

*Review*

# Clinical Characteristics of Coronavirus Disease 2019

## --A Review on Laboratory Tests, Comorbidity, and Complication

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**ABSTRACT**

Coronavirus Disease 2019 (COVID-19), a new respiratory disease caused by severe acute respiratory syndrome virus 2, has emerged as an ongoing pandemic and global health emergency. This article primarily aims to describe laboratory tests, comorbidities, and complications, specifically comprising 1) the incubation period and basic epidemiological parameters, 2) clinical manifestations, 3) laboratory tests, including routine blood tests, inflammatory biomarkers, cardiac biomarkers, liver and renal function, and blood coagulation function, 4) chest imaging features, 5) significant comorbidities and complications. This information on the disease conditions would help dissect the disease heterogeneity for appropriately selecting clinical treatment strategies and therapeutic development.

**KEYWORDS**

Clinical characteristics; COVID-19; SARS-CoV2, complication.

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Coronavirus Disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a highly transmissible viral pathogen that has caused the ongoing worldwide pandemic. The World Health Organization (WHO) declared COVID-19 to be a global pandemic on March 11, 2020. SARS-CoV-2 infection may be asymptomatic or present a broad spectrum of clinical symptoms, from mild upper respiratory tract infection to life-threatening sepsis. The COVID-19 pandemic has caused a sudden significant increase in hospitalizations for pneumonia with multi-organ injuries. This review summarizes current evidence regarding the incubation period and clinical characteristics and conditions, particularly laboratory tests, imaging findings, comorbidities, and complications in patients with COVID-19.

**INCUBATION PERIOD**

The incubation period (IP) is defined as the time from virus exposure to illness onset. The IP varies with pathogens and is primarily associated with the number of pathogens, pathogenicity, and infected hosts (1). Estimating IP for infectious diseases is crucial for public health professionals to determine the time of possible exposure that causes the infection, track the infection source, and determine the transmission (2, 3). It also provides essential evidence for implementing related public health strategies for quarantining individuals who have had exposure to a confirmed infection source and taking necessary measures to protect susceptible people.

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Compared with other coronaviruses causing the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), the SARS-CoV-2 virus may cause less severe pathogenesis but has a rapid transmission mode (4) (Table 1). The evolution from outbreaks to a pandemic of the disease has also supported this observation (5). Through an investigational analysis of 88 patients with COVID-19 who had a history of travel to Wuhan, China, Backer et al. (6) estimated the disease's mean IP to be 6.4 (95% Confidence Interval, 5.6 to 7.7) days. Another study based on publicly available information on cases estimated that the mean IP was about five (range 2 to 14) days (7). In 181 confirmed cases who had an identifiable time window from exposure to symptom onset, the median IP was estimated to be five (95% confidence interval [CI]: 4.5 to 5.8) days (2). In addition, a study of 1099 patients with laboratory-confirmed

infections found the median IP to be four (range: 2-7) days (8). A national retrospective study of 1519 cases in Saudi Arabia estimated the median IP to be six days (9). Therefore, the general estimates of IP range from 2-14 with medians of 5-6 days between infection and the disease's clinical symptoms. The WHO recommends that the follow-up with contacts of confirmed cases with COVID-19 is 14 days.

Of note, there are reports that the IP for COVID-19 could be much longer. Cases with IP of 19 and longer were reported (10). Therefore, the patients' IP can vary significantly. Even so, it is widely accepted that the average duration of quarantine or social isolation for SARS-CoV-2 is 14 days. When necessary, it is possible to extend the duration appropriately.

**Table 1** Epidemiology of SARS-CoV, MERS-CoV, and SARS-CoV-2

Epidemiologic parameters	SARS-CoV	MERS-CoV	SARS-CoV-2
Number of countries affected (n)	29	27	216
Confirmed cases (n)	8,096	2,494	>10 million
Basic reproduction number	0.3-4.1	<1	2.2-2.6
Severe cases ratio (%)	34%	63.4%	15.7%
Crude case fatality rate (%)	9.6%	40%	1.4-6.9%

Note: The table was adapted from Zhang et al. (4) published under the Creative Commons Attribution License (CC BY) with no change.

## CLINICAL MANIFESTATIONS

### Common manifestations

According to several studies published in the worldwide populations of patients with COVID-19, the mean age is mainly between 45 and 65 years (8, 11-18), and males seem to be disproportionately affected by severe cases compared to females (8, 11-16, 19, 20). Age is a decisive risk factor for hospital admission, especially for older people of 65 and above (odds ratio [OR], OR=3.4), and so even more (OR=37.9) for ages of 75 and above (15, 17). Moreover, patients with COVID-19 who received intensive care unit (ICU) care were significantly older (21), and older patients also were more likely to die in hospital (22, 23). Advanced age has a significant association with complications and mortality in patients with COVID-19 (17). Sex difference in hospital admission was reported, and males were two-fold more likely to be hospitalized than females (15) and predominantly among patients who received ICU care (11).

Patients with COVID-19 tend to have a variety of clinical symptoms (Table S1). The most common and typical symptom clusters involved the respiratory system: cough and shortness of breath; fever was also common and a decrease or loss of taste and/or smell were reported common in some countries. In 1,099 patients admitted to hospital in China, fever was present in 43.8% of the patients at the time of admission but developed in 88.7%

during hospitalization; cough was present in 67.8% of patients (8). A study of 20,133 hospitalized patients with COVID-19 in the UK (20) reported that the most common symptoms were fever (71.6%, 12,499/17,452), shortness of breath (71.2%, 12,107/16,999), and cough (68.9%, 12,896/18,730), consistent with other two studies of 1,000 and 393 patients in New York (11, 12).

In addition, some individuals with SARS-CoV-2 infection had upper respiratory tract signs and symptoms (e.g., sore throat, rhinorrhea, or sneezing) (11), indicating that the target cells also might be located in the upper airway. Other symptoms, such as neurological symptoms (e.g., headache and myalgia) and digestive system symptoms (nausea or vomiting, diarrhea, and abdominal pain), are common in patients with COVID-19.

There was a geographic variation in the gastrointestinal symptoms of patients with COVID-19. In the UK, 29% of patients complained of enteric symptoms on hospital admission (20), which were generally similar to those in a study of 393 consecutive inpatients from New York (12), including diarrhea (23.7%) and vomiting (19.1%). However, for unknown reasons, the gastrointestinal symptoms appear to be less frequent and/or severe in patients in China (8).

Many patients, especially mild cases, had a broad spectrum of neurological manifestations (24). Lechien et al. examined 1,420 European patients with mild-to-moderate

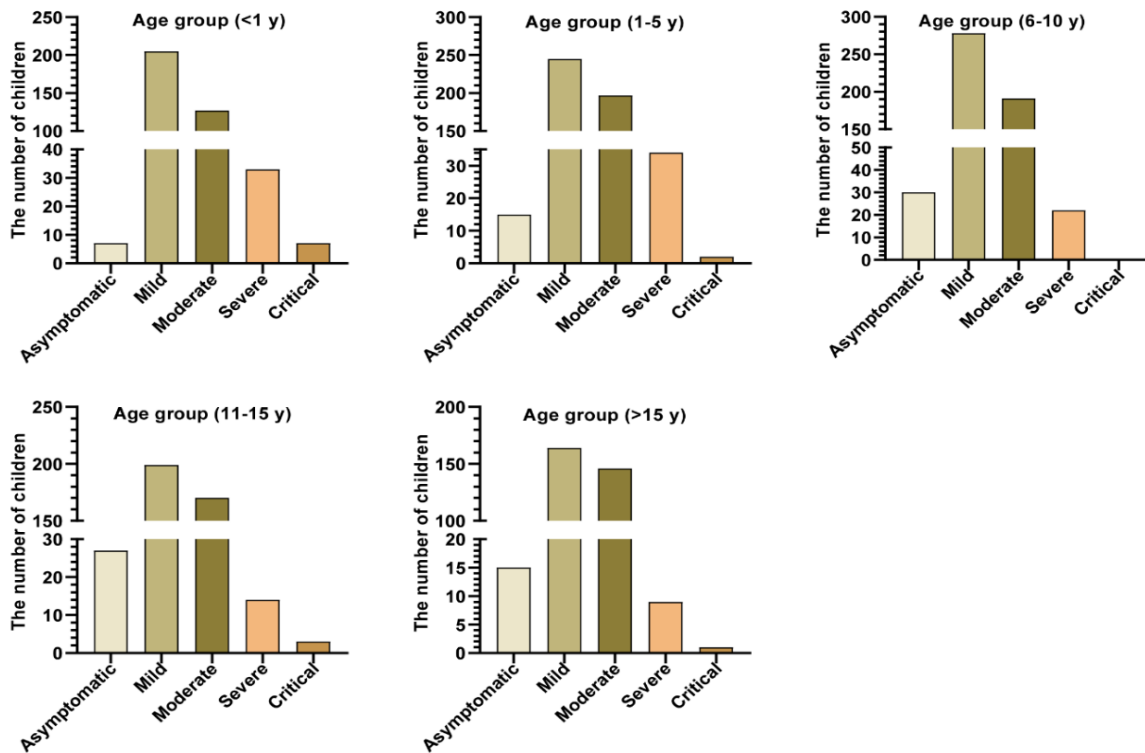
disease. They found that the most common neurological symptoms were headache (70.3%), loss of smell (70.2%), asthenia (63.3%), myalgia (62.5%), and gustatory dysfunction (54.2%) (25). Another study also showed that headache, loss of smell, or taste were reported more often among non-hospitalized patients (15). The loss of taste and/or smell can be one symptom that may help differentiate COVID-19 from the typical respiratory infection with influenza viruses.

**Population differences**

*COVID-19 in the children*

Children infected with SARS-CoV-2 seems to be less likely than adults to develop symptoms. Children were infected mostly through close contact with other infected family

members (26) and accounted for a small proportion (1.5%) of patients that require hospitalization (20). The majority (90%) of infected children are asymptomatic or have mild or moderate disease (**Figure 1**), according to a nationwide case series of 2,143 pediatric patients with COVID-19 (27), and some experience gastrointestinal symptoms, including abdominal discomfort, nausea, vomiting, abdominal pain, and diarrhea (28). Pediatric patients seem to have a better prognosis and usually recover within 1-2 weeks after the disease (27, 29). Notably, treatment with large doses of antiviral drugs or empirical antibiotics is unnecessary unless patients have severe disease (30). Of note, because most pediatric patients are asymptomatic or have mild and sometimes atypical symptoms, a correct diagnosis may be overlooked, leading to a potentially dangerous situation in community-acquired infections (28).



**Figure 1.** Different severity of illness by age group [plot was made based on data reported by Dong et al (27)]

*COVID-19 in pregnant women and infants*

Pregnant women can be infected and have common symptoms similar to other adults infected with SARS-CoV-2. In a cohort of 20,133 hospitalized patients in the UK, pregnant women accounted for 10% (20), slightly lower

than an observed proportion (18%) in pregnant women during the H1N1 influenza pandemic 2009 but who were three times more likely to be infected than non-pregnant women in reproductive age of 15-44 years (31). Most pregnant women infected with SARS-CoV-2 and hospit-

alized were in the late second or third trimester (32), the mean age was 32 (range 29 to 34) years, and the mean gestational age was 39<sup>+1</sup> (range 37 to 41<sup>+2</sup>) days. The typical clinical characteristics of these pregnant women with COVID-19 were primarily fever, cough, and shortness of breath, similar to those of non-pregnant adults with COVID-19 (33, 34). Most pregnant women infected with SARS-CoV-2 had a good prognosis, but a small proportion of severe patients underwent preterm delivery, predominantly maternal indication in the third trimester (35). One study reported that approximately 2% (6/265) of newborns were positive for the viral testing within 12 hours of birth (36), which suggests that mother-to-fetal vertical transmission might occur, whereas another study of nine pregnant patients with livebirths report no intra-uterine infection (34). Most neonates born to mothers with established SARS-CoV-2 infections were asymptomatic and discharged home well, with only a minority having signs or symptoms of illness and needing neonatal specialist care (36-38).

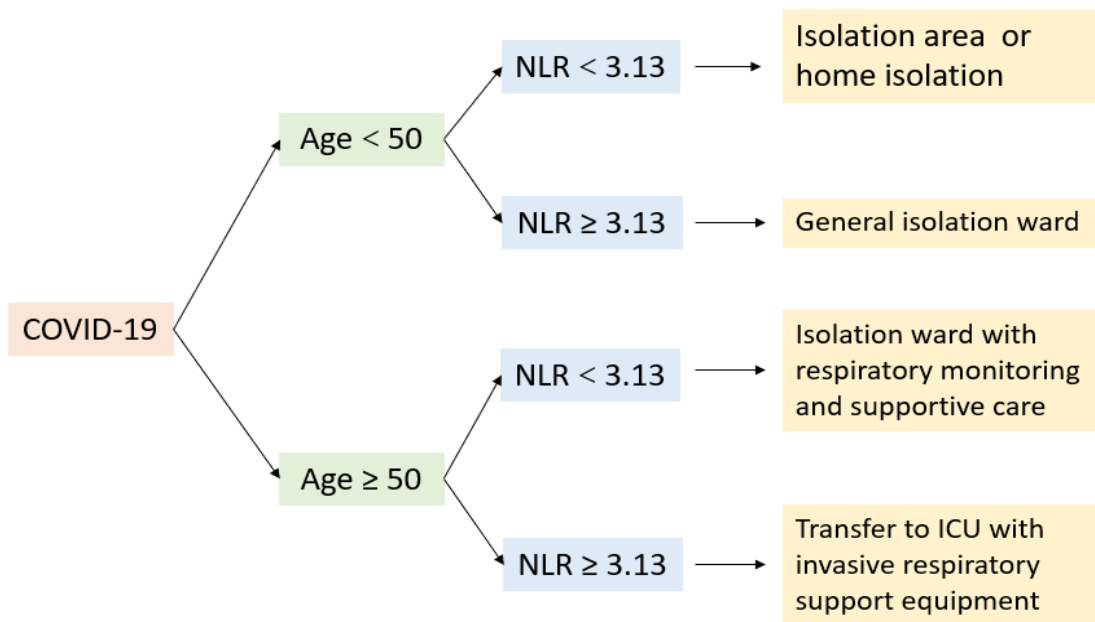
**LABORATORY TESTS**

**Routine blood tests**

A reduction in the peripheral lymphocyte counts is usually observed at the early stage of the disease, while other peripheral blood cell counts are normal or slightly

decreased. Patients with poor outcomes (including severe illness, admission to ICU, or death) usually have abnormal routine blood tests, including lower platelet counts, but a higher WBC and neutrophil counts (8, 17, 23, 39). More details from a few significant clinical studies are summarized in **Table 2**.

Lymphopenia is a prominent characteristic in adults with COVID-19, although lymphocyte count is mostly normal in children with SARS-CoV-2 infection. Decreased lymphocyte counts occur more often in non-survivors than survivors of patients (23). Survivors usually had the lowest lymphocyte counts on day seven after illness onset and improved gradually after that during hospitalization. Of note, severe lymphopenia was observed in patients who ended with death (40). In addition, lymphocyte-related derivative measures, especially the neutrophil-to-lymphocyte ratio (NLR), were important prognostic factors in patients with COVID-19. Liu et al (41) have reported that NLR is a predictive factor for early-stage prediction of patients with COVID-19 who are likely to develop a critical illness. For patients aged 50 and above, having an NLR  $\geq 3.13$  predicted the development of a critical illness (**Figure 2**). The disease progression stratified by NLR and age may facilitate patient management, and NLR was identified as an independent risk factor of the in-hospital mortality of patients (41).



**Figure 2.** Management strategy for patients with COVID-19 by age and NLR [adopted from original by Liu et al (41) published under <http://creativecommons.org/licenses/by/4.0/>, with no change].

**Table 2** Routine blood routine of COVID-19 patients in selected studies

Author	Region	Type of patients (N)	Routine blood	Mean*	Normal range	p-Value
Berenguer J. et al.	Spain	Total (4035) Death (1131) Alive (2904)	White cell count, ×10 <sup>9</sup> /L	5.91 (4.49-7.99) 6.9 (5-9.47) 5.64 (4.33-7.42)	-	<0.001
			Neutrophil count, ×10 <sup>9</sup> /L	4.2 (2.92-6.12) 5.3 (3.53-7.7) 3.92 (2.8-5.56)	-	<0.001
			Lymphocyte count, ×10 <sup>9</sup> /L	0.9 (0.64-1.3) 0.78 (0.54-1.16) 1.0 (0.7-1.36)	-	<0.001
			Platelet count, ×10 <sup>9</sup> /L	178 (139-226) 168 (130-221) 181 (143-229)	-	<0.001
			White cell count, per mm <sup>3</sup>	4.7(3.5-6) 4.9(3.8-6) 3.7(3-6.2)	-	-
Guan et al.	China	Total (1099) Non-severe (926) Severe (173)	Lymphocyte count, per mm <sup>3</sup>	1.0 (0.7-1.3) 1.0 (0.8-1.4) 0.8 (0.6-1)	-	-
			Platelet count, per mm <sup>3</sup>	168 (132-207) 172 (139-212) 137.5 (99-179.5)	-	-
			Lymphocyte count, ×10 <sup>9</sup> /L	0.8 (0.6-1.2) 0.9 (0.6-1.2) 0.8 (0.5-1.1)	-	-
Petrill et al.	New York	Total (2,729) Non-critical (1,739) Critical (990)	Lymphocyte count, ×10 <sup>9</sup> /L	0.8 (0.6-1.2) 0.9 (0.6-1.2) 0.8 (0.5-1.1)	-	-
			White cell count, ×10 <sup>9</sup> /L	5.8 (4.3-8.2) 9.6 (7.8-14.0) 5.2 (3.7-7.0)	3.5-9.5	<0.001
Shi et al.	China	Total (671) Death (62) Survivors (609)	Neutrophil rate	72 (62-84) 91 (86-93) 68 (59-76)	40-75	<0.001
			Lymphocyte rate	19 (10-26) 6 (4-10) 26 (16-28)	20-50	<0.001
			Platelet count, ×10 <sup>9</sup> /L	210 (155-270) 153 (75-204) 215 (172-284)	125-350	<0.001
			Erythrocyte count, ×10 <sup>12</sup> /L	4.1 (3.6-4.5) 4.0 (3.4-4.4) 4.1 (3.8-4.5)	3.8-5.1	0.05
			Hemoglobin, g/L	124 (111-135) 128 (103-140) 125 (118-135)	115-150	0.545
			White cell count, ×10 <sup>9</sup> /L	5.39 (2.11) 5.19 (1.71) 6.22 (3.15)	-	<0.001
			Neutrophil, ×10 <sup>9</sup> /L	3.25 (1.92) 2.93 (1.36) 4.57 (3.00)	-	<0.001
Lee, J. Y. et al	South Korea	Total (694) Milder case (557) Severe case (137)	Lymphocyte count, ×10 <sup>9</sup> /L	1.59 (0.71) 1.70 (0.71) 1.13 (0.52)	-	<0.001
			Monocyte count, ×10 <sup>9</sup> /L	0.45 (0.17) 0.45 (0.16) 0.47 (0.24)	-	0.449
			Platelet count, ×10 <sup>9</sup> /L	235.65 (85.37) 240.46 (83.17) 215.87 (91.56)	-	0.003
			Hemoglobin, g/Dl	37.95 (4.28) 38.31 (4.10) 36.47 (4.66)	-	0.001
			White cell count, ×10 <sup>9</sup> /L	5.39 (2.11) 5.19 (1.71) 6.22 (3.15)	-	<0.001

Note: ICU, intensive care unit. All studies involved hospitalized patients, except that Shi et al study focused on severe COVID-19; \*, Mean, or median, mean was with a standard deviation in the bracket, while the median was with an interquartile range [IQR] in the bracket

## Inflammatory biomarkers

Adults with severe COVID-19 are known to have an elevation of inflammatory markers, mainly including C-reactive protein (CRP) and procalcitonin (PCT) (8, 17, 18, 21, 23, 39, 42-44)(Table 3). A prospective cohort study of 5279 patients with COVID-19 in New York indicated that patients with critical illness were more likely to present with higher levels of CRP and PCT (17), consistent with a nationwide study of 1099 cases in China (8) and also a

study in South Korea (21). Patients in the ICU had higher CRP levels than those treated in hospital (not ICU) or the emergency department only (11). A meta-analysis including 5912 patients with COVID-19 showed that elevated serum CRP was present in 57.4% (1494/2603), while elevated PCT was found in 12.2% (256/2099) of patients. Moreover, compared with non-severe patients, the levels of CRP (60.91 vs. 19.83 mg/l) and PCT (0.14 vs 0.07 ng/ml) were significantly elevated in severe patients (45).

**Table 3** Inflammatory biomarkers in COVID-19 patients in selected large sample studies

Author	Region	Type of patients(N)	Inflammatory biomarkers	Mean*	Normal range	p-Value
Guan et al.	China	Total (1099) Non-severe (926) Severe (173)	CRP $\geq$ 10 (mg/liter)	481/793 (60.7) 371/658 (56.4) 110/135 (81.5)	-	-
			PCT $\geq$ 0.5 (ng/ml)	35/633 (5.5) 19/516 (3.7) 16/117 (13.7)	-	-
Petrilli et al.	New York	Total (2,729) Non-critical (1,739) Critical (990)	CRP (mg/L)	108.3 (53.3-169.0) 89.1 (41.9-148) 136.3 (85.8-204.2)	-	-
			PCT (ng/mL; SI $\mu$ g/L)	0.14 (0.06-0.40) 0.1 (0.05-0.23) 0.27 (0.12-0.82)	-	-
Shi et al.	China	Total (671) Death (62) Survivors (609)	CRP	41 (12-81) 111 (64-191) 30 (8-59)	< 10 mg/L	<0.001
			PCT	0.06 (0.04-0.13) 0.46 (0.14-1.58) 0.05 (0.03-0.09)	< 0.1 ng/mL	<0.001
Berenguer et al.	Spain	Total (4035) Death (1131) Alive (2904)	CRP (mg/dL)	0.11 (0.06-0.25) 0.22 (0.10-0.56) 0.09 (0.05-0.16)	-	<0.001
			PCT (ng/mL)	54 (20-116) 87 (38-168) 44 (16-95)	-	<0.001
Lee et al.	South Korea	Total (694) Mild case (557) Severe case (137)	CRP (mg/L)	2.00 (4.10) 0.86 (1.85) 6.66 (6.69)	-	<0.001
			PCT (ng/ml)	2.00 (2.64) 1.62 (2.23) 3.31 (3.41)	-	<0.001

Note: CRP, C-reactive protein; PCT, procalcitonin; ICU, intensive care unit. All the studies involved hospitalized patients, except the Shi et al study focused on severe COVID-19. \*. Mean, percent or median, mean was with a standard deviation in the bracket, while the median was with an interquartile range [IQR] in the bracket.

## Blood biochemistry tests

### Cardiac biomarkers

COVID-19 is an evolving pandemic with predominant respiratory manifestations. However, abnormalities of cardiac biomarkers feature heavily in this disease. The most commonly tested cardiac-specific biomarkers in COVID-19 were creatine kinase (CK, also known as creatine phosphokinase, CPK) and cardiac troponin (cTn). Myoglobin (MYO), N-terminal pro-B-type natriuretic peptide (NT-proBNP).

CK is an enzyme primarily found in skeletal muscle, brain, heart tissues, and cardiac cells where ATP is consumed

rapidly and is elevated when a condition cause damage to the heart, muscle, and brain. It catalyzes the creatine using ATP to create phosphocreatine (Pcr) and ADP. Because this reaction is reversible, Pcr is usually served as an energy reservoir for a rapid buffering to gene-rate ATP when necessary. There are three isoenzymes, CK-MM is located in the skeletal muscle and heart, CK-BB is in the brain and CK-MB, creatine kinase-myocardial band, primarily located in the heart muscle cells. The CK-MB test is often used to measure CK levels, which elevation in the blood may indicate possible damage to the heart. Also, cardiac troponin, cTn, a regulatory protein of cardiac muscle contraction, is composed of three subunits: troponin T(cTnT), troponin I (cTnI), and troponin C (cTnC), in which

cTnT and cTnI are extensively used as diagnostic and prognostic indicators in the management of myocardial infarction and acute coronary syndrome. Thus CK-MB, cTn, electrocardiogram, and clinical signs should be carefully examined and considered when making a diagnosis.

In addition, MYO is a sensitive marker for muscle injury and potential for heart attack in patients with chest pain. Elevated myoglobin may have low specificity for acute myocardial infarction. NT-proBNP, is a non-active pro-hormone released from the same molecule that produces BNP, a hormone produced by the heart. Both BNP and NT-proBNP are released in response to changes in volume and pressure inside the heart related to heart failure and other cardiac problems. It is usually used for screening or making a diagnosis of acute congestive heart failure.

Patients may present with early sign of myocardial injury secondary to COVID-19 which might be highly frequently in severe patients who died in hospitals. Several selected studies measuring some cardiac-specific biomarkers such as creatine kinase and troponin (**Table 4**). An elevated troponin is believed to commonly reflect non-coronary

disease in COVID-19. Patients with critical COVID-19 often presented with elevated levels of troponin (8, 17), and multiple logistic regression analysis revealed that a high level of troponin (>1) was strongly associated with critical illness compared to age or comorbidities (17). A retrospective study of patients with COVID-19 (n=671) indicated that cardiac troponin I was more elevated in non-survivors with SARS-CoV-2 infection than survivors (23). Additionally, two studies have indicated that CK is more elevated in severe patients than non-severe cases with COVID-19 (8, 43).

In addition, Shi et al.(23) specifically examined the myocardial injury in 671 severe patients with COVID-19, of whom 62 patients died. They found that CK-MB, MYO, cTn and NT-proBNP were also significantly elevated in non-survivors compared to survivors (**Table 4**). These studies might suggest either direct viral invasion of cardiac myocytes and/or inflammatory myocardial injury in "cytokine storm," but may need further studies to determine the cause.

**Table 4** Cardiac biomarkers of COVID-19 patients in selected large sample studies

Authors	Region	Type of patients(N)	Cardiac biomarkers	Mean/median	Normal range	p-Value
Guan et al.	China	Total (1099)	CK ≥200 (U/liter)	90/657 (13.7)	-	-
		Non-severe (926)		67/536 (12.5)		
		Severe (173)		23/121 (19.0)		
Wang et al.	China	Total (138)	Hypersensitive troponin I (pg/mL)	6.4 (2.8-18.5)	<26.2	0.004
		ICU (36)		11.0 (5.6-26.4)		
		Non-ICU (102)		5.1 (2.1-9.8)		
Mao et al.		Total (214)	CK (U/L)	64.0 (8.8-12,216.0)	-	0.004
		Non-severe (88)		59.0 (19.0-1260.0)		
		Severe (126)		83.0 (8.8-12,216.0)		
Petrilli et al.	New York	Total (2,729)	Troponin I (ng/mL)	0.03 (0.01-0.10)	-	-
		Non-critical (1,739)		0.02 (0.01-0.10)		
		Critical (990)		0.07 (0.01-0.10)		
Shi et al.	China	Total (671) Death (62) Survivors (609)	CK-MB (0-5 ng/mL)	0.96 (0.63-1.82)	0-5	<0.001
				3.6 (2.4-6.9)		
			MYO (0-110 lg/L)	42 (27-85)	0-110	<0.001
				268 (92-768)		
			cTn (0-110 lg/L)	32 (24-63)	0-0.04	<0.001
				0.006 (0.006-0.016)		
NT-pro BNP (0-900 pg/mL)	0.235 (0.042-1.996)	0-900	<0.001			
	0.006 (0.006-0.011)					
				189 (67-494)		
				1,819 (759-5164)		
				132 (58-237)		

Note: CK, Creatine kinase; CKMB, Creatine kinase-MB; MYO, myoglobin; cTn, cardiac troponin; NT-pro BNP, N terminal pro-brain natriuretic peptide; ICU, intensive care unit. All the studies involved hospitalized patients; only Shi et al study focused on severe COVID-19. \* Mean, percent or median, mean was with a standard deviation in the bracket, while the median was with an interquartile range [IQR] in the bracket.

### Liver function tests

Abnormal liver functions are prevalent in patients with COVID-19 (8, 14, 17, 46, 47). A routine liver function includes total protein, albumin, total bilirubin (TBIL),

direct bilirubin, alkaline phosphatase (ALP), aspartate amino-transferase (AST, formally known as glutamate oxalo-acetate transaminase), and alanine aminotransferase (ALT, glutamate pyruvate transaminase). The most observed abnormalities were hypoalbuminemia (61-65%),

followed by ALT (12-23%), AST (14-23%)(45, 48), and bilirubin (6.7%)(45). In a multicenter study (n=788), 28.2% of patients with COVID-19 presented with elevated liver enzymes at hospital admission, and they were mostly milder patients. No liver failure was observed in the follow-up (46). A report on 675 patients found that 37.5% of patients had abnormal liver function measurements during hospitalization(49). A meta-analysis showed that the incidence of elevated liver chemistries in COVID-19 was 23.1% at initial presentation and 24.4% during illness (50). Patients who are male, overweight, and smokers had a higher risk of liver enzyme elevation (46).

The degree of elevation of liver chemistries, which could be impacted by coexisting chronic hepatitis and pharmacological treatment (47), was associated with the outcome of COVID-19. Severe patients with COVID-19 were observed with elevated ALT, AST, TBIL, and reduced albumin than non-severe patients (45). Additionally, patients with elevated liver chemistries had an increased mortality risk than patients with routine liver function tests (23, 39). The details of the liver function of COVID-19 patients in large sample studies are shown in **Table S2**. ALT/AST elevation

was independently associated with adverse clinical outcomes, including ICU care, use of invasive mechanical ventilation, and/or death in patients with COVID-19 after adjusting for the presence of diabetes mellitus and hypertension, and albumin level (47). However, elevated liver chemistries might not affect the outcomes of COVID-19 if early medical intervention was taken (46).

### Renal function

Abnormal renal function in patients with COVID-19 is not rare. According to a multicenter registry conducted in Europe and America, up to 35% of patients with COVID-19 had evidence of kidney dysfunction on admission. In contrast, only 8.5% of patients had a history of pre-existing kidney disease (CKD) (51). Severe patients with COVID-19 had an elevated blood urea nitrogen/creatinine but decreased creatinine clearance/ estimated glomerular filtration rate (17, 18, 42). Non-survivor patients had a decreased creatinine clearance compared with survivors (23, 39) (**Table 5**). Those patients with renal dysfunction evidence were more likely to have severe disease and were associated with risk of death during hospitalization.

**Table 5** Renal function of COVID-19 patients in selected large sample studies

Author	Region	Type of patient (N)	Renal function	Mean*	Normal range	p-Value
Wang et al.	China	Total (138) ICU (36) Non-ICU (102)	BUN (mmol/L)	4.4 (3.4-5.8) 5.9 (4.3-9.6) 4.0 (3.1-5.1)	2.8-7.6	<.001
			Cr (μmol/L)	72 (60-87) 80 (66-106) 71 (58-84)	64-104	0.004
			Cr (μmol/L)	58 (48-70) 87 (59-160) 55 (48-63)	41-73	<0.001
Shi et al.	China	Total (671) Death (62) Survivors (609)	Ccr (ml/min)	97 (88-97) 67 (35-94) 99 (92-107)	> 90	<0.001
			Cr (mg/dL)	1.0 (0.80-1.39) 0.95 (0.79-1.23) 1.11 (0.88-1.61)	-	-
Petrilli et al.	New York	Total (2,729) Non-critical (1,739) Critical (990)	BUN (mmol/L)	0.92 (0.74-1.18) 1.10 (0.84-1.46) 0.88 (0.72-1.07)	-	<.001
Berenguer et al	Spain	Total (4035) Death (1131) Alive (2904)	Cr (μmol/L)	78.4 (56.5-93.6) 60.2 (40.1-80.4) 84.1 (65.3-97.4)	-	0.03
			Cr (mg/dL)	0.78±0.34 0.74±0.22 0.96±0.57	-	<0.001
			eGFR (mL/min/1.73 m <sup>2</sup> )	94.48±25.59 99.01±23.82 75.87±24.24	-	<0.001
Lee et al	South Korea	Total (694) Mild case (557) Severe case (137)	BUN (mg/dL)	14.68±7.00 13.58±4.83 19.20±11.40	-	<0.001

Note: BUN, blood urea nitrogen; Cr, creatinine; ICU, intensive care unit; eGFR, estimated glomerular filtration rate; Ccr: Creatinine clearance. All the studies involved hospitalized patients, except the Shi et al study focused on severe COVID-19. \*. Mean, or median, mean was with a standard deviation in the bracket, while the median was with an interquartile range [IQR] in the bracket



A retrospective study in the UK indicated that more impaired renal function was observed in non-survivors, with higher levels of urea and creatinine but a lower estimated glomerular filtration rate (eGFR) on admission than survivors (32), consistent with another study from Spain (39). A study from Wuhan confirmed that elevated creatinine and blood urea nitrogen were independent risk factors associated with in-hospital death after adjusting for potential confounding factors (34). Therefore, physicians should closely monitor anyone with COVID-19 and impaired renal function at the time of admission or during illness, regardless of respiratory status.

### Blood coagulation function

Coagulation function in patients with COVID-19 is often abnormal compared with healthy people. A prospective study of 94 cases and 40 healthy controls (52) found that D-dimer, fibrin/fibrinogen degradation products (FDP), and fibrinogen were significantly elevated in patients with COVID-19, and the mean levels of D-dimer and FDP in

severe cases were significantly higher compared with milder COVID-19. The findings are consistent with another study in Wuhan, including 71 severe patients with confirmed SARS-CoV-2 infection and 61 healthy people (53).

Abnormal coagulation function may be helpful for an early identification of severe cases with COVID-19. The severe or critical patients appear to have coagulation dysfunction (8, 17, 18, 39, 43), including elevated D-dimer, international normalized ratio, a standardized measurement of prothrombin time (PT), and activated partial thromboplastin time (Table 6). While a retrospective study (n=138 hospitalized patients) found no difference in prolonged PT between patients who did receive and not receive ICU care (18), a meta-analysis of 23 studies provided substantial evidence that increased D-dimer (1.29 vs. 0.47 mg/L; a normal value below 0.5 mg/L) was associated with severe patients (45).

**Table 6** Blood coagulation function of COVID-19 patients in selected large sample studies

Authors	Region	Type of patient (N)	Coagulation function	Mean*	Normal range	p-Value
Wang et al.	China	Total (138) ICU (36) Non-ICU (102)	Prothrombin (time, s)	13.0 (12.3-13.7)	9.4-12.5	0.37
				13.2 (12.3-14.5)		
				12.9 (12.3-13.4)		
			Activated partial thromboplastin (time, s)	31.4 (29.4-33.5)	25.1-36.5	0.09
30.4 (28.0-33.5)						
31.7 (29.6-33.5)						
D-dimer (mg/L)	203 (121-403)	0-500	<0.001			
	414 (191-1324) 166 (101-285)					
Guan et al.	China	Total (1099) Non-severe (926) Severe (173)	D-dimer ≥0.5 (mg/liter)	260/560 (46.4)	-	-
				195/451 (43.2)		
				65/109 (59.6)		
Petrilli et al.	New York	Total (2,729) Non-critical (1,739) Critical (990)	D-dimer (ng/mL; SI μg/L)	386.5 (237.0-713.8)	-	-
				324 (208.0-545.0)		
				528 (319.0-1174.0)		
Mao et al.	China	Total (214) Non-severe (88) Severe (126)	D-dimer (mg/L)	0.5 (0.1-20.0)	-	<0.001
				0.4(0.2-8.7)		
				0.9(0.1-20.0)		
Berenguer J. et al	Spain	Total (4035) Death (1131) Alive (2904)	INR	294/3112 (9.4)	-	<0.001
				133/880 (15.1)		
				161/2232 (7.2)		
			D-dimer	1.1 (1.0-1.2)	-	<0.001
1.2 (1.1-1.3)						
1.1 (1.0-1.2)						
D-dimer	580 (339-1040)	-	<0.001			
	740 (410-1590)					
	548 (328-934)					

Note: ICU, intensive care unit; aPTT, Activated partial thromboplastin; INR, international normalized ratio. \*. Mean, or median, mean was with a standard deviation in the bracket, while the median was with an interquartile range [IQR] in the bracket

### CHEST IMAGING

The diagnosis of COVID-19 is predominantly based on viral nucleic acid testing and a history of exposure to a source of confirmed infection. However, many factors, such as the testing kit's quality, type of sample and collection, and assay errors, can lead to false-negative testing. Because

coronavirus diseases mainly cause respiratory tract infections, chest imaging modalities, including chest X-ray and computed tomography (CT), are critical diagnostic approaches to detect abnormal lung changes. Chest CT examination is more sensitive and specific than chest X-ray in discovering abnormal imaging for respiratory diseases

and may play an important role in diagnosing pneumonia of COVID-19 (54). Of 975 CT scans performed at the time of admission, 86.2% of patients featured abnormal imaging (8). The rapid development of abnormalities can occur in the first two weeks after symptom onset of COVID-19, after which they subside gradually (55, 56). The most common CT imaging abnormalities for COVID-19 are diffuse, peripheral ground-glass opacities (8, 56, 57).

Individuals infected with SARS-CoV-2 can be divided into three chest imaging stages according to the disease's development.

- 1) The early stage, CT manifestations mainly present as local lesions where are patchy and segmental in distribution, predominantly seen in the outer 1/3 lung fields and subpleural zones;
- 2) The progressive stage, the lesions increase in number and involve multiple pulmonary lobes, mostly the lower lobes;
- 3) The critical stage usually reveals diffuse lesions, lung consolidation, distorted structure, and "white lung" (58, 59). Imaging findings of COVID-19 can play a crucial role in early diagnosis, which is particularly important for early treatment in epidemic time (30, 56, 60).

However, while chest CT imaging may be suggestive for COVID-19, they may overlap with other pulmonary infections caused in the lungs. There is a relatively high proportion of patients with COVID-19, especially those with mild disease, who have regular CT scans (61). A large sample study from China indicated no radiologic abnormalities found on initial presentation in 2.9% of patients with severe disease and 17.9% of those with non-severe disease (8). Therefore, CT is not recommended as a lone first-line diagnostic or screening tool for COVID-19 (61), considering the viral testing and history of exposure to confirmed infection.

## COMORBIDITIES

Comorbidity is a powerful predictor of hospitalization and is also associated with the patients' risk of poor clinical outcomes (17, 18, 62). In a nationwide sample of 1,590 laboratory-confirmed cases with COVID-19 from China, patients with any comorbidity yielded poorer clinical outcomes. A more significant number of comorbidities are correlated with poorer prognosis (63). The most common comorbidities reported to be associated with a poorer prognosis include hypertension (23, 63, 64) diabetes (23, 49, 63, 64), chronic obstructive pulmonary disease (COPD) (63, 64), cardiac diseases (23), cerebrovascular disease (23, 64), chronic renal failure (23), and malignancy (63, 65). In a study of 1591 Italian patients, coexisting cardiac disease in hospitalized patients with COVID-19 significantly increased the rate of death (36% vs. 15%), thromboembolic events (23% vs. 6%), and septic shock (11% vs. 0%) during the hospitalization, compared to non-cardiac disease (66).

The prevalence of comorbidity in patients with COVID-19

appears to have a geographic variation but could be affected by age and the criteria and conditions for hospitalization. According to several selected clinical reports, the prevalence of any major comorbidity was 23% in China (n=1099, median age 47), 68% in Italy (n=1591, mean age 67), 94% in New York (n=5700, median age 63), and 77% (n=20,133) in the UK (**Figure 3**). The lower level of comorbidity in patients with COVID-19 in China was probably due to the patients' younger median age in the selected study, compared to 63 years in New York patients.

The type of comorbidity was also different across countries. The significant comorbidities in patients with COVID-19 in a selected study from China were hyper-tension and diabetes (**Figure 3A**), consistent with the estimates based on the nationwide confirmed cases with COVID-19 (n=44,672). Patients with COVID-19 in Italy have a similar pattern of comorbidities but with a higher prevalence, at least partly due to the older age (**Figure 3B**), the major ones being hypertension, cardiovascular disease, hypercholesterolemia, and diabetes. US patients with similar mean age had different comorbidities (**Figure 1C**), including hypertension, obesity, diabetes, and coronary artery disease. The oldest reported cohort of patients was in the UK (mean age 73 years), and they were unique compared to the other three countries in having nine comorbidities prevalent at 10% or more in patients with COVID-19 (**Figure 1D**). These comorbidities include chronic cardiac disease, diabetes without complications, a chronic obstructive pulmonary disease without asthma, chronic kidney disease, asthma, dementia, chronic neuro-logical disorder, obesity, and malignancy.

## COMPLICATIONS

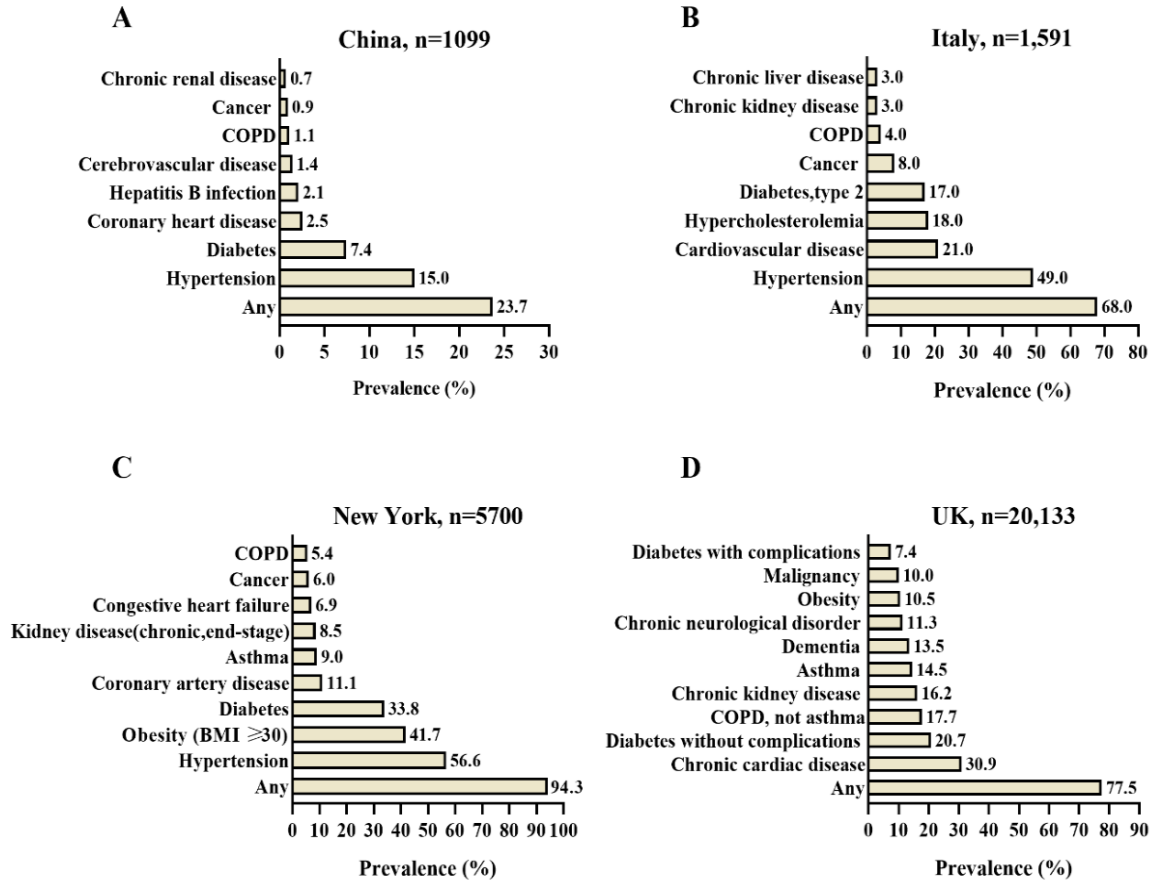
SARS-CoV-2 infection can cause both pulmonary and systemic inflammation, leading to injury or dysfunction in multiple organs. The common complications in patients with COVID-19 are acute respiratory distress syndrome (ARDS), acute respiratory failure (ARF), acute myocardial injury (AMI), heart failure (HF), and acute kidney injury (AKI) (**Table S3**). Vascular microangiopathy is also common with thrombotic sequelae, especially with severe disease. The rapid deterioration of the respiratory function was the leading cause of death in patients with COVID-19. In a nationwide study in China, most of the patients with COVID-19 (91.1%) received a diagnosis of pneumonia from a physician during hospital admission; and severe pneumonia was independently associated with admission to ICU, mechanical ventilation, or death (8). Additionally, acute cardiac injury and acute kidney injury should not be overlooked in the prognosis of patients with COVID-19 (21, 67).

### Acute myocardial injury

Acute myocardial injury was not uncommon in patients with severe COVID-19, especially among those who died. Notably, an American College of Cardiology clinical bulletin has highlighted the cardiac implications of COVID-19, suggesting that patients with the underlying cardio-

vascular disease face higher risks and recommend them to be triaged and treated with priority. In a clinical report on 671 hospitalized patients with severe COVID-19, 62 patients (9.2%) who died had a higher rate of myocardial injury than survivors did (75.8% vs. 9.7%;  $p < 0.001$ ). The risk of death among hospitalized patients with severe COVID-19 can be predicted by a marker (cardiac troponin I) of myocardial injury (23). Risk factors for pneumonia-associated cardiac complications include pre-existing

cardiovascular disease, older age, and greater severity of pneumonia at presentation (23, 68, 69). However, about one-third of cardiac complications occur in patients with no history of cardiac disease (69). The presence of pre-existing cardiovascular disease or abnormal cardiac biomarkers on admission or during hospitalization, such as elevated serum troponin or CPK (creatine phosphokinase) warrants a closer observation, often in an ICU setting (23).



**Figure 3.** Prevalence of comorbidity in Patients with COVID-19 in China(8), Italy(13), New York(40), and UK (20). (Note: cardiovascular disease in the study from Italy only includes cardiomyopathy and heart failure; COPD, chronic obstructive pulmonary disease).

**Acute kidney injury**

Individuals with COVID-19 can develop an acute kidney injury (AKI) manifested by a sudden reduction in kidney function, at any time before or during hospital admission (70). AKI can have clinical presentations ranging from mild proteinuria to progressive AKI necessitating renal replacement therapy (RRT) and can usually be observed in 8-19% of patients with COVID-19 (71-74). However, Argenziano et al.(11) reported that 33.9% of patients with COVID-19 and

78.0% of patients in the ICU developed AKI, the second most common complication after ARDS.

Several possibilities in patients with COVID-19 can cause a higher rate of AKI. Restrictive fluid management in treating patients with ARDS can lead to higher rates of AKI. The inherent renal toxicity may be associated with the pathophysiology of COVID-19. Also, AKI might be related to comorbidities. Hypertension and diabetes are the most common in patients with COVID-19, which often accom-

pany chronic kidney disease.

To evaluate kidney histopathologic parameters in patients with AKI and COVID-19, Sharma et al. (75) evaluated ten hospitalized patients infected with SARS-CoV-2 by viral testing. They found in all biopsy varying degrees of acute tubular necrosis, but there was no evidence of SARS-CoV-2 infection in immunohistochemical staining of the kidney biopsy sample. However, two other studies found direct virus-induced damage and viral particles had been observed in kidney biopsies performed in patients with COVID-19 (76, 77).

During hospitalization, the development of AKI in patients with COVID-19 is associated with in-hospital severity and mortality (72, 78). Patients with AKI had a more significant number of complications such as sepsis and respiratory failure, and an increased likelihood of in-hospital death (51). One study found that AKI in patients with COVID-19 was associated with an approximately 13-fold increased likelihood of death but with a wider confidence limit (OR 13.33, 95% CL 4.05 to 43.91) (73). Besides, continuous renal replacement therapy was significantly more frequent in severe cases, and patients ended with death (72). The incidence of renal replacement therapy among all patients with COVID-19 was 3.6-13.8% (11, 73). Meanwhile, 35.2% of ICU patients required inpatient dialysis (11).

## CONCLUSIONS

This review primarily focused on the clinical characteristics and conditions of patients with COVID-19 in hospital-case series. The average IP range ranges from 2-14 days, but it might be much longer in some people. The clinical symptoms of COVID-19 patients are heterogeneous. While the main initial symptoms encompassed the respiratory system, gastrointestinal but neurological symptoms are also common. Besides the clinical symptoms, laboratory tests are necessary and reflect the underlying pathophysiological abnormalities for individual patients and predict the clinical course. The abnormalities in routine blood tests, inflammatory markers, abnormal liver, kidney test, abnormal partial thromboplastin time and other coagulation parameters, elevated cardiac biomarkers, and chest imaging abnormalities are all important in assessing the disease severity, determining treatment strategies and predicting prognosis. Also, to detect viral damage to human cells, SARS-CoV-2 infection can cause pulmonary and systemic inflammation, resulting in multi-organ injury, which is often the cause of death in patients with COVID-19.

Currently, specific drugs and vaccines are in the process of development; attention should be paid to clinical symptoms, comorbidities, and complications indicated by laboratory tests to make reasonable judgments about the level of care required and guide them in clinical practice.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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