

## REVIEW ARTICLE

**COVID-19 in China, Italy and the United States of America: a short review***COVID-19 em China, Itália e Estados Unidos da América: uma breve revisão*

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**ABSTRACT:** In December 2019, a novel coronavirus was discovered and associated with a cluster of pneumonia of unknown cause in China. SARS-CoV-2 rapidly spread and is now characterized as a pandemic. The objective of this study is to discuss COVID-19 general features, including epidemiology, transmission, control measures, virology, diagnosis, clinical characteristics and radiological and laboratory results. In this context, literature was assessed to compare the three most affected countries in Asia, Europe and Americas on March 31, 2020. The main form of transmission is human-to-human by respiratory secretions, and studies indicated substantial involvement of asymptomatic patients in this process. COVID-19 patients are predominantly men and may present multiple symptoms, especially fever and cough. Arterial hypertension and diabetes mellitus were the most common comorbidities. Worse outcomes are associated with increased age, comorbidities, and complications. Abnormalities in computed tomography of the chest are frequent, with pulmonary ground-glass opacity and bilateral patchy shadowing as the most common patterns, but a significant percentage of patients do not present any findings at time of admission. Laboratory results often present lymphocytopenia, increased neutrophils and platelet counts, erythrocyte sedimentation rate, lactate dehydrogenase, C-reactive protein, ferritin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, creatinine, creatine phosphokinase, myoglobin, glucose and cytokines. Although radiological findings and laboratory results presented similarities in China, Italy and USA, case-fatality rates can be conflicting suggesting, therefore, the need for studies according to each region.

**Keywords:** Coronavirus infections; Epidemiology; Signs and symptoms; Pandemics.

**RESUMO:** Em dezembro de 2019, um novo coronavírus foi identificado e associado à ocorrência de pneumonia de causa desconhecida na China. SARS-CoV-2 rapidamente disseminou-se, e, atualmente, a COVID-19 é classificada como pandemia. O objetivo desse estudo consiste em discutir as características gerais da COVID-19, incluindo a epidemiologia, transmissão, medidas de controle, virologia, diagnóstico, apresentações clínicas e achados radiológicos e laboratoriais. Nesse contexto, foram consultados artigos publicados em base de dados com a finalidade de comparação entre países mais afetados na Ásia, Europa e América até 31 de março de 2020. A principal forma de transmissão ocorre entre humanos por secreções respiratórias, e estudos indicam um substancial envolvimento de pacientes assintomáticos nesse processo. Pacientes com COVID-19 são predominantemente homens e podem apresentar inúmeros sintomas, especialmente febre e tosse. Hipertensão arterial e diabetes mellitus foram as comorbidades mais comuns. Pior prognóstico está associados a aumento da idade, comorbidades e complicações. Anormalidades na tomografia computadorizada de tórax são frequentes, sendo opacidades em vidro fosco e infiltrados bilaterais os padrões pulmonares mais comuns, contudo porcentagem significativa dos pacientes não apresenta alterações na admissão. Exames laboratoriais normalmente apresentam linfocitopenia, aumento de contagem de neutrófilos e plaquetas, velocidade de hemossedimentação, lactato desidrogenase, proteína C reativa, ferritina, bilirrubina total, aspartato aminotransferase, alanina aminotransferase, creatinina, creatina fosfoquinase, mioglobina, glicose e citocinas. Apesar dos achados radiológicos e laboratoriais apresentarem similaridades na China, Itália e EUA, as taxas de mortalidade podem ser conflitantes, sugerindo, portanto, a necessidade de estudos de acordo com cada região..

**Palavras-chave:** Infecções por Coronavírus; Epidemiologia; Sinais e sintomas; Pandemia.

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## INTRODUCTION

In December 2019, there were several reports about patients with acute respiratory infection of unknown cause in hospitals of Wuhan, China<sup>1-3</sup>. The pathogen was identified as a new coronavirus and first named as 2019-nCoV<sup>1,2</sup>. In February 2020, the Coronavirus Study Group (CSG) of the International Committee officially named the virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)<sup>1</sup>. The coronavirus-related disease was named COVID-19 by the World Health Organization (WHO)<sup>4</sup>.

In this review article, we intend to discuss COVID-19 general features, including epidemiology, transmission, control measures, virology, diagnosis, clinical characteristics and radiological and laboratory results. Thus, literature was assessed to summarize similarities and differences between the three most affected countries in Asia, Europe and Americas on March 31, 2020, according to the WHO 71<sup>st</sup> report<sup>5</sup>.

## DISCUSSION

### Epidemiology

The first cases of the disease were linked to a seafood market in Wuhan, province of Hubei, China, in which the majority of the patients had been there or stayed nearby before getting sick<sup>1,2</sup>, suggesting that the origin of the virus was from the market; although, this hypothesis was not confirmed so far<sup>1</sup>.

The number of cases rapidly increased and spread to other locations inside and outside China<sup>2</sup>. On January 30, 2020, WHO declared the COVID-19 outbreak a public health emergency of international concern (PHEIC)<sup>6</sup>, and on March 11, 2020 characterized the disease as a pandemic<sup>7</sup>.

According to data of WHO on May 5, 2020, COVID-19 was present in every continent, except in Antarctic, with 3,525,116 confirmed cases and 243,540 deaths<sup>8</sup>. The United States of America (USA) was the country with more confirmed cases worldwide, accounting nearly 78% of the cases in the Americas; when comparing continents, Europe had the higher number, with almost 44% of the total amount<sup>8</sup>.

### Transmission

The main form of transmission of COVID-19 is human-to-human by respiratory secretions, with droplets or contact<sup>9,10</sup>. Wang et al.<sup>11</sup> evaluated the presence of SARS-CoV-2 in other sites, including nasal samples, sputum, pharyngeal swabs, bronchoalveolar lavage fluid, fibrobronchoscope brush biopsy, blood, urine, and feces. In this analysis, besides urine samples, all the other sites had a percentage of positive results (Table 1).

**Table 1:** Study of Wang et al. evaluating the presence of SARS-CoV-2 in 1070 specimens of 205 patients with COVID-19

Specimens	Presence of SARS-CoV-2
Blood	Positive
Bronchoalveolar lavage fluid	Positive
Feces	Positive with live virus
Fibrobronchoscope brush biopsy	Positive
Nasal samples	Positive
Pharyngeal swabs	Positive
Sputum	Positive
Urine	Negative

Other study identified SARS-CoV-2 in gastrointestinal tract, saliva, and urine, suggesting potential routes of transmission<sup>12</sup>. COVID-19 may also have a systemic component, supported by the presence of viral RNA in the blood of some patients<sup>10,11</sup>. These findings endorse the possibility that testing of specimens from multiple locations may reduce the risk of false-negative results<sup>11</sup>. However, there is not enough data for decisive conclusions, reaffirming that more studies are needed to fully understand the forms of transmission of the novel coronavirus.

Moreover, the period during the illness that an infected patient can transmit the disease is uncertain, but it can start before the development of symptoms<sup>10,13</sup>.

Arons et al.<sup>14</sup> evaluated an outbreak of COVID-19 in a nursing facility in the USA, where 56% of patients with SARS-CoV-2 infection reported no symptoms at the moment of the test. Of those asymptomatic patients, 86% developed symptoms later, being classified as presymptomatic patients. It is suggested that asymptomatic and presymptomatic patients had a contribution to the extent of the spread of COVID-19 in this facility, with a potential of viral shedding.

On top of that, studies have shown high viral load in the beginning of the symptomatic phase, suggesting more risk of transmission in this stage<sup>15</sup>. Similar values were found in symptomatic and asymptomatic patients, reasserting the transmission of the disease by asymptomatic patients<sup>15</sup>. Therefore, evidence of SARS-CoV-2 transmission from presymptomatic individuals has been shown in other investigations<sup>14,16-18</sup>.

### Control measures

WHO suggested some measures to control the transmission of the virus, such as rapid case identification, rapid testing and isolation of cases, comprehensive contact

tracing and quarantine of contacts<sup>19</sup>. These actions may reduce the spread of COVID-19, avoiding the health systems overload and allowing them to efficiently take care of the demand.

Several countries, which had a large number of community transmission, implemented other measures to contain the outbreak, for example, widespread population-level physical distancing measures and movement restrictions<sup>19</sup>. However, these actions significantly impact the society, causing innumerable psychological consequences<sup>20,21</sup> and negative impacts in economy<sup>19,22</sup>. Moreover, some groups can be more affected, such as people in poverty, immigrants, refugees and those who live in overcrowded and under-resourced settings<sup>19,23</sup>.

## Virology

SARS-CoV-2 is a single-stranded positive RNA virus that belong to the *Coronaviridae* family, which can infect humans and animals, causing respiratory,

gastrointestinal diseases, and other affections<sup>2,24</sup>.

Besides the recently discovered SARS-CoV-2, there are six known coronavirus that infect humans: HCoV-NL63, HCoV-229E, HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)<sup>1-3,24</sup>. The majority of them causes mild diseases, but two were responsible for thousands of deaths in the twenty first century, SARS-CoV, which caused severe acute respiratory syndrome outbreak in 2002, especially in Asia, and the MERS-CoV, which caused Middle East respiratory syndrome outbreak in 2012<sup>3,24,25</sup>.

SARS-CoV-2 is a beta coronavirus, as SARS-CoV and MERS-CoV, but it is considered to be more infectious than them, because it has a higher transmissibility<sup>9</sup>. Studies demonstrated that SARS-CoV-2 uses the same receptor as SARS-CoV to enter host's cells, the angiotensin-converting enzyme 2 (ACE2), different from MERS-CoV, which uses the dipeptidyl peptidase 4 (DPP4)<sup>1,26-28</sup> (Table 2).

**Table 2** - Comparison between SARS-CoV-2, SARS-CoV and MERS-CoV.

	MERS-CoV	SARS-CoV	SARS-CoV-2
Similarity with SARS-CoV-2	51,8%	79,0%	-
Target receptor in human's cells	DPP4	ACE2	ACE2

ACE2: angiotensin-converting enzyme 2; DPP4: dipeptidyl peptidase 4

Furthermore, many studies were made to elucidate the distribution of ACE2 through the body, aiming to identify which cells might represent a way of entrance for SARS-CoV-2<sup>4,29</sup>. High expression of this receptor was found in type II alveolar cells (AT2) of the lung, upper esophagus and stratified epithelial cells, absorptive enterocytes from ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells<sup>4,29</sup>. These findings support the idea that other organs might be at risk of infection by the SARS-CoV-2.

Genetically, SARS-CoV-2 is more similar to coronavirus of bat origin: bat-SL-CoVZC45 and bat-SL-CoVZXC21<sup>4,25</sup>. In fact, in nucleotide identity, it has 79.0% of similarity to SARS-CoV, 51.8% with MERS-CoV, and over 90% to a bat coronavirus<sup>24</sup>. These findings suggest that SARS-CoV-2 might be originated from bats, which are a natural reservoir of many coronavirus<sup>1,28</sup>, and could be transmitted to human directly from them or by an unknown intermediate<sup>1,2</sup>.

## Evaluation and Diagnosis

As a new disease that presents flu-like symptoms, which lead to many possible differential diagnoses, the suspicion can occur in three possible scenarios<sup>30</sup>. The first is a person presenting acute respiratory disease, with fever and symptoms of respiratory disease, such as shortness

of breath and cough, and with a history of travel to or residence in areas with reported community transmission within 14 days of the beginning of symptoms<sup>30</sup>. The second is a symptomatic individual presenting acute respiratory illness with a history of contact with a suspect or confirmed case within 14 days of the beginning of symptoms<sup>30</sup>. The third is a patient presenting severe respiratory illness, with fever and symptoms of respiratory disease, requiring hospitalization and without other diagnosis that explain all the findings<sup>30</sup>. These cases are labeled as suspect and require laboratory confirmation of SARS-CoV-2 infection.

The confirmed diagnosis is made by nucleic acid amplification tests (NAAT), such as real-time reverse-transcription polymerase chain reaction (rRT-PCR), based in the detection of parts of the viral RNA<sup>31</sup>. The chosen samples are respiratory secretions, especially from the upper respiratory tract for initial testing<sup>31,32</sup>. The Centers for Disease Control and Prevention (CDC) of the USA recommends nasopharyngeal, oropharyngeal specimen, nasal swab specimen, nasopharyngeal wash/aspirate or nasal wash/aspirate specimen<sup>32</sup>. The test of lower respiratory tract also can be done<sup>31,32</sup>.

As a matter of fact, because COVID-19 is a new disease, most laboratories were not prepared to deal with the high number of cases that need to be evaluated<sup>33</sup>. So, in order to test the patients that are more likely to have the disease, some criteria can be established, such as prioritize

individuals with more severe illness and contact with confirmed cases<sup>33,34</sup>.

**Clinical characteristics**

First, in January 2020, Huang et al.<sup>35</sup> reported the main clinical features of 41 SARS-CoV-2 infected patients in Wuhan, observing male prevalence (73%) and a median age of 49 years (IQR, 41-58). Subsequent studies conducted in the same hospital presented similar features<sup>36,37</sup>.

In February 2020, also at the epicenter of the COVID-19 pandemic, 138 patients presented similar results, with a prevalence of men (54.3%) and a median age of 56 years (IQR, 42-68)<sup>38</sup>.

Guan et al.<sup>12</sup>, in a larger study, with data regarding 1099 patients from 30 provinces in China, also showed a preponderance of men (58%) and a median age of 47 years (35-58).

In Italy, a retrospective case series of 1591 patients with COVID-19 referred for Intensive Care Unit (ICU) admission, where 82% were male and the median age was elevated [63 years (IQR, 56-70) years]<sup>39</sup>, which is possibly associated with demographic characteristics in this country.

Similarly, in the USA, a multicenter retrospective analysis in Seattle also presented that 63% of patients were men and had a mean age of 64 years<sup>40</sup>.

**Clinical Features**

The median time from onset of symptoms to first hospital admission was seven days<sup>35,38</sup>. Almost 90% of patients infected with SARS-CoV-2 presented multiple symptoms<sup>37</sup>. Initial studies about clinical manifestations of the disease included fever as the most common symptom (83-98.6%), followed by cough (59.4-82%) and fatigue/myalgia (38.1%-69.6%), resembling SARS-CoV and MERS-CoV infections<sup>12,35-37</sup>.

Guan et al.<sup>12</sup>, however, suggested that fever was not the hallmark of COVID-19 onset, since it was present in only 43.8% of the patients at the time of admission, but 88.7% of the patients developed during hospitalization.

Gastrointestinal symptoms were uncommon and included nausea and vomiting (1-5%), and diarrhoea (2-3.8%). When analyzing only critically ill patients, the prevalence of those symptoms increased to 10.1%<sup>38</sup> (Table 3).

**Table 3** – Summary of Clinical Manifestations in COVID-19 patients in China, Italy and United States of America

	Huang et al. n=41	Yang et al. n=52	Chen et al. n=99	Wang et al. n=138	Guan et al. n=1099	Arentz et al. n=21
Fever	98.6%	98%	83%	98%	43.8%	52.4%
Cough	76%	77%	82%	59.4%	67.8%	47.6%
Fatigue	44%	-	-	69.6%	38.1%	-
Diarrhoea	3%	-	2%	10.1%	3.8%	-
Nausea/Vomiting	5%	4%	1%	10.1%	5%	-

**Comorbidities**

The presence of any comorbidity varied from 23.7% to 46.7% according to studies in China<sup>12,38</sup>. Arterial hypertension, cardiovascular disease, and diabetes mellitus were the most common comorbidities associated with COVID-19<sup>7,12,35-38,40-42</sup>.

Furthermore, studies showed a higher prevalence of underlying diseases in Italy (86%) and USA (37.6-86%)<sup>39,41,43</sup>. Moreover, an analysis of critically ill patients in Washington, USA, reported that almost half of the patients had chronic kidney disease (CKD) (47.6%) and congestive heart failure (42.9%)<sup>41</sup> (Table 4).

**Table 4** - Summary of Comorbidities in COVID-19 Patients in China, Italy and United States of America

	Huang et al. n=41	Yang et al. n=52	Chen et al. n=99	Wang et al. n=138	Guan et al. n=1099	Onder et al. n=355	Grasselli et al. n=1591	Arentz et al. n=21
Coexisting disorder	32%	40%	51%	46.4%	23.7%	99.2%-	68%	86%
Arterial hypertension	15%	-	-	31.2%	15%	-	49%	-
Diabetes mellitus	20%	17%	12%	10.1%	7.4%	35.5%	17%	33.3%
Cardiovascular disease <sup>a,b,c</sup>	15%	10%	40%	14.5%	2.5%	54,5%-	21%	42.9%
COPD	2%	8%	-	2.9%	1.1%	-	4%	33.3%
Malignancy	2%	4%	1%	7.2%	0.9%	20.3%	8%	-
Cerebrovascular disease	-	13.5%	-	5.1%	1.4%	9.6%-	-	-
CKD	-	-	-	2.9%	0.7%	-	3%	47.6%

COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease. <sup>a</sup> Cardiovascular and cerebrovascular diseases grouped (Chen et al.). <sup>b</sup> Cardiovascular disease included atrial fibrillation and ischemic heart disease (Onder et al.). <sup>c</sup> Congestive heart failure (Arentz et al.).

## Complications

Acute respiratory distress syndrome (ARDS) was the main complication for COVID-19, suggesting a stronger component of respiratory affection, according to studies from Wuhan, China<sup>12,35-38</sup>. Additionally, the prevalence of acute cardiac injury, acute kidney injury (AKI), and liver dysfunction revealed that other organ systems were also compromised<sup>12,35-38,41</sup>.

Analysis of 1099 COVID-19 patients across China revealed that ARDS and AKI only occurred in 3.5% and 0.5% of cases, respectively<sup>12</sup>. Differently,

the analysis of severe COVID-19 patients presented an increased prevalence of ARDS (81%), AKI (29%), and a higher demand for medical ventilation (71%) and renal replacement therapy (RRT) (17%)<sup>36</sup>.

In Washington, the first description of COVID-19 critically ill patients in the USA, revealed that 95.2% of all the patients presented ARDS and that 71% of them required mechanical ventilation<sup>41</sup>. Grasselli et al.<sup>39</sup> presented compatible outcomes in Italy, revealing that 99% (95% CI, 98%-99%) of ICU patients needed respiratory support, including 88% (95% CI, 87%-90%) who received invasive mechanical ventilation (Table 5).

**Table 5** - Summary of Complications in COVID-19 Patients in China, Italy and United States of America

	Huang et al. n=41	Yang et al. n=52	Chen et al. n=99	Wang et al. n=138	Guan et al. n=1099	Arentz et al. n=21	Grasselli et al. n=1591
Pneumonia	100%	-	-	-	91.1%	-	-
ARDS	29%	67%	17%	19.6%	3.4%	95.2%	-
Invasive mechanical ventilation	10%	71%	4%	47.2%	6.1%	71%	88%
Acute cardiac injury; Cardiomyopathy	12%	23%	-	7.2%	-	33.3%	-
AKI	7%	29%	3%	3.6%	0.5%	19.1%	-
RRT	7%	17%	9%	-	0.8%	-	-
Liver dysfunction	-	29%	-	-	-	14.3%	-

ARDS: Acute respiratory distress syndrome; AKI: Acute kidney injury; RRT: renal replacement therapy.

<sup>a</sup> Defined as evidence of a globally decreased left ventricular systolic function on transthoracic echocardiogram in addition to clinical signs of cardiogenic shock, an elevation in level of creatinine kinase or troponin I, or a decrease in central venous oxygen saturation (Arentz et al.)

## Risk factors for ICU admission

Initially, only the presence of complications was statically significant for admission to ICU<sup>35</sup>. Subsequent studies demonstrated that the elderly and patients with any underlying disease were prone to poor clinical outcomes and increased risk of death, correlating these findings with a weaker immune response and cytokine storm in those patients<sup>36-38</sup>.

Patients in ICU in Wuhan, China, were older [median age 66 years (IQR, 57-78) vs 51 years (IQR, 37-62);  $p < 0.001$ ] and more likely to have complications and chronic illness (72.2% vs 46.6%;  $p < 0.001$ ), including arterial hypertension (58.3% vs 21.6%), diabetes mellitus (22.2% vs 5.9%), cardiovascular disease (25.0% vs 10.8%), and cerebrovascular disease (16.7% vs 1.0%) than non-ICU patients<sup>38</sup>. COVID-19 in Wuhan, China, also tended to progress faster in the elderly, with shorter days between the occurrence of the first symptoms until death among people aged 70 years or more than those aged less than 70 years (11.5 vs 20 days,  $p=0.033$ )<sup>44</sup>.

In agreement, an Italian cohort referred that 68% of the ICU patients had at least one comorbidity. However, the median age of severe patients was 63 (IQR, 56-70)

years, the same as the median age of all positive Italian cases with COVID-19, suggesting that older age alone is not a risk factor for admission to the ICU<sup>39</sup>. On this basis, USA studies also referred a higher percentage of chronic illness among patients requiring ICU<sup>45</sup>, and an increased risk of poor outcomes among people aged  $\geq 85$  years<sup>42,43</sup>.

In Wuhan, China, non-survivors were mostly men (66%), and 50% of them had chronic medical illness. Even more, these patients were more likely to receive mechanical ventilation (94% vs 35%), either invasively or non-invasively, when compared with survivors<sup>36</sup>. Likewise, in Italy, non-survivors were predominantly men (70%) and 48.5% of them had 3 or more underlying diseases<sup>34</sup>.

Comparison of fatalities between China and Italy initially evidenced equivalent case fatality rates (2.3)<sup>46</sup>. Furthermore, the current difference between the overall case-fatality rate in Italy (7.2) and China (2.3) was suggested to be related with: demographic differences between those countries, including older patients with more comorbidities in Italy; the classification method of COVID-19-related deaths and different strategies for SARS-CoV-2 infection diagnosis<sup>34</sup>. In this context, Lippi et al.<sup>13</sup> also suggested that the higher risk of death in Italy could be associated to the variable frequency of risk factors

across different populations.

### Radiological Findings

Huang et al.<sup>35</sup> revealed that all patients showed abnormalities in computed tomography (CT) of the chest at admission and 98% had bilateral pulmonary involvement, findings consistent with posterior studies also realized in Wuhan, China<sup>36-38</sup>.

A larger study in China including 1099 patients revealed no CT abnormalities at the time of admission in 13.8% of them and absence of radiologic or CT abnormalities in 17.9% of those with no severe disease. Pulmonary ground-glass opacity (56.4%) and bilateral patchy shadowing (51.8%) were the most common patterns<sup>12</sup>.

An abnormal chest radiograph was observed in 20 patients (95%) at admission in ICU patients in Washington, USA at admission. The most common findings on initial radiograph were bilateral reticular nodular opacities (11 patients [52%]) and ground-glass opacities (10 [48%]). By 72 hours, 18 patients (86%) had bilateral reticular nodular opacities and 14 (67%) had evidence of ground-glass opacities<sup>41</sup>.

In another retrospective study in Seattle, USA, almost equal results were observed. A chest radiograph was obtained in 23 patients (96%) on ICU admission, and all the radiographs showed bilateral pulmonary opacities<sup>40</sup>.

### Laboratory Results

In China, lymphocytopenia (lymphocyte count  $<1.0 \times 10^9/L$ ) was present in 35%-83.2% of the patients<sup>1,12,35-38</sup>. In retrospective studies with critically ill adult patients, low lymphocyte count occurred in more than 80% of them, a feature that is also prominent in SARS-CoV and MERS-CoV infection<sup>36</sup>. However, in other studies, only 35% of non-severe COVID-19 patients had lymphocytopenia, suggesting that a lower lymphocyte count reflects the severity of SARS-CoV-2 infection<sup>37</sup>. In the USA, Bhatraju et al.<sup>40</sup> exhibited common lymphocytopenia (75%) among patients admitted to ICU, and Arendtz et al.<sup>41</sup> presented that 67% of the ICU admitted patients had absolute lymphocyte count of less than 1000 cells/ $\mu L$ .

In China, the blood counts of patients on admission showed that 25%-33.7% had leukopenia (white blood cell count  $<4.0 \times 10^9/L$ )<sup>12,35</sup>. In USA, Arendtz et al.<sup>41</sup> presented that 67% of the patients had white blood cell count in the normal range.

Lactate dehydrogenase was increased in 39.9% to 75% of the patients<sup>37,38</sup>. D-dimer, C-reactive protein, aspartate aminotransferase, and interleukin (IL)-6 were also elevated in plasma (36%, 86%, 34%, 52%, respectively)<sup>37</sup>. Other findings included decreased albumin and increased levels of neutrophils, platelets, erythrocyte sedimentation

rate, total bilirubin, alanine aminotransferase, ferritin, creatinine, creatine kinase, myoglobin and glucose<sup>12,35,37</sup>.

There were also differences in laboratory findings between patients that required ICU and those who not. ICU patients presented higher white blood cell and neutrophil counts, as well as higher levels of D-dimer and creatine kinase than those not admitted to the ICU<sup>38</sup>.

### Immune response and Cytokine Storm

The spread of SARS-CoV-2 particles through the respiratory mucosa infects other cells and triggers immune responses, inducing a systemic cytokine storm that generates changes in peripheral white blood cells or immune cells. At the same time that the immunological response is vital for the control and resolution of infections, it can also lead to immunopathogenesis when out of control<sup>1,38</sup>.

COVID-19 patients had increased levels of plasma cytokines and chemokines, including IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, granulocyte colony-stimulating factor (GCSF), macrophage colony-stimulating factor (MCSF), 10kD interferon-gamma-induced protein (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1- $\alpha$  (MIP-1 $\alpha$ ), hepatocyte growth factor (HGF), interferon gamma (IFN- $\gamma$ ) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ )<sup>1</sup>.

Cytokines in plasma were elevated in individuals infected by SARS-CoV-2 that required ICU admission, suggesting an association with COVID-19 severity. Neutrophil count, D-dimer, blood urea nitrogen (BUN), and creatinine levels were significantly higher in severe patients, while the lymphocyte counts were decreased. Inflammatory factors IL-2, IL-6, IL-7, IL-10, and TNF- $\alpha$  were also elevated<sup>1,35</sup>.

Lymphocytopenia was higher in ICU patients (85% vs 54%,  $p < 0.045$ ) when compared with non-ICU patients<sup>35</sup>. Some studies suggested that a substantial decrease in the total number of lymphocytes indicates that coronavirus induces the consume of many immune cells and inhibition of the body's cellular immune function. Thus, damage to T lymphocytes might be an important factor leading to exacerbations of patients<sup>37</sup>.

Moreover, strengthening of immune support could be beneficial to populations with low immune function with COVID-19, such as the elderly, diabetics, people with long-term use of immunosuppressive agents, and pregnant women<sup>37</sup>.

### CONCLUSION

SARS-CoV-2 is a coronavirus that emerged in China. The infection is now a pandemic that rapidly spread throughout the world and led to a global effort to contain it. Studies suggested that asymptomatic patients contributed

to the extent of the spread of the disease. COVID-19 predominantly affects men and may present with multiple symptoms. COVID-19 worse outcomes are associated with increased age, comorbidities, complications, lymphocytopenia, and cytokine storm. Clinical features,

radiological findings and laboratory results presented similarities in different populations, but case-fatality rates can be conflicting, exposing the necessity of studies according to each region.

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