COVID-19, A New Outlook on Pandemic Symptoms and Diagnostic Approach

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ABSTRACT	ARTICLE DETAILS

Background: The main objective of this research is to learn the symptoms that occur in this pathology, since we are currently still fighting COVID-19, because of this, it is important to keep us informed about the different diagnostic methods available, which help us reach an earlier and more effective diagnosis. Various articles have been compiled to identify as soon as possible the active cases and thus reduce the number of infections.

Materials and methods: This research was conducted on the basis of scientific articles and books, related to COVID-19.

Methods: This research was conducted based on 15 scientific articles and 3 books, related to COVID-19.

Results: The most important risk factors are diabetes mellitus, hypertension, obesity, age and sex. The most common symptoms in Latin America are dry cough, fatigue, sore throat, and fever. The preferred diagnostic test for COVID-19 is the polymerase chain reaction for its specificity and sensitivity

Conclusions: As a conclusion, the main objective of the research was achieved, which is to inform the reader about the most relevant symptoms of SARS-CoV-2 in order to improve the identification of suspected cases. Furthermore, we compare various diagnostic methods that exist to date and determine that PCR is the most specific and sensitive.

KEYWORDS: COVID-19, symptoms, diagnosis, risk.

INTRODUCTION

Coronavirus is a virus which contributes to the onset of respiratory tract symptoms and can progress to severe symptoms (1). The world has faced a pandemic since December 2019 caused by Coronavirus Disease 2019 (COVID-19) (2). After cases of "flu" started in Wuhan, China that were not consistent with any disease it was decided to perform metagenomic RNA sequencing of the patient's sample; the complete viral genome data suggested that it was a novel RNA virus related to the Coronaviridae family, later designated as '2019-nCoV' or Novel CoV-19 (3).

Coronavirus is named after its crown-like surface projections which can be observed under a microscope (4). Its glycoprotein "crown" allows the virus to withstand the conditions of the gastrointestinal tract and spread by the fecal-oral route (4). It belongs to a group of unsegmented,

Spherical, large (100-160 nm) single-stranded RNA with a genome number of 26 to 32 kb (the largest among known RNA viruses). COVID-19 is a viral infectious disease with high mortality, highly contagious and has caused an international collapse in the health system (5). It is among the 10 most lethal viruses known to humans with a high mortality rate of up to 36% for MERS-CoV during 2012 (3), SARS-CoV-2 is the seventh coronavirus to be identified to date (6). Latin America became the epicenter of the pandemic, although the United States led the world in the number of diagnosed cases and reported deaths, as of September 5, 2020 (7).

Coronaviruses are commonly found in humans and in many species of animals such as bats, camels, cattle, and wild cats (8). SARS-CoV enters through the respiratory tract (1); the

virus is transmitted from person to person through respiratory droplets produced by talking, coughing, or sneezing. The contagious period is two days before the onset of symptoms, peaks on the day of onset and decreases 7 days later. The incubation period is 14 days, with an average of 4 to 5 days. Although it can vary greatly from 0 to 24 days (9). The average recovery time is 2 weeks, but if the disease is severe, it takes from 3 to 5 weeks (10).

The risk factors associated with SARS-CoV-2 are age, chronic degenerative diseases, however, we must keep in mind that the risk of suffering COVID-19 is for everyone (5). A study was conducted in hospitalized patients in New York and the most common risk factors were hypertension, obesity, and diabetes (9); this is due to the endothelial damage that these diseases cause as well as their impact on oxidative metabolic processes and inflammation produced at the cellular and tissue level (5). In Puerto Padre from March to May 2020, it was found that the age with the highest prevalence was 45 to 59 years, followed by 30 to 44 years, with an average of 50 years of age and it was also found to affect more males than females. In Mexico, 19,224 cases were reported, the most affected sex was also male with 11,186 cases, the average age was 46 years, the patients who died had multiple comorbidities 43.53% had AHT, 39.39% DM, 30.4% obesity, as shown in the table 1. (5). Smoking is also an important comorbidity because on one hand, smoking seems to induce a positive regulation of the natural SARS-CoV-2 receptor angiotensin converting enzyme 2 (ACE2) in human cells. On the other hand, ACE2 enables the conversion of angiotensin II to angiotensin 1-7 (Ang1-7), a peptide with anti-inflammatory properties. Therefore, smokers may have a higher risk of infection but a lower risk of developing a severe form of the disease (2).

Table 1. The most frequent comorbidities among 5,700 hospitalized patients in New York. (9)

Risk factors	Prevalence %
Hypertension	57
Obesity	42
Diabetes	34
Cardiovascular diseases	32
Chronic lung diseases	18

METHODS

This article was carried out through a research based on several books such as: "Harrison Principles of Internal Medicine", "Clinical Diagnosis and Treatment", "Medical Microbiology"; in addition to articles obtained from "Springerlink", "Clinicalkey", "Scielo" and "Revista Mexicana de Gastroenterological". Fifteen articles and three books on the disease, its symptomatology and the diagnostic approach for SARS-CoV-2 were chosen in order to identify the most common symptoms and the most accurate methods of diagnosis.

THEORETICAL FRAMEWORK

The SARS-CoV-2 contains a protein called Spike protein which recognizes the host angiotensin-converting enzyme receptor 2 and these bind, causing the serum transmembrane protease type 2 to cleave the Spike protein and fuse the viral and cell membranes. The angiotensin-converting enzyme 2 receptor is expressed in the airway, in alveolar type 2 pneumocytes and in the rest of the respiratory tract, as well as in the heart, kidney and gastrointestinal tract. However, it is known that the lungs are the most susceptible to the virus because it carries large numbers of type 2 pneumocytes that will act as a reservoir to replicate the virus. (9) Viral load is known to peak in the upper respiratory tract around the time of symptom onset. The immune response may vary due to the patient's risk factors, which will affect the severity of the disease and the duration of illness. (11)

As for the clinical picture of SARS-CoV-2 manifests with fever, adynamia, headache and myalgia, these being the most common, in addition to odynophagia, rhinorrhea and conjunctivitis, on the other hand, also come to present digestive symptoms such as nausea, vomiting or diarrhea, however, these are manifested before fever and respiratory symptoms low, like anosmia and ageusia; The most severe that a patient may present with is pneumonia manifested by fever, cough, dyspnea, and bilateral pulmonary opacities seen on chest radiograph. Additionally, in pediatric patients the symptoms are usually mild, with high respiratory symptoms, although the risk exists, and deaths have been reported in children under one year of age. Talking about the physical examination, fever, polypnea and reduction in oxygen saturation will be found. However, 40% of patients may have COVID-19 and be asymptomatic (9).

In a study carried out in June 2020 with 104 patients, the most frequent symptoms were identified as the following, due to their prevalence percentage, as you can see in the table 2. (11)

Table 2. Prevalence of the most common symptoms. (11)

Common symptoms	Prevalence %
Dry cough	57.7
Fever	56.6
Fatigue	33.0
Myalgia	29.3%

In a study conducted in the Department of Internal Medicine and Otolaryngology with 791 patients, it was found that the best indicators for SARS-CoV-2 were anosmia, fever, myalgia, and cough, with anosmia being a marker that tells us that it is 7 times more likely to be positive for COVID-19. Laboratory findings included lymphopenia in 90% of patients, elevated C-reactive protein, D-dimer, LDH, ferritin and liver transaminases with decreased albumin and platelets (9).

In 8 Latin American countries between March 1 and July 30, 2020, a study was conducted that revealed that the most common symptoms were dry cough, fatigue, sore throat, and

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fever; the most reported comorbidities were obesity, hypertension, and DM. It should be taken into account that in Mexico, only patients with severe disease are hospitalized and there is less access to advanced care available to the general population (7).

In Zhongnan Hospital of Wuhan University 1141 cases were evaluated in which their symptoms were only gastrointestinal, men outnumbering women, the most reported were anorexia, followed by nausea and vomiting, diarrhea occurred in 37% of patients and 25% abdominal pain (12).

Meanwhile, at Wuhan Children's Hospital, it was found that the most striking feature was that the first symptoms in these children with probable COVID-19 were apparently nonspecific or covered by other diseases. The patients' symptoms did not always include fever or cough; some pediatric patients were brought to the emergency department because of digestive tract symptoms such as vomiting, diarrhea, and abdominal pain, as well as nervousness or symptoms such as seizures. Only when the chest CT scan showed signs of pneumonia where they hospitalized as probable or confirmed cases of COVID-19 (6).

We must take into consideration that there are patients who are classified as suspects of being carriers of COVID-19 since they presented dyspnea and fever, after all, the CT scan of the chest did not suggest COVID-19, the main diagnoses were others such as infectious diseases, heart failure, COPD; so, we must remember that although we are currently dealing with this pandemic, not all diagnoses will be COVID-19 (2).

Getting deeper into the gastrointestinal symptoms, a study was conducted in the United States in which adults 18 years of age were considered who underwent nasopharyngeal swab testing for severe acute respiratory illness, the indications for this test were respiratory symptoms such as cough, fever, and shortness of breath. The primary exposure was the presence of gastrointestinal symptoms including diarrhea, nausea, or vomiting documented anywhere in history. A total of 278 patients tested positive for COVID-19 and 238 tested negatives, of which 61% had gastrointestinal symptoms and 39% did not course with any gastrointestinal symptoms, which tells us that patients with gastrointestinal symptoms were more likely to test positive for SARS-CoV- 2. (13) The Mexican journal of gastroenterology notes that in patients with these symptoms, there was a trend toward lower ICU admission rates and a lower rate of death and that symptoms varied widely with diarrhea, nausea, anorexia being the most frequently reported. There are other rare symptoms such as abdominal pain, belching and reflux. (14) Since there are ACE II receptors in the oral mucosa and epithelial cells of the tongue, both can serve as infection routes thus could explain the presence of gastrointestinal symptoms. (12)

In turn, neurological conditions may precede typical respiratory symptoms by several days or even be the only indicators of SARS-CoV-2 infection. They may occur before, during, or even after respiratory involvement. Conditions found to include gustatory and olfactory dysfunction or impairment that are associated with peripheral nervous system involvement develop early in the course of the disease and are considered useful diagnostic markers. Myalgias are a common symptom related to generalized inflammation, where cytokines are involved. Altered mental status, confusion and delirium may be part of the primary manifestations, since one hypothesis that has been put forward, is the ability of SARS-CoV-2 to access the central nervous system either by systemic hematogenous dissemination or neuronal retrograde dissemination, which compromises the blood-brain barrier that causes apoptosis of neuronal cells and favours the entry of COVID-19 through the olfactory bulb. Some of the neurological complications mentioned are seizures and epilepsies. SARS-CoV-2 can infect endothelial cells leading to endothelial dysfunction and both microvascular and macrovascular arterial and venous complications. It also induces local inflammation and a vasculitis process in the cerebral arterial walls, which may cause ischemic CVE (15).

Various methods are used to diagnose a patient suspected of SARS-CoV-2. The standard testing protocol according to WHO involves 5 steps:
1. Collecting samples from the patient
2. Adequate transport of collected samples to the laboratory.
3. Provide demographic and clinical information to the laboratory
4. Laboratory testing of the sample
5. Prepare and report correct and appropriate test results (3).

The reverse transcriptase polymerase chain reaction (PCR), the microbiological diagnosis, is based on the detection of viral RNA genetic material, from obtaining respiratory samples from patients with compatible symptoms. PCR is a very sensitive and specific technique, which is why it is currently the diagnostic technique of choice. If the initial tests are negative and there is a high suspicion of the disease, it is necessary to extend to blood, urine, or stool tests. According to the European CDC, it can only be confirmed that a patient has overcome the disease when 2 negative rt-PCR results are obtained after 24 hours between them (16).

Another method used is the IgG and IgM antibody detection test because the antibodies begin to be produced from the sixth day after the onset of symptoms and at the same time a decrease in viral load is observed. At seven days almost half of the cases have total antibodies and at fifteen days almost 100%, both mild and severe cases. Antibody techniques seek to detect the immune response of patients, which increases as the infection progresses; if both immunoglobulins are detected it is an ongoing subacute infection, IgM may take up to two weeks to appear. The detection of IgG after day seven indicates previous infection with the virus but is not useful to

confirm the presence of the virus, this test is performed in capillary blood. The method is the enzyme-linked immunosorbent assay (ELISA), which requires trained personnel, since it is a blood sample by venepuncture and specific equipment. It has the advantage of knowing the class, subclass and quantification of immunoglobulin, the results take one to three hours, however, cannot diagnose an acute infection. The antigen detection test in nasopharyngeal exudate, detects the presence of antigens expressed by COVID-19 in a sample of the respiratory tract of a person, gives results within 30 minutes, the antigens are only expressed when the virus is actively replicating, so these tests are to identify acute or early infections. If it is negative, it is necessary to perform PCR to confirm (16).

Chest CT scan is also one of the highly sensitive diagnostic techniques so many researchers recommend its use as one of the necessary ancillary diagnostic methods for COVID-19, and its results come even before clinical symptoms appear. Typical features of the CT scan of the chest of a patient with COVID-19 include bilateral multilobar ground-glass opacities with different distributions in the posterior and in the peripheral ones, together with subpleural ascites, thickened lobular septa with variable alveolar filling and amalgamation (3).

LAMP (Loop-Mediated Isothermal Amplification), a comparatively novel technique that is in the process of approval for the diagnosis of COVID-19. It is a molecular amplification technique that can amplify any genomic material with high efficiency and in less time. The technique is based on the synthesis of target DNA at a constant temperature of 60-65°C using a specially designed primer sand enzyme (DNA polymerase) that has strand displacement activity instead of heat denaturation as in other PCR techniques and in one hour or less (3).

Screening of patients with suspected COVID-19 has been based on nasopharyngeal RT-PCR and chest CT. When RT-PCR and chest CT scan results are combined, a sensitivity of 88% and a specificity of 100% can be achieved. However, chest CT is a longer process and other types of tests may be used to reach the diagnosis (2).

A study approved by Osaka Habikino Medical Center on April 30, 2020, sought to evaluate qRT-PCR vs RT-LAMP for detecting SARS-CoV-2, including specificity, sensitivity, and minimum amount of RNA detected. A total of 151 nasopharyngeal and 88 sputum samples were tested. Using the conventional RT-PCR assay, 79 of 151 nasopharyngeal samples and 29 of 88 sputum samples were positive, whereas with RT-LAMP 71 of 151 nasopharyngeal samples and 25 of 88 sputum samples were positive. (17)

Check the table below to see the comparison between the specificity and sensitivity of the different diagnostic tests.

Table 3. Comparison between sputum and Nasopharyngeal diagnostic tests. (10)

	Specificity	Sensitivity	Positive predictive values	Negative predictive values
Nasopharyngeal	98.6%	88.6%	96.0%	92.1%
Sputum	98.3%	82.8%	98.6%	88.8%
Totals	98.5%	87.0%	97.9%	90.2%

It was concluded that RT-LAMP is a simple, low-cost, rapid, and highly reliable method, equivalent to RT-PCR, especially for patients with relatively high viral loads. (17)

A study was carried out in oncological patients, in which patients were identified who presented incidental findings suggestive of an infectious pulmonary process in asymptomatic patients. (10) During the study period a total of 129 PET/CT studies were performed for oncological indications. Of these, 11 showed findings suspicious for an infectious pulmonary process in 8 men and 3 women aged 30 to 79 years.

In 4 of the cases there was a single infiltrate with ground-glass density that had reappeared or was previously unknown. The remaining 7 cases had multiple bilateral ground-glass infiltrates. Of the 7 patients with multiple bilateral infiltrates, 5 (71%) were confirmed by PCR. Two of these patients, who showed the most extensive involvement, developed manifestations of infection in the days following the study, consisting of fever, cough, malaise, and dyspnea and died from the process of pneumonia 7 and 12 days after the study. Therefore, special attention should be paid to pulmonary evaluation in PET/CT studies. (10)

One article compiled evidence-based studies discussing the controversy in the use of chest CT scanning, analysing a study of 51 symptomatic patients; 2 reported a sensitivity of 98% for CT scanning compared to 71% for reverse transcription polymerase chain reaction (RT-PCR) in symptomatic patients. An additional study of 103 symptomatic subjects 3 showed an initial sensitivity of chest CT of 93%, a specificity of 53%, a positive predictive value of 92% (18). Chest CT data from asymptomatic individuals from the "Diamond Princess" cruise ship, 5 where 41 of 76 asymptomatic subjects (54%) had lung opacity on CT is not relevant for screening, as all were RT-PCR positive. One patient referred for a CT scan for "COVID-19" (but no symptoms of COVID-19). The radiologist reported it as negative for COVID-19, due to the presence of pulmonary edema from aortic valve stenosis. The patient was treated for heart failure and improved dyspnea, with no development of COVID-19 symptoms and no positive RT-PCR. (18)

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DISCUSSION

Considering what was collected during this article we can see that the most important risk factors are being male, since several articles showed that they are more susceptible, have diseases such as diabetes mellitus, hypertension, and obesity. Age is also a significant risk factor since the population aged 46-50 years was the most affected.

As for the symptoms that stood out the most were respiratory symptoms which we know are caused because the lungs have many types 2 pneumocytes that act as a reservoir to replicate the virus. The clinical manifestations that were most reported in Latin American patients who tested positive for COVID-19 were dry cough, fatigue, sore throat and fever, however, we must not lose sight of the gastrointestinal manifestations due to the study that was conducted in the United States in which they mention that 61% of patients who tested positive for COVID-19 had gastrointestinal symptoms, which can tell us that patients with suspected COVID-19 who present gastrointestinal symptoms are more likely to give a positive result. Thanks to this research we have a very interesting hypothesis which is that SARS-CoV-2 can access the central nervous system either by systemic hematogenous dissemination or neuronal retrograde dissemination and this compromises the blood-brain barrier that causes apoptosis of neuronal cells and favours the entry of COVID-19, this hypothesis is still under study, although it could justify why some patients have neurological manifestations such as ageusia and anosmia.

As for the diagnostics we mentioned several, despite this, it is known that the PCR is the diagnostic test of preference because it is a very sensitive and specific test, on the other hand, the antibody detection test seeks more than anything else the detection of the immune response of patients, the ELISA test has the advantage of being more specific because thanks to this we know the class. The nasopharyngeal exudate test has the advantage of being very fast but can give false negative results. Chest computed tomography is recommended as an auxiliary diagnostic method because it is very sensitive, and finally, LAMP is a diagnostic test that is still under investigation because it is very new.

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BOOK CHAPTER

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