1.85-2.19)
End-stage kidney disease	17	-	72	0.70 (0.60-0.80)
Chronic liver disease	17	0.09 (0.00-0.19)	72	0.67 (0.57-0.67)
Cirrhosis	17	-	72	0.15 (0.10-0.20)
Hepatitis B	17	-	72	0.14 (0.10-0.19)
Hepatitis C	17	-	72	0.01 (0.00-0.02)
Tuberculosis	17	-	72	0.04 (0.02-0.07)
Digestive system disease	17	-	72	0.54 (0.46-0.63)
Hyperlipidaemia	17	-	72	10.20 (9.84-10.56)
Hypercholesterolemia	17	-	72	0.71 (0.61-0.81)
Obesity	17	-	72	9.77 (9.41-10.13)
Diabetes	17	0.21 (0.05-0.36)	72	15.37 (14.93-15.80)
Endocrine system disease	17	-	72	0.51 (0.42-0.60)
Rheumatologic disease	17	-	72	0.02 (0.00-0.04)
Immunosuppression	17	-	72	1.09 (0.96-1.21)
HIV infection	17	-	72	0.18 (0.13-0.23)
Transplant	17	-	72	0.22 (0.16-0.27)
Blood disorder	17	-	72	0.04 (0.01-0.06)
Myelodysplastic syndrome	17	0.06 (0.00-0.14)	72	-
Malignancy	17	0.03 (0.00-0.09)	72	2.22 (2.04-2.39)
Allergic rhinitis	17	-	72	0.39 (0.32-0.47)
Hyoxemia	17	-	72	0.02 (0.00-0.03)
Pregnancy	17	-	72	0.03 (0.01-0.05)
Smoking	17	-	72	2.75 (2.55-2.95)

**Prognosis**

Characteristics	N. of studies	SARS-CoV-1 % (95% CI)	N. of studies	SARS-CoV-2 % (95% CI)
<b>Patients, n.</b>	17	3,365	75	38,318
<b>Gender</b>				
Male, n. (%)	17	1,360 (40.4)	71	15,532 (58.1)
Female, n. (%)	17	2,005 (59.6)	71	11,215 (41.9)
<b>Prognosis</b>				
Hospital admission	17	55.66 (53.98-57.34)*	73	91.60 (91.17-91.83)*
Discharge	17	91.41 (90.46-92.36)*	65	52.53 (51.92-53.15)*



Death

17

5.26 (4.51-6.01)\*

72

7.80 (7.48-8.12)\*

\* At the time of writing reports; for clinical features: 4 studies do not report gender differences, 1 study do not report age group; for comorbidities: 4 studies do not report gender differences; for prognosis: 2 studies do not report hospital admission, 10 studies do not report discharge, 3 studies do not report death.

## Prognosis

Of the 3,365 patients hospitalized for SARS-CoV and the 38,318 patients hospitalized for SARS-CoV-2 that were included in our analysis, 55.66% and 91.60%, respectively, were admitted to hospital.

At the time the reports were written, 91.41% of patients hospitalized for SARS-CoV and only 52.53% of patients with SARS-CoV-2 were discharged.

Based on data from 17 studies on SARS and 72 studies on COVID-19, the percentage of deaths stood at 5.26% and 7.80% for SARS-CoV and SARS-CoV-2, respectively.

## Diagnostic tests

The 2003 pandemic of SARS profiled the ability of modern diagnostic microbiology and molecular biology to identify, isolate and characterize, within weeks, a previously unknown virus. On 10 April 2003, quantitative TaqMan-format assay for SARS-associated coronavirus was published for the first time [51]. Diverse protocols were proposed within the different molecular testing approaches over time. Most conventional polymerase chain reaction (PCR) assays were designed with the Orf1b or nucleoprotein gene for nucleic acid amplification, and SYBR Green based PCR protocol was reported as a benefit to screen samples with sequence variations in the virus [52]. Also, monoclonal antibodies or monospecific polyclonal antibody directed to the nucleocapsid (N) protein were found to be a sensitive and specific test for antigen detection; however, most of these rapid tests have never been exhaustively investigated in prospective cohort studies owed to the short-lived epidemic [48].

Given the current epidemiology and the high risk of transmission, the rapid and accurate identification of the infection is crucial for effective COVID-19 containment. At writing time, real-time PCR molecular assays for detecting SARS-CoV-2 in respiratory specimens are the current reference standard for infection diagnosis. The technique is generally very sensitive and specific and may be used for routine diagnostics of COVID-19 [53]. However, Yong and colleagues showed the ineffectiveness of real-time PCR as the only diagnostic test due to its inability to detect previous infections highlighting the importance of using serological tests as well [54]. Where epidemiological information warns people might have been node of disease transmission, but they had recovered from sickness, SARS-CoV-2 IgG serology allows establishing past infection. In addition, if carried out within the correct timeframe after symptoms onset, serology assays can detect both active

and past infections [55]. Remarkably, the importance of serological tests for epidemiological investigation of COVID-19 cases rapidly emerged in a much more pressing way than in SARS full epidemic happened.

At the end of April 2003, tests to detect antibodies produced in response to the SARS coronavirus infection are under development but not still commercially available. ELISA (Enzyme Linked ImmunoSorbant Assay) test for the detection of IgM and IgG antibodies in serum produced positive results reliably after 21 from the onset of the disease and IFA (Immunofluorescence Assay) test for the detection of IgM produced positive results after about 10 days of illness [56].

Later studies revealed that specific serum antibodies against whole SARS-CoV by indirect immunofluorescence or neutralization tests starts to appear at about day 7 and, while IgM were not detectable after 2 to 3 months, IgG maintained for over one year [57].

The titer of neutralizing antibodies peaked from 20 to 30 days after infection and was sustained for a long time in those who survived, while the neutralizing antibody level of those who died peaked at day 14 and then gradually diminished [58].

In these months, a flood of novel rapid serologic immunoassays designs as long as point-of care technologies are proposed, and a lot of them are commercially available. Despite the considerable role they play, some evidences suggest that many kits currently available are not adequately accurate [59] and several challenges remain, to which we must pay attention. Recognizing the disease, during the acute phase of infection, needs high sensitivity and specificity; cross-reactivity with other viral agents should be weighed; antibody kinetics over time must also be investigated, to determine thresholds of immunity [60]. Both these testings, molecular and serological, are expected to support welfare decision-makers about measures to contain the outbreak.

## Containment measures

During an unpredictable and unprecedented pandemic such as that caused by COVID-19, anxiety and stress – often boosted by the media as well as by the political decisions themselves – alter how people perceive new diseases and their consequent actions. Moreover, whenever decision-making involves risks, individuals can become irrational in several dysfunctional ways [61]. Consequently, the ideal approach to improve decision-making and crisis management should be reducing anxiety and stress through rapid diagnosis [62]



and specific antiviral treatments. However, in the real world, most countries are usually unprepared to face such a pandemic. In particular, during COVID-19, an initial lack of positive control, primers and/or probes as long as a lack of personnel/time and of specific therapies together with a large number of paucisymptomatic and asymptomatic people yielded most policies to shift towards lockdown measures rather than modern laboratory-based testing and consequent quarantine [62, 63]. European countries, for instance, implemented a series of containment measures, ranging from lockdown to an intermediate safe distancing (Italy, France, Spain, Denmark, Norway, Switzerland, Austria, Belgium, UK and Germany), with only one country that has chosen not to adopt lockdown (Sweden) [64]. Most States in the world added in an unprecedented way lockdown measures to the other traditional containment measures adopted during the last epidemics, such as SARS [65]. However, this widespread governance resolution generated new research challenges. Currently, scientific and political institutions do not require any type of comparative study on the risks and benefits before implementing lockdown measures. This happens despite the consequences of these old measures to the overall mental and physical health of the population's remain mostly unexplored [66].

## Conclusions

COVID-19 and SARS are infections with similar phylogenetic and pathogenetic characteristics that primarily affect the respiratory and gastrointestinal systems. The knowledge acquired so far has allowed us to highlight some distinctive features of COVID-19 in comparison to SARS. SARS has a high prevalence of severe illness but with a low infectivity in the first days of illness, before the development of severe illness. Conversely, COVID-19 can be considered as a disease with a lower lethality rate but with high risk of transmission compared to SARS even in the presence of mild symptoms or in the absence of any visible signs of infection.

A rather high percentage of SARS patients had typical symptoms such as fever, cough, chills, headache, fatigue and myalgia. Among the most common symptoms in COVID-19 patients are cough, fever, myalgia, and headache, but there is no highly prevalent symptom such as fever that was detected in almost 90% of the SARS patients analyzed. Gastrointestinal and cardiovascular symptoms seem to be more common in SARS. Based on reports of more than 23,000 COVID-19 cases, numerous other less common and atypical manifestations including neurological symptoms (ageusia, anosmia), dermatologic manifestations and ocular symptoms, have also been identified. In light of this, the detection of fever, cough and shortness of breath as an identification method should be reviewed. In addition, COVID-19 patients exhibit a wide range of comorbidities. Therefore, it is very important to know what signs and symptoms to

look out for and recognize and which diagnostic tests to use for prompt treatment and prevention of further infections.

If clinical manifestations are mild and there is no need to seek medical care, it is very important that symptoms are monitored and national public health measures are followed in order to control the spread of the first epidemic wave in the countries where it is still in place or prevent a further wave of COVID-19.

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## Conflicts of interest statement

The authors declare no conflict of interest.

## Authors' contributions

AZ reviewed the articles related to virological, epidemiological, and transmission aspects; VR investigated the containment strategies; AA examined the diagnostic laboratory tests; MG carried out the analysis of data on clinical features and comorbidities. All authors contributed to the preparation of the manuscript related to their sections and approved the final version to be submitted.

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