



Imagenological Findings and Correlation with the Degree of Severity of COVID-19

Hallazgos imagenológicos y correlación con la escala de gravedad de la COVID-19

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Summary

The SARS-CoV-2 virus is responsible for the current pandemic, declared a public health emergency by the WHO, which began in Wuhan, China, with the initial cases described as pneumonia of unknown origin. The virus continues to spread. Next, we carry out a review of the disease from its epidemiological, etiology, clinical manifestations, laboratory findings and findings in radiography and computed tomography. Some societies propose a correlation between tomographic findings and the quantification of the severity of the disease.

Resumen

El virus SARS-CoV-2 es el responsable de la pandemia actual, declarada como una emergencia de salud pública por la OMS, que inició en Wuhan, China, con los casos iniciales descritos como neumonía de origen desconocido. El virus sigue avanzando en su diseminación. A continuación, realizamos una revisión de la enfermedad desde sus características epidemiológicas, etiología, factores de riesgo, manifestaciones clínicas, hallazgos en laboratorio, en las imágenes por radiografía y tomografía computarizada. Algunas sociedades científicas proponen una correlación entre los hallazgos tomográficos y la cuantificación de la gravedad de la enfermedad.

1. Introduction

The current pandemic —caused by SARS-CoV-2 infection and the associated disease called COVID-19— is a public health emergency, as declared by the WHO, which began in Wuhan, China, with initial cases described as pneumonia of unknown origin. Currently, cases are reported in more than 188 countries and the number of infected people and mortality is increasing every day; in some countries it has led to the collapse of health systems, as many of them were not prepared to handle the situation to the point where it has arrived. The mortality rate is variable, according to the form of presentation of the disease —mild, moderate or severe—, in mild cases it can reach 1% and in moderate or severe cases, up to 10-35%, which is why it is key to identify these patients early through clinical manifestations, laboratory studies, the requirement of ventilatory support, and imaging findings, which have taken on an important role as a diagnostic aid.

Although little has been described about the correlation of imaging findings with the severity

of the clinical picture, the resolution of the findings, and the chronicity of the picture.

2. Epidemiology

Since its inception in China, the greatest impact on mortality has been recorded in the United States with over 154,793 deaths, making it the most affected country. The virus continues to advance its spread, reaching figures (August 2, 2020) of more than 18 million cases in 188 countries (1, 2), with the United States, Brazil, India, Russia and South Africa being the most affected.

Although the mortality rate by COVID-19 is around 1% in the general population (3), other reports mention that they are up to 10% and 35% (4). Among patients who progress to severe disease, hospital mortality is as high as 28% —much higher than in other reports that had incomplete follow-up data— and higher among patients who required invasive mechanical ventilation (5). In a study carried out by Auld and collaborators, it was found that among 217 critical patients, the mortality among those who required mechanical ventilation was 35.7% (6).

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Early data from China suggest that the age group with the most deaths from IDOC-19 is the over-60s with severe comorbidities and among people of other ages with severe underlying health conditions.

The March 18 report from the U.S. Centers for Disease Control and Prevention (CDC) indicates that mortality is highest in people over 85, ranging from 10% to 27%, followed by 3% to 11% among people aged 65-84; 1% to 3% in people aged 55-64; <1% among people aged 20-54; and no deaths among people aged ≤ 19 . (7)

In Colombia, within 90 days of the virus entering the country, there were 38,000 cases and 1,200 people (1.1%) died, most of them between the ages of 50 and 60. Currently there are more than 300,000 confirmed cases and more than 10,000 deaths (3%) (8).

2.1 Etiology

SARS-CoV-2 is a positive chain RNA virus that belongs to the family Coronaviridae, of the order Nidovirales, subfamily Orthocoronavirinae and this, in turn, is classified in four genera Alphacoronavirus (α CoV), Betacoronavirus (β CoV), Deltacoronavirus (δ CoV) and Gammacoronavirus (γ CoV). It has been determined that SARS-CoV-2 is part of the β CoV and the source of these, as well as α CoV, are probably bats and rodents (9).

It has been demonstrated that within the coronaviruses that affect humans, SARS-CoV, SARS-CoV-2 and MERS-CoV (β CoV from lineage B and C, respectively), are responsible for epidemics with variable clinical severity that present respiratory and extra-respiratory manifestations. In relation to SARS-CoV and MERS-CoV, mortality rates are up to 10% and 35%, respectively (9).

In a study conducted by Chan and collaborators, they describe that the 2019-nCoV genome has an 89% general nucleotide identity with the CoV related to the SL-Co-VZXC21 bat SARS, and 82% with the human SARS-CoV BJ01 2003 and the human SARS-CoV Tor2. Some studies suggest that certain intermediate hosts could be different mammals, such as minks, as well as some other mammals; however, this is not clear at this time (10).

Like SARS, SARS-CoV-2 has been shown to use the angiotensin-converting enzyme 2 (ACE2) as a receptor, the surface unit (S1) binds to it, and then uses the host serine protease (TMPRSS2), which allows the virus to enter the cell. This virus mainly invades the cells of the alveolar epithelium resulting in symptoms of respiratory origin. Since ACE2 is expressed mainly in the lungs and heart, it has been suggested that the most severe presentation of symptoms in patients with cardiovascular pathologies may be due to this virus tropism (11). The main pathogenesis of SARS-CoV-2 infection, as a virus directed at the respiratory system, is severe pneumonia, combined with the incidence of frosted glass opacities and acute cardiac damage (12).

2.2 Risk factors and clinical manifestations

Common risk factors include: age over 65, cardiovascular disease, diabetes, chronic respiratory disease, hypertension and immunosuppression status. If the patient is infected with COVID-19 has one or more of these comorbidities, which gives it a higher level of risk of complications from a clinical point of view (13).

COVID-19 is believed to have an incubation period of 14 days from exposure (14,15), but develops symptoms between 2.2 and 11.5 days (4).

It affects people of any age, but most often middle-aged and older adults (15, 16). Symptoms in children are usually mild, similar to those of adults (17), although cases of severity have been reported (18, 19) in which patients develop multisystemic inflammatory syndrome (with or without Kawasaki disease criteria) (20).

Fatal cases have occurred in the elderly or with underlying medical comorbidities (21).

Asymptomatic infections, whose frequency is unknown, have been described (22); however, they have clinical abnormalities that can be identified. Hu and co-workers performed chest tomography on 24 asymptomatic patients, 50% of which showed alterations compatible with the image infection; they developed mild symptoms a few days after diagnosis (23). Bandirali et al. describe in a series of 170 patients, that 59% of the asymptomatic or minimally symptomatic patients may have chest X-rays with findings of infection after 14 days of quarantine (24).

There are no specific clinical characteristics that distinguish COVID-19 from other viral infections (22, 25, 26).

The course of symptomatology can vary in a range from asymptomatic that progresses to mild symptoms and subsequent development of dyspnea with requirement of hospital admission, studies vary as to the times in which this can occur, between 7 and 8 days (15, 27).

The onset of the disease includes fever in most patients (99%), dry cough (59%), fatigue (70%), anorexia (40%), myalgias (40%), dyspnea (31%), cough with sputum (27%) (15, 28, 29).

Other less common symptoms include headache, odynophagia and rhinorrhea. Gastrointestinal symptoms, such as nausea and diarrhea, have also been described less frequently (15, 27).

Severe patients have pneumonia characterized by fever, cough, dyspnea, and bilateral opacities on chest imaging (15, 27).

Critical patients present multiorgan dysfunction with ventilatory failure and requirement of mechanical ventilation in intensive care unit. One of the most important complications in the critical patient is acute respiratory distress syndrome (ARDS) observed in 12-41% of the patients studied (27, 30). Other complications are arrhythmias, acute cardiac injury and shock (27).

The WHO reports that recovery time appears to be two weeks for mild infections and three to six weeks for severe illnesses; however, studies are still lacking to determine this accurately, as well as the long-term consequences (31).

2.3 Laboratory demonstrations

The white blood cell count is variable among leukocytosis, leukopenia and lymphopenia, and the latter is more common (15, 27); it presents with elevated levels of lactate dehydrogenase, ferritin and aminotransferases. Procalcitonin may be normal on admission and may become elevated as the infection progresses (15, 28).

Mortality has been associated with high levels of D-dimer and severe lymphopenia (27).

3. Diagnosis

The diagnosis is made by RT-PCR on samples isolated from respiratory tract secretions obtained by bronchoalveolar lavage, oropharyngeal swabbing or blood. The result is obtained within 15 minutes to 8 hours, depending on the technique used (32). This test has a sensitivity of 60-70 % with a high number of false negatives, for which some guidelines recommend for the initial diagnosis the tomographic findings associated with the clinical manifestations (33).

Computed tomography (CT) began to be used as a diagnostic test in some regions, due to the lack of the reagent for chemical detection. Given the low global availability of this and the exposure to radiation, radiological societies such as ACR (34), BSTI (35) and SERAM (36), advise against its use for diagnosis or screening. The Fleischner Society says that, based on the panelists' experience and despite recommendations from other societies, many do use the images for diagnosis, especially in patients with a high prior clinical probability, as they could reveal an alternative diagnosis to COVID-19, and management is based on established guidelines or standard clinical practice; furthermore, it highlights that sensitivity is higher in the context of low availability of diagnostic tests, as well as long waiting times that delay patient management.

CT imaging findings have a sensitivity of 94%. Their specificity is low, because the radiological patterns in COVID-19 overlap with those found in other viral respiratory infections, such as H1N1, MERS, and SARS, among others. X-ray and CT scans are more sensitive to the extent of the patient's clinical severity, since at this point the imaging findings are evident. Fifty percent of imaging studies can be normal, when the patient is in the early stages of the disease or has no or only mild symptoms (37).

The Fleischner Society consensus (32) makes recommendations for the use of chest radiography and tomography in adults, given that at the time of publication children did not present serious infections; however, later reviews describe radiological findings in children similar to those in adults; they highlight a higher prevalence of reverse halo consolidations in this age group (33).

Chest radiography is insensitive in mild or early COVID-19 infection (34); however, in hospitalized patients, both chest radiography and tomography can be useful in assessing disease progression and arriving at alternative diagnoses (e.g., lobar pneumonia suggestive of bacterial overinfection, pneumothorax, and pleural effusion) (38).

In a patient who initially has a negative PCR, with imaging findings highly suggestive of COVID-19, PCR should be performed again to confirm or rule out infection (38).

If the patient is asymptomatic, but has radiological findings highly suggestive of infection, PCR testing is suggested (39) to potentially identify a hidden infection and limit further transmission in the community and in the environment where the patient receives medical care.

3.1 Images

The candidate for tomography is the patient who presents clinical criteria of severity, rapidly worsening, in whom it is necessary to

detect complications and propose alternative diagnoses, therefore, this decision is individualized (35).

Regarding acquisition, Nakajima and collaborators recommend making ideally fine cuts, such as those used for TACAR (1-1.5 mm collimation), in order to adequately characterize fine details given their high resolution; it should also be performed in supine position and in final inspiration. The use of contrast medium is not necessary and axial and coronal projections should be evaluated (40).

The recommended terminology for descriptions is that used in Fleischner's glossary, in order to unify a clear radiological language (37).

The imaging findings described so far as typical are: the frosted glass pattern, which is usually the first finding in both plain radiography and CT, with incidences of 85.49%; the mostly peripheral and subpleural distribution (incidence 76.95%) with predominance towards the lower lobes in posterior segments and less frequently within the right middle lobe (Figure 1). Initially, it may be unilateral, and then a bilateral involvement is observed (incidence 81.80%). Less commonly, there may be thickening of the interlobular septa (48.46 %) (Figure 2), bronchiectasis and pleural thickening (52.46 %), in later stages of the disease as it progresses and the severity increases, patients with a "crazy paving" pattern can be seen (Figure 3), (14.81 %) (39, 41).

The consolidations indicate severity; therefore, if the initial CT scan has these findings, it is a serious patient (Figure 4). Its distribution is that described for frosted glass and, in fact, it overlaps with this in a smaller number of cases, more frequently in the elderly (43).

In most of the literature reviewed, less frequent findings are described, which can be observed according to the progression of the disease, pleural or pericardial effusion, lymphadenopathies, cavitations, pneumothorax, reverse halo or atoll sign (Figure 5) and bronchial dilatation with wall thickening (Figure 6) (44).

Below, some guidelines published by different international entities are described for the imaging evaluation.

The Fleischner Society proposes three scenarios depending on the clinic and the availability of resources. The recommendation to perform radiological imaging in patients with moderate-severe clinical manifestations, regardless of the outcome of the COVID-19 test, is highlighted, since it establishes the baseline lung status and helps to identify underlying cardiopulmonary abnormalities or even caused by the same infection, and that may facilitate risk stratification, in addition to being done in the patient who is clinically deteriorating.

On the other hand, multiple classifications have been developed by the different societies to report tomographic findings in patients with suspected or diagnosed COVID-19; it is recommended that the use of one or the other be arranged by the clinical team. In Colombia, those with the greatest acceptance are the Simpson classification, the British Society of Thoracic Imaging, and the Diagnosis and treatment protocol for novel coronavirus pneumonia.



Figure 1. Chest axial CT. A 50-year-old patient with an epidemiological link, frosted glass opacities are visualized distributed in a peripheral way (arrow).

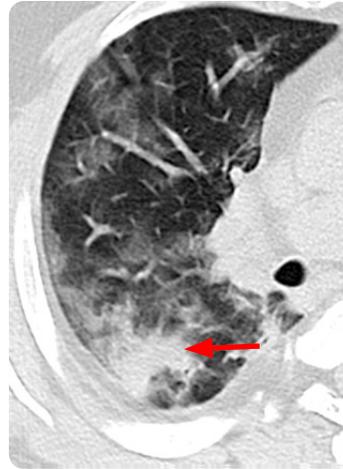


Figure 4. Chest CT scan. Patient of 34 years old, right basal consolidation is observed (arrow).

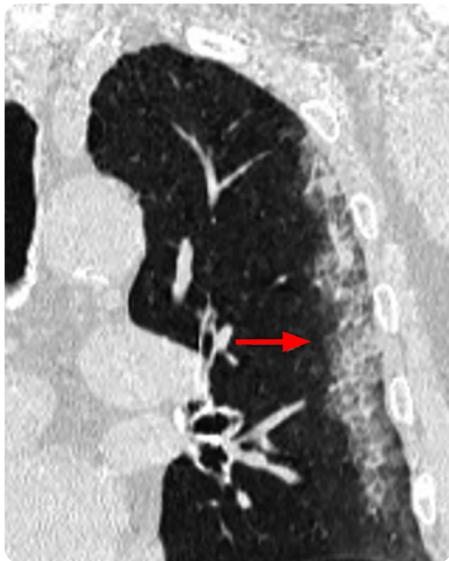


Figure 2. CT of the thorax, axial. Thickening of interlobular septa in a peripheral way (arrow).

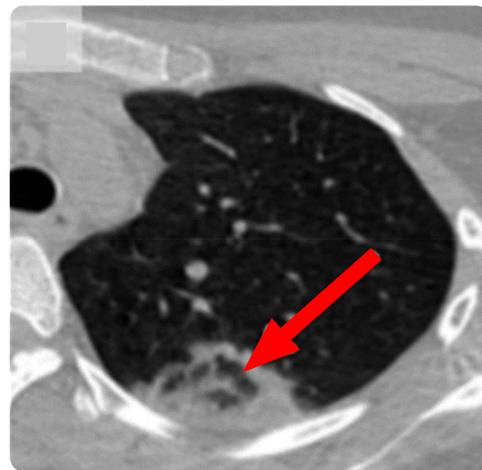


Figure 5. Reverse halo sign. Axial CT scan. 22-year-old woman. An area of frosted glass opacity is observed with a dense consolidation ring towards the left upper lobe (arrow). This finding corresponds to the sign of the reverse halo. Source: Taken with permission of publication of Bernheim and collaborators. (45).

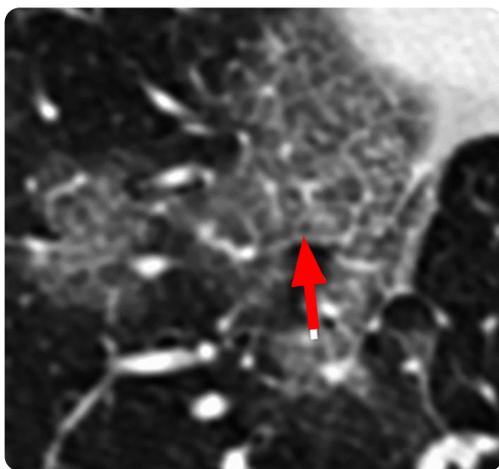


Figure 3. Paved pattern. Axial CT scan, without contrast medium. 65 year old patient with recent travel history to Wuhan, with fever and productive cough. A cobblestone pattern is observed, which is characterized by opacity in frosted glass associated with thickening of the interlobular septa towards the lower right lobe. Source: Taken with publication permission from Chung and collaborators (42).

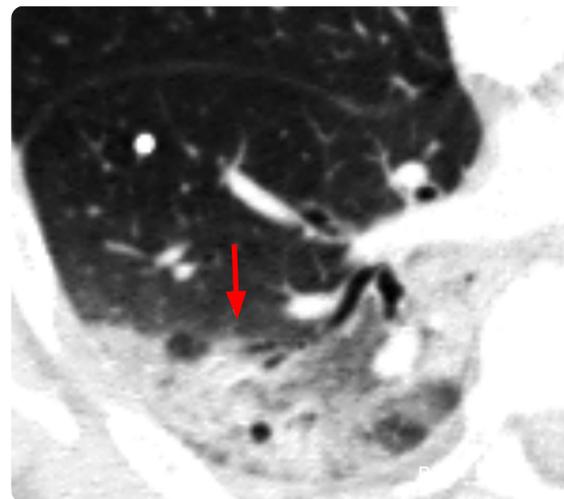


Figure 6. Axial thorax CT. 58-year-old patient, with suspicion of infection by COVID 19, which shows bronchial dilatation and thickening of the bronchial walls.

Table 1. Proposed language for the report of tomographic findings related to COVID-19

CT screening for the diagnosis or exclusion of COVID-19 is not currently recommended by most organizations or the U.S. Centers for Disease Control and Prevention.			
Imaging Classification of COVID-19 Pneumonia	Fundamentals	Tomographic findings	Suggested language for the report
Typical appearance	Commonly reported imaging findings with higher specificity for COVID-19 pneumonia.	Peripheral frosted glass areas, bilateral with or without consolidation, or interlobular septa (cobblestone pattern). Multifocal frosted glass areas of rounded morphology with or without consolidation, or interlobulillary septa (cobblestone pattern) Reverse halo sign and other findings of organizational pneumonia (seen later in the disease)	“Commonly reported findings of COVID-19 pneumonia are found. Other processes, such as influenza and organizational pneumonia, as seen in drug toxicity and connective tissue disease, may cause a similar imaging pattern”.
Undetermined Appearance	Non-specific findings of COVID-19 pneumonia.	Absence of typical characteristics and presence of: Multifocal, diffuse, perihilar or unilateral frosted glass areas with or without consolidation, without a specific distribution and not rounded or not peripheral Some small areas of frosted glass with a non-peripheral distribution, not rounded.	“There are imaging findings that can be seen in COVID-19 pneumonia; however, they are not specific and can occur with a variety of infectious or non-infectious processes”.
Atypical	Uncommon or unreported findings of COVID-19 pneumonia.	Absence of typical or indeterminate findings and presence of: Isolated or segmental lobar consolidation without frosted glass. Small nodules (centrilobular, “tree in gemination”). Lung cavitation. Smooth thickening of interlobulillary septa with pleural effusion.	“There are imaging findings that have been reported atypically in COVID-19 pneumonia (alternative diagnoses should be considered)”.
Negative for pneumonia	No findings of pneumonia.	There are no tomographic findings suggesting pneumonia.	“No tomographic findings suggesting pneumonia. (Note: CT scan of the chest may be negative in early stages of COVID-19 pneumonia)”.

Notes: 1. Inclusion in a report of items noted in parentheses in the “Suggested Reporting Language” column may depend on clinical suspicion, local prevalence, patient status, and local procedures regarding the report. CT is not a substitute for RT-PCR, consider testing according to local recommendations and procedures and the availability of RT-PCR.

Source: Taken and translated from Simpson et al.

The British Society of Thoracic Imaging (BSTI) classifies patients in the COVID-19 setting into three clinico-radiological categories and makes a quantification of the severity of the disease (46).

Table 2. Correlation between radiological findings and quantification of clinical severity

	Findings	Changes in the lung parenchyma	Gravity
Suggested COVID-19 infection	• Peripheral opacities in frosted glass	Up to 3 focal anomalies < 3 cm	Moderated
	• Diffuse alveolar pattern • Paved pattern • Organizational pneumonia	More than 3 focal anomalies or > 3 cm	Moderate/Severe
	• Distortion of architecture		Severe
Indeterminate of COVID-19 infection	• Peripheral opacities in frosted/ patched/non-peripheral glass • Fibrosis with frosted glass • Pleural effusion • Adenopathies • Complex patterns	Up to 3 focal anomalies < 3 cm	Moderated
		More than 3 focal anomalies or > 3 cm	Moderate/Severe
Unlikely of COVID-19 infection	• Lobar Pneumonia • Cavitated infections • Gemmation tree pattern		

Source: Adapted from The British Institute of Radiology (37, 47).

Table 2 shows that patients with a mild clinic generally have lesions with a diameter on the long axis of less than 3 cm and are characterized by being frosted glass lesions. Those who present in the images consolidations, frosted glass pattern and consolidation, cobblestone pattern or architectural distortion, and/or these lesions measure more than 3 cm in long axis, are patients with a moderate/severe clinical state. Zhon and collaborators found similar findings in their study (48).

The BSTI also recommends extending the chest CT study if a CT scan of the abdomen finds basal lung findings.

The severity of COVID-19 is categorized as mild, moderate, severe, or critical, depending on the absence or presence of significant lung dysfunction or damage, and other clinical parameters specified in table 3 (49).

Tabla 3. Criterios clínicos de gravedad de la infección COVID-19

Types	Findings
Mild	Mild clinical symptoms (fever \leq 38 °C [untreated], with or without cough, without dyspnea, without - chronic diseases).
Moderate	Fever, respiratory symptoms, images of pneumonia.
Severe	Any of the following: <ul style="list-style-type: none"> • Respiratory Distress, FR \geq 30/min. • SpO2 \leq 93 % at rest. • PaO2/FiO2 \leq 300 mm Hg. • Rapid image progression between 24-48 h.
Critical	Any of the following: <ul style="list-style-type: none"> • Respiratory failure, with requirement for mechanical ventilation. • Shock. • Multi-organ failure, ICU admission.

Abbreviations: RF: Respiratory frequency. SpO2: Oxygen saturation. PaO2: Partial pressure of oxygen. FiO2: Inspired oxygen fraction.

Source: Adapted from Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial version 7) (49).

Additionally, radiological findings related to the clinical course of the infection in time have been described, in which early stages (0-4 days) changes given by opacities in frosted glass, irregular paving and few compromised lobes have been observed; in progressive stage (approximately 5-8 days), it is associated with changes given by increase in both extension and number of lesions by frosted glass and irregular paving, with greater lobe commitment directly related to the degree of severity (44); in maximum stage (9-13 days), it is related to the appearance of consolidations, and in regression stage (more than 14 days), it is associated with decrease of findings and gradual resolution (50).

The follow-up CT images showed that the lesions are migratory: they manifest themselves as the absorption of the primary lesions and the appearance of new lesions, which had not yet been reported (51).

In summary, the imaging progression initially shows the pattern described in frosted glass, followed by the thickening of interlobular

septa and consolidations. The pattern in cobblestone and the consolidations are patterns that suggest that the patient is serious or in a critical state and are usually seen 10 days after the onset of symptoms (50). Patients considered for hospital discharge should have clinical stability, with resolution of symptoms and a negative RT-PCR (49).

3. Follow-up

Currently, there is no indication to perform imaging studies to evaluate the resolution of the disease; however, it has been described that patients with clinical improvement show gradual resolution of consolidations, as well as decrease in the number-size of lesions and lobes involved, parameters that are considered determinant for the evaluation of disease severity, which indicates the importance of accurately describing these findings from the initial imaging studies.

No significant differences have been demonstrated (mortality, length of stay and days of ventilation) in the daily performance of X-rays for ICU patients (52).

The resolution time of imaging findings is still under investigation, although some articles talk about resolution in approximately 2 weeks. Likewise, lung lesions that indicate chronicity are under study; some authors describe that residual fibrosis may be related to the latter (44).

4. Conclusion

SARS-CoV-2 infection has increased exponentially and although its mortality is low in the general population, in the high-risk population (elderly patients > 60 years and with comorbidities) it is high. The clinical severity is variable from the point of view of pulmonary and extrapulmonary manifestations. Knowing the radiological findings is important for the diagnosis, even more so when RT-PCR is not available or the result is not available in the immediate days. It is important to make a structured report, take into account the comorbidities, try to recognize the radiological findings and propose a degree of severity in the radiological report. In this review, the importance of recognizing the classification of severity, according to the image findings, which can be helpful to know the state in which the disease is found and, additionally, the response to treatment, is made known. It is proposed, then, that in future research the relationship of the imaging findings with ventilatory parameters (for example, levels of PaO2/FiO2) can be demonstrated, in order to know the state of the disease and the response to treatment.

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