COVID-19: clinical and laboratory manifestations in novel coronavirus infection
COVID-19: manifestações clínicas e laboratoriais na infecção pelo novo coronavírus

Analucia R. Xavier1, 2; Jonadab S. Silva3; João Paulo C. L. Almeida3; Johnatan Felipe F. Conceição3; Gilmar S. Lacerda1, 4; Salim Kanaan1, 2

1. Laboratório Multissectório de Apoio à Pesquisa em Nefrologia e Ciências Médicas, Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brazil.
2. Departamento de Patologia, Faculdade de Medicina, Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brazil.
3. Faculdade de Medicina, Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brazil.
4. Serviço de Patologia Clínica, Hospital Universitário Antônio Pedro, Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brazil.

ABSTRACT
COVID-19 is a highly contagious disease caused by the coronavirus of severe acute respiratory syndrome 2 (SARS-CoV-2). In 2020, due to the outbreak, it was considered by the World Health Organization (WHO) as a pandemic. The infection caused by the novel coronavirus has high mortality in a small portion of the infected population, especially in elderly, immunosuppressed, diabetic, cardiac, and hypertensive individuals. Many infected are asymptomatic (and may be carriers) or present mild or moderate flu-like symptoms. The most severe clinical picture of COVID-19 is characterized by an inflammatory cytokine storm, with hematological changes and coagulation dysfunction, which can lead to tissue damage and death. Nonspecific laboratory biomarkers may be either increased or decreased as the course of the disease progresses and are often useful in predicting complications of the disease, such as the use of D-dimer and platelet/lymphocyte ratio. Specific laboratory diagnosis is based on the detection of viral ribonucleic acid (RNA) by real-time polymerase chain reaction (RT-PCR) of nasal and oropharyngeal swab samples; it is more effective when performed in the first days after symptom onset. Serological tests are useful in detecting the immune response, since both class M (IgM) and class G (IgG) immunoglobulin antibodies can be detected seven days after the onset of clinical symptoms, and may extend for more than 25 days, although not exempting the individual from remaining infectious, depending on their viral load and clinical presentation. The rational use of specific laboratory markers must respect the disease chronology, and the correct interpretation may provide subsidies for a better management of affected patients, as well as identifying asymptomatic carriers or those with mild symptoms.

Key words: coronavirus infections; SARS virus; immunologic tests; reverse transcriptase-polymerase chain reaction; biomarkers; clinical pathology.

RESUMO
COVID-19 é uma doença altamente contagiosa provocada pelo coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2). Em 2020, devido ao surto, foi caracterizada pela Organização Mundial da Saúde (OMS) como pandemia. A infecção causada pelo novo coronavírus tem alta mortalidade em uma pequena parcela da população infectada, especialmente em indivíduos idosos, imunodeprimidos, diabéticos, cardiopatas e hiper tensiones. Muitos infectados são assintomáticos (e podem ser portadores) ou apresentam sintomas leves a moderados, semelhantes ao estado gripal. O quadro clínico da COVID-19 na forma mais severa é caracterizado por uma tempestade inflamatória de citocinas, com alterações hematológicas e da coagulação que podem levar ao dano tecidual e morte. Exames laboratoriais inespecíficos podem apresentar-se mais elevados ou diminuídos conforme o curso da doença, e muitas vezes são úteis na predição de complicações, como o uso do D-dímero e a razão plaqueta/linfócitos. O diagnóstico laboratorial específico se baseia na detecção do ácido ribonucleico (RNA) viral por reação em cadeia da polimerase em tempo real (RT-PCR) de amostras de suabe nasal e orofaríngeo; é mais efetivo nos primeiros dias após o início dos sintomas. Testes sorológicos são úteis na detecção da resposta imune, pois tanto os anticorpos da imunoglobulina da classe M (IgM) quanto da classe G (IgG) podem ser detectados após sete dias do início dos sintomas clínicos, podendo se estender por mais de 25 dias, embora não sênte o indivíduo de continuar infectante, dependendo de sua carga viral e apresentação clínica. O uso racional
INTRODUCTION AND DEFINITION

Coronaviruses (CoVs) are enveloped viruses with 60 to 130 nm diameter, that contain a positive sense, single-stranded ribonucleic acid (RNA) genome, with genome size ranging from 26 to 32 kilobases (kb) in length (1, 2). The virus can present pleomorphic capsids and have corona or crown-like surface projections, hence the name coronavirus (2).

The Novel Coronavirus, order Nidovirales, family Coronaviridae, subfamily Orthocoronavirinae, was named severe acute respiratory syndrome – coronaviruses-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV), and the World Health Organization (WHO) announced COVID-19 (coronavirus disease) as the name of this new disease on February 2020 (3, 4).

Coronaviruses can be divided into three groups according to genetic and antigenic criteria: α-CoVs, β-CoVs, and γ-CoVs. Coronaviruses infect mainly birds e mammalian, being α- and β-CoVs also capable of infecting mammals and, therefore, may cause infection in humans (5). The infection mainly affects the superior respiratory tract similar to a simple cold but it may compromise the inferior respiratory tract causing severe acute respiratory syndrome (SARS) (6).

Another coronaviruses species cause mild respiratory diseases in humans (HCoV.HKV1, HCoV-OC43, HCoV-NL63, and HCoV-229E) (4, 6). Six coronaviruses are known to infect humans, but two of them are capable of causing SARS with worst prognosis: SARS-CoV and middle east respiratory syndrome coronaviruses (MERS-CoV), which have led to outbreaks in China and the Middle East, respectively (4, 7).

Some CoVs were originally discovered as a cause of limited enzootic infections only in animals but progressed to establish zoonotic disease in humans. Due to the similarity of 96.2% RNA with the coronavirus that infects Chinese horseshoe bats...
(Rhinolophus sp.), this mammal is thought to be the host of origin of the novel coronavirus. In addition to having a 79.5% similarity with the genetic code of SARS-CoV and exerts the same molecular mechanism of infection observed in human COVID-19, which involves binding to the angiotensin-converting enzyme 2 (ACE-2), acting as a cell receptor for the virus(5,7).

The first reports of SARS appeared in November 2002, in Southern China – Guangdong Province, but only in February of the following year, 305 cases and five deaths from the still unknown pneumonia, were reported. The disease spread mainly among health professionals, who disseminated it into their homes, and China’s Ministry of Health reported that it was an unknown and atypical pneumonia outbreak. Countries such as Vietnam, Hong Kong, Singapore, and Canada had also been affected by this unknown syndrome. Due to the spread of this atypical syndrome, several countries and laboratories gathered for a multicentric research collaboration on search for the etiological agent of the infection, performing laboratory tests for its identification(8).

The Centers for Diseases Control on Prevention (CDC) from the United States of America (USA) and Hong Kong, in March 2003, isolated this coronavirus from patients with SARS. They observed that this new virus was phylogenetically different from the other organisms in the human disease-causing group. In April 2003, WHO proposed the implementation of a global surveillance system to prevent international dissemination. The tests used to identify this new causative agent of the disease included polymerase chain reaction (PCR), cell culture, and electron microscopy studies. After the description of this virus, it was called a new coronavirus, SARS-CoV, which causes SARS(9).

In December 2019 and January 2020, cases of atypical pneumonia (COVID-19) occurred in Wuhan, China(10). These patients had tested negative for real-time PCR (RT-PCR) from bronchoalveolar lavage for SARS-CoV. However, the virus found in this samples underwent phylogenetic and recombination analyses, which revealed a 99.9% similarity to the Coronavirus family(11), being a β-Co-Rnaviruses of the subgenus Sarbecoviruses, in the SARS-like coronaviruses group (SL-CoVs), in whom the horseshoe bat (Rhinolophus sp.) is a reservoir(12).

It is hypothesized that the first cases of COVID-19 were associated with a free-seafood market in Wuhan, where contaminated patients used to consume food. It is assumed that the mechanism of transmission occurred from animal to human. However, the manifestation of other cases was due to human-to-human interactions(13), and that transmission may occur before the onset of symptoms of the disease by asymptomatic individuals(13).

It is crucial to notice that the risk of symptomatic infection increases with age; thus, young individuals and children may be asymptomatic carriers(14). This reinforces the importance of self-isolation and measures of hygiene, even in the absence of clinical manifestations. The transmission of viral particles between individuals is related to the viral load in the upper respiratory tract(15), and it may occur through droplets from coughing, sneezing and saliva, handshake, or fomites, such as cellphones, doorknobs, cups, and keys, with subsequent contact with mucous membranes(12,16,17).

Some studies have shown that the temporal viral viability differs in different materials, such as plastic and metal. Viral particles may remain viable from a few hours up to nine days, and viral viability depends not only on the type of material but also on physicochemical factors, as temperature and pH. Thus, disinfection with 0.1% sodium hypochlorite or 70% alcohol (62%-91%) significantly reduces the number of infecting viral particles on such surfaces(17,18).

Incubation period after exposure to infection can range from two to 14 days(19). The first patients reported common prodromal symptoms of infection such as fever, cough, fatigue, myalgias. These may be accompanied by respiratory secretions, headache, hemoptysis, and diarrhea, and the complications of infection may lead to SARS and cardiac or renal impairment, secondary infection, and shock(19). Mortality is significant in the elderly, mainly over the age of 80 years(20,21). Death rates are related to critical cases and the presence of comorbidities as heart diseases, hypertension, diabetes, chronic respiratory diseases, and neoplasia(20,22).

After the detection of this new etiologic agent, named COVID-19/2019nCoV, the number of contaminated individuals in China grew exponentially, taking a large proportion in other countries, the disease was considered as a pandemic by the WHO in March 2020. More than four million cases and over 283 thousand related deaths have been reported worldwide as of May 13, 2020(20,23,24).

In Brazil, the first case was confirmed in São Paulo city on February 26, 2020, and the disease has spread across the country, reaching over 177 thousand notified cases and 12 thousand related deaths as of May 12, 2020, and, on March 26, 2020, the community transmission was declared in all national territory(26,27,28). The transmission rate has grown exponentially daily.

Based on the patterns of transmission visualized in China, after COVID-19 detection, dynamic epidemiological models have been proposed(26-28). According to WHO, the number of secondary infections generated from an affected individual is between 2% and 2.5% for COVID-19, and the worldwide crude mortality rate was around 3%-4% (April 2020), reaching 6.3% (May 2020), and is related to quality access to health care(22,29).
CLINICAL MANIFESTATIONS

SARS-CoV-2 infection may present clinically as one of these three main pictures: asymptomatic carriers, individuals with acute respiratory disease (ARD), or patients with pneumonia in different degrees of severity[39].

In the largest disease epicenters, the first cases arose from asymptomatic individuals with confirmed laboratory diagnosis, but such screening of asymptomatics through molecular tests proved complex since the conduct in suspected cases varies across different countries. This challenge becomes even more considerable in the observation of pediatric cases, which contribute to a large portion of the asymptomatic carriers, requiring heightened attention to avoid transmission[21, 31]. However, symptoms are more evident in patients with positive molecular tests and who have respiratory manifestations and imaging compatible with the diagnosis of pneumonia. Clinical records from patients at the beginning of the infection indicate that the most common symptoms of infection are fever, cough, myalgia, and fatigue, and may also be accompanied by respiratory secretion, headache, hemoptysis, and diarrhea[16, 19, 25].

Some of the initial symptoms may resemble those of other viral respiratory infections, such as Noroviruses and Influenza. Dyspnea and high fever are symptoms that define the main clinical difference between COVID-19 and the common cold, which is accompanied by nasal congestion, lacrimation, sneezing, and coryza, initially hyaline that over the days becomes greenish-yellow. On the other hand, when compared to Influenza infection, COVID-19 presents with similar clinic symptoms, but with a higher proportion of evolutions to severe and critical infections, demanding oxygen therapy and ventilatory support[32, 53].

Different studies show that about 86% of patients do not present disease severity, only about 14% require oxygen therapy in a hospital unit, and less than 5% of this group require intensive care[39]. Lu et al. (2020)[35] performed a meta-analysis involving the clinical presentation of patients from different studies. The main symptoms were: fever (88.3%); cough (68.6%); myalgia or fatigue (35.8%); expectoration (23.2%); dyspnea (21.9%); headache or dizziness (12.1%); diarrhea (4.8%); and vomiting or nausea (3.9%).

Most patients progress with a good prognosis, and it is essential to highlight that in the elderly or individuals with previous comorbidities, such as diabetes, cardiovascular and kidney diseases, COVID-19 can progress more aggressively, with pneumonia and acute respiratory distress syndrome (ARDS) being observed accompanied by cardiac, hepatic and kidney dysfunction[5, 36]. Patients with signs and symptoms such as high fever, tachypnea, and dyspnea, and clinical indications of the severity, require closer attention from the medical care team[20]. The progression of the first symptoms from COVID-19 to sepsis is slow, and extrapulmonary involvement is characterized mainly by refractory heart failure and kidney damage, leading about 25% of such critically ill patients to renal replacement therapy[28, 37]. The severe evolution to sepsis and septic shock is also cited in the literature, and it can reach an incidence rate 50% higher in critically ill patients, as described by Zhou et al. (2020)[30], demonstrating the intrinsic capacity of SARS-CoV-2 to lead to sepsis, especially when worsened by secondary infections.

Thus, the use of screening tools such as Sequential Organ Failure Assessment (SOFA) helps in the early diagnosis and management of patient's condition at hospital admission, favoring the improvement of clinical outcomes[56, 39]. In a previous study, the SOFA score on the first day of hospitalization of patients who did not survive was on average six points (range 4-8), while patients who survived presented a mean of four (range 3-4), evidencing the predictive potential of mortality of nonspecific, yet highly presumptive, clinical and laboratory criteria that compose this index[28].

Although less described in the reported cases, something that has been gaining prominence is the presence of hyposmia/anosmia and hypogeusia/ageusia in patients without rhinorrhea or nasal congestion, raising the possibility of direct neurological impairment by SARS-CoV-2, although more studies are necessary for such statement[40].

The estimated frequency of the symptoms and the evolution of COVID-19 in the general population is illustrated in Figure 1.

![Figure 1 - Symptoms and evolution of COVID-19](image-url)
LABORATORY DIAGNOSIS – NONSPECIFIC AND SPECIFIC EXAMS

The clinical laboratory is an important and essential tool for the diagnosis, follow-up, and evolution, as well as in the prognosis of any pathology that is active or not. In the COVID-19 pandemic, the involvement of several biomarkers as indicators of the current state of the disease has been reported, while others have proved to be useful prognostic markers. General laboratory findings in SARS-CoV-2 infection sometimes indicate leukocytosis or leukopenia, with marked lymphopenia in the early stages of the disease, as well as the presence of neutrophilia, that has been related to an unfavorable prognosis46-48.

The most frequent laboratory alterations in patients with COVID-19 are the 75%-95% increase in C-reactive protein (CRP) with 50%-98% decreased serum albumin, and total leukocytes count with considerable variation as reported in the literature, sometimes appearing increased, sometimes decreased, but with the evident presence of lymphopenia (35%-75%). There is also a decrease in hemoglobin, around 41% to 50%, and increase of erythrocyte sedimentation rate (ESR) by 15% to 85%, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) around 8% to 37%, and lactate dehydrogenase (LDH) in approximately 12%44.

Infection-related biomarkers values, including CRP, procalcitonin (PCT) and ESR increase gradually as the clinical status deteriorates, as well as increased D-dimer, creatine kinase (CK), creatine kinase-MB fraction (CK-MB), LDH, ALT, AST, urea, creatinine, cardiac troponin, and serum amyloid A protein (SAA)11, 44-48.

Because it is part of the inflammatory cascade involved in the pathogenesis of COVID-19, serum interleukin-6 (IL-6) is also increased according to the progression of SARS49. In the first week, the disease may progress to pneumonia, respiratory disease, and even death. This progression is associated with the extreme increase of inflammatory cytokines, including interleukins IL-2, IL-7, IL-10, granulocytes colony stimulating factor (GCSF), interferon gamma-induced protein of 10 KDa (IP-10), monocyte chemoattractant protein (MCP-1), macrophage inflammatory protein 1α (MIP-1α), and transforming growth factor α (TGFα)50. In intensive care units (ICU), patients have shown high plasma levels of these cytokines (IL-2, IL-7, IL-10, GCSF, IP-10, MIP-1α, and TGFα)51. Laboratory characteristics of COVID-19 in ICU patients include lymphopenia with CD4 and CD8 lymphocyte depletion, prolonged prothrombin time (PT), LDH, D-dimer, PCR, transaminases, and increased cytokines – and such increases are higher than those found in patients not admitted to an ICU. Laboratory abnormalities were similar to those previously observed in patients with SARS-CoV and MERS-CoV infection52.

Another proposed systemic marker is the platelet/lymphocyte ratio (PLR), whose prognostic value was associated with length of hospital stay and the case outcomes53. In severe cases, the reduction of partial oxygen pressure (PaO2) and [PaO2/oxygen inspired fraction (FiO2)] ratio has also been observed54, 55. Besides, an innovative parameter called monocyte distribution width (MDW) was significantly increased in all patients with COVID-19, especially in those in worse clinical conditions. For prognostic purposes, it is observed that the values of LDH, AST, ALT, total bilirubin, creatinine, cardiac troponin, D-dimer, PT, PCT, and CRP are increased while serum albumin is decreased56. Serum PCT quantification with serial titrations has been used to indicate bacterial coinfection in patients with COVID-19. Coinfection leads to greater severity to the patient’s condition, and PCT concentration may indicate the most appropriate therapeutic options early on, but more studies are needed to support this approach57-59.

Several articles have proposed possible correlations between laboratory findings and the potential severity of COVID-19, such as the relationship between hypoalbuminemia, lymphopenia, high levels of CRP, D-dimer, LDH and higher occurrence of SARS, as well as a higher viral load is related to greater disease severity, but these pieces of information and correlations are not uniform, requiring even more significant evidence for its clinical use55 .

The viral nucleic acid detection test is the main technique for laboratory diagnosis and is essential in the current context of the pandemic by the novel coronavirus. The use of RT-PCR is considered the gold standard for viral identification in patients with clinical symptoms in the acute phase of the disease, being part of different screening protocols in suspected cases5. The RT-PCR method is based on the amplification of nucleic acids, and the samples for this analysis need to come mainly from nasal and oropharyngeal swabs, or sputum, tracheal secretion, and bronchoalveolar lavage in critically ill patients57. However, implementing RT-PCR in the protocol requires an improved and adequate technological structure for its performance, besides having pre-analytical interfering factors such as sample collection, transportation, and storage, which, when performed inappropriately, may result in errors in the laboratory analysis5, 54, 56.

Regarding the laboratory testing for the evaluation of suspected cases with a probability of infection or an epidemiological detection of individuals who have had contact with a confirmed case of COVID-19, RT-PCR should be used, even if the individuals are asymptomatic or oligosymptomatic. When
the results are conflicting, a new sample should be collected and from this material, performed either the sequencing of the viral RNA or the amplification of the genetic material using the nucleic acid amplification test (NAAT), thus providing a reliable result(3, 56).

The Brazilian Ministry of Health recommends the RT-PCR technique to be performed between days three and nine after the onset of the symptoms because, in this phase, the highest viral load can be found. Nevertheless, the sample collection can be acceptable if performed up until the 10th day. Studies show that after the 7th day, RT-PCR positivity begins to drop, reaching 45% between days 15 to 39 after the onset of the symptoms (Figure 2).

Due to the high sensitivity and specificity of this technique, positive results confirm the infection in the epidemiological presence of the pandemic, requiring no further complementary investigations besides positive laboratory results in the presence of signs and symptoms of the disease. False-negative results are possible since due to several factors, such as sample collection at a very early stage, improper samples collection, storage, or transportation, as well as for reasons inherent to the test, such as viral mutations or the presence of inhibitory factors for the PCR method(57-59).

Immunological tests are still under development and validation to allow their insertion as a reliable diagnostic tool and easier to use dynamically as the pandemic goes on. Individual factors regarding immunological response depend on both the patient and the characteristics of the antigen used, and the surge of antibodies may be early or late, depending on the patient (Figure 2). The scientific literature discussing the immune response to the new coronavirus is still quite limited. Reports indicate that immunoglobulin class A (IgA) and class M (IgM) antibodies have an average serological detection around the 7th day after the onset of symptoms, followed by a rise in immunoglobulin class G (IgG) levels, concurrently. The negative predictive value of these tests is low when performed in the acute phase of the disease, which means that the negative results do not rule out the disease, and these individuals may be infected and are, therefore, a source of contamination to other people. In relation to positive test results, these show high predictive values(3, 16, 54-59).

Several studies have indicated the role and characteristics of serological analysis in SARS-CoV-2 infection. According to some authors, the production of IgM and IgA against the antigen protein S (viral spicule protein) and N (structural helical nucleocapsid protein) occurs on average seven days after the onset of symptoms, and soon after it, IgG can be detected almost simultaneously to the IgM, but there is not necessarily a decrease in viral load. These individuals may still be infected and potentially spreading the virus(52, 31, 60).

In general, immunological tests should not play a role in the screening or diagnosis of patients with a recent clinical presentation, and their use is intended for hospitalized patients with a not so recent condition and the diagnosis of health professionals (symptomatic from the 7th day of symptom onset) to facilitate the dynamics of leaving and returning to the healthcare workforce. However, it should be clear that negative results do not exclude the disease(3, 60).

The Table below establishes a test sensitivity pattern after the onset of symptoms.

| TABLE — Sensitivity tests in relation to the days after the onset of symptoms. |
|-----------------|-----------------|-----------------|-----------------|
|                 | Day after the onset of symptoms | 1-7            | 8-14           | 15-36          |
| RNA by RT-PCR   |                 | 67%            | 54%            | 45%            |
| Total antibody  |                 | 38%            | 90%            | 100%           |
| IgM             |                 | 29%            | 73%            | 94%            |
| IgG             |                 | 19%            | 54%            | 80%            |
| Source: adapted from Zhao J, et al., 2020(56). |
| SARS-CoV-2: acute respiratory syndrome – coronaviruses-2; RNA: ribonucleic acid; RT-PCR: real-time polymerase chain reaction; IgM: immunoglobulin class M; IgG: immunoglobulin class G. |

**FINAL CONSIDERATIONS**

COVID-19 is a highly contagious disease caused by the novel coronavirus SARS-CoV-2, and it was considered a world pandemic by WHO in 2020. This disease can lead to potentially fatal consequences among susceptible individuals. The rate of fatal cases ranges globally and is near to 6.9% between diagnosed individuals as of early May 2020, and it varies depending on factors such as age, immunological status, social and hygiene conditions, and accessibility to health
care\(^{62}\). It is important to account for underdiagnosis and underreporting, especially in lower-income countries, which may inflate the mortality rate and skew the distribution curve according to how much testing a given country has performed.

SARS-CoV-2 spreading occurs most frequently from mild/moderated symptomatic or asymptomatic individuals, who may unknowingly transmit the virus\(^{30}\). A smaller proportion of infected patients has a severe presentation of COVID-19, but in this population, the mortality is higher than in the clinically milder counterparts\(^{30, 62}\).

Initial clinical manifestations resemble *Norovirus* and *Influenza* infections, but pulmonary involvement is similar to that of complicated influenza H\(^{1}\)N\(^{1}\), SARS, and MERS-CoV infections\(^{29, 32, 51}\). Many unspecific laboratory parameters are altered during the COVID-19 course of infection, but some have shown prognostic value to monitor the disease evolution, revealing additional value beyond the presence of SARS-CoV-2 or the clinical diagnosis or immunological status assessment in specific exams. Thus, laboratory analysis has a fundamental role in defining diagnosis, assessing development, and more accurately predicting prognosis of COVID-19 patients. Additionally and importantly, laboratory investigations are on the basis of epidemiological studies that drive effective healthcare-related governmental strategies and evidence-based medical decisions.

RT-PCR positivity and seroconversion may vary in different groups of infected individuals, including the large population of asymptomatic individuals, where there can be underdiagnosed and underreported cases. Despite several and timely articles about COVID-19 and its pathophysiological mechanisms, many questions remain unanswered, particularly about the long-term potential immunity patterns in individuals with different clinical and laboratory presentations, including symptomatic or asymptomatic cases, and about the applicability of laboratory tests according to the phase of infection.

For epidemiological surveillance, it would be necessary to collect clinical specimens for viral detection or immune response in mass scale to define a real situation of this disease worldwide. Because of the elevated costs of mass people testing, the rational use of laboratory tools is essential. Using available evidence from international literature, a clinically useful approach for suspected individuals, and a toolbox for interpretation of diagnostic markers used for detection of COVID-19 has been devised to guide, in part, the rational use of specific exams by the clinicians. The diagram of laboratory biomarkers’ applicability is detailed in Figure 3.

| FIGURE 3 — Laboratory approach of individuals suspected of COVID-19
| Source: By the authors.
| IgM: immunoglobulin class M; IgG: immunoglobulin class G; Ac: antibodies; Ag: antigen; RT-PCR: real-time polymerase chain reaction; “transmission time: five to more than 25 days” — medical criteria; “rapid test — point-of-care”; “gold standard test” — with negative RT-PCR; \(^*\): local and medical criteria.

### REFERENCES

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