Clinical, anatomopathological manifestations and laboratory findings of COVID-19 in adults: a narative review

Manifestações clinicas, anatomopatológicas e achados laboratoriais da COVID-19 em adultos: uma revisão narrativa

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ABSTRACT
Introduction: SARS-CoV-2, the causative agent of the COVID-19 pandemics can cause anything from asymptomatic infections to several clinical manifestations. This study aims to present signs, symptoms, anatomopathological diagnosis, clinical diagnosis and laboratory findings in patients with COVID-19 in a narrative review. Methods: Narrative review of studies available in PubMed/Medline database about clinical manifestations in adult patients which were published in English, Portuguese and Spanish. Results: 547 articles were found, out of which 450 were excluded and 3 studies were added to the existing ones, totalizing 100 articles that composed the analyzed data. The main signs and symptoms were fever, dry cough, fatigue, dyspnea, pneumonia, headache, myalgia, vomiting, diarrhea, productive cough, acute myocardial injury, coagulopathy and olfactory and taste disorders. Conclusions: The findings suggest a great variety and complexity of Covid-19 clinical presentations indicating that, many differential diagnoses must be considered.

Keywords: COVID-19, signs and symptoms, diagnosis, adult population.

RESUMO
Introdução: O SARS-CoV-2, agente causador da pandemia da COVID-19, pode causar desde infecções assintomáticas até diversas manifestações clínicas. Este estudo tem como objectivo apresentar sinais, sintomas, diagnóstico anatomopatológico, diagnóstico clínico e achados laboratoriais em doentes com COVID-19, numa revisão narrativa. Métodos: Revisão narrativa

de estudos disponíveis na base de dados PubMed/Medline sobre manifestações clínicas em pacientes adultos, publicados em inglês, português e espanhol. Resultados: Foram encontrados 547 artigos, dos quais 450 foram excluídos e 3 estudos foram adicionados aos já existentes, totalizando 100 artigos que compuseram os dados analisados. Os principais sinais e sintomas foram febre, tosse seca, fadiga, dispnéia, pneumonia, cefaléia, mialgia, vômitos, diarréia, tosse produtiva, lesão miocárdica aguda, coagulopatia e distúrbios olfativos e gustativos. Conclusões: Os resultados sugerem uma grande variedade e complexidade das apresentações clínicas da Covid-19, indicando que muitos diagnósticos diferenciais devem ser considerados.

Palavras-chave: COVID-19, sinais e sintomas, diagnóstico, população adulta.

1 INTRODUCTION

SARS-CoV-2 was identified in December 2019 in Wuhan, China, and on January 30th, 2020, the World Health Organization (WHO) declared that the outbreak of the new coronavirus (CoV) constitutes a Public Health Emergency of International Concern (PHEIC)[1]. This is the third coronavirus epidemic in the 21st century, called Coronavirus Disease 19 (COVID-19), following SARS-CoV-1 in China, 2003, and MERS-CoV-2 in Saudi Arabia, 2012. SARS-CoV-2 transmission usually occurs through the air or contact through saliva droplets or by touching or shaking hands with infected people, then, the contamination takes place by touching your own mucous membranes, such as mouth, eyes and nostrils[1].

New symptoms and signs of Covid-19 disease are constantly being discovered, the main ones being respiratory ones resembling a common cold. More severe cases usually occur in people at risk, such as the elderly, the immunocompromised and those with chronic diseases. These people can develop pneumonia, severe acute respiratory syndrome (SARS) and die[1]. The symptoms of the disease are quite diverse[2], ranging from inapparent infection occasionally found only through laboratory tests, passing through mild symptoms, mistaken for common colds, up to severe conditions with respiratory impairment and abrupt coagulopathies, of which pathophysiological mechanisms are still little known, although exhaustively studied in a short period[1]of time. Based on the above, the present study aims to broadly present signs, symptoms, anatomopathological diagnosis, clinical diagnosis and laboratory findings known so far, among adults through a narrative review.

2 METHODS

In accordance with PICO, P – population or problem (adult population with COVID-19); I – intervention or exposure (not applicable); C – comparison (not applicable) and O – outcome (signs, symptoms, anatomopathological diagnosis, clinical diagnosis, and laboratory

findings); the research question is: which are the signs, symptoms, anatomopathological diagnosis, clinical diagnosis, and laboratory findings of COVID-19 in adults? A search for scientific publications was carried out in PUBMED /Medline database about clinical manifestations of COVID-19. On July 27th 2021, 547 articles were found; 320 articles were excluded by the title analysis using the following exclusion criteria: specific population group (children, pregnant women, HIV positive, transplanted patients); being included by title, 227; then 92 were excluded after reading the abstract because of the following exclusion criteria: patients without confirmed Covid-19 diagnosis, studies about treatment protocols, diagnostic tests, image exams, risk factors, angiotensin converting enzyme inhibitors, vaccines, reinfection, other coronaviruses, telemedicine. 135 studies were elected and 3 studies were added later and 38 papers were excluded after full reading because they were about post-acute and chronic patients, severe and critical cases, resulting in 100 articles which composed the analyzed data. Different combinations of the following descriptors were used: “COVID-19”, “signs”, “symptoms”, “clinical manifestations”, “clinical pictures”. The filters used were free full texts, article types: Clinical Trial, Meta-Analysis, Randomized Controlled Trial and Systematic Review in English, Portuguese and Spanish.

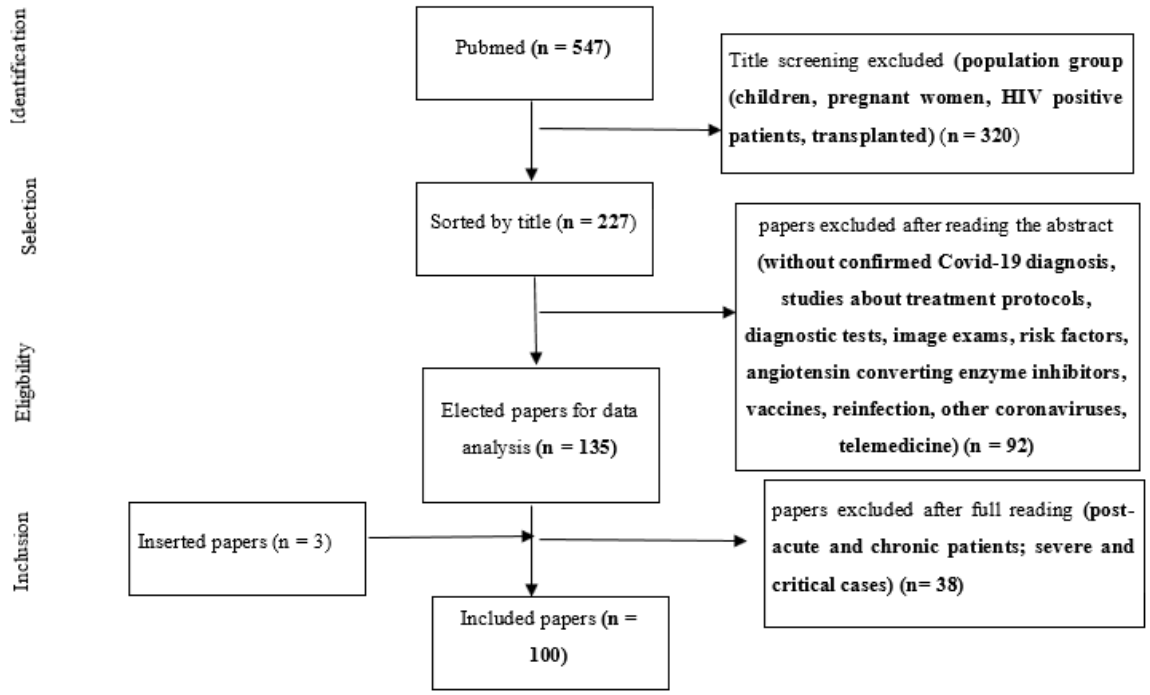
Original and primary studies (observational and experimental) and systematic reviews of clinical manifestations in patients with confirmed diagnosis of COVID-19 with mild or moderate forms, acute stage, outpatient and hospitalized ones were selected.

Data extraction:

Data were collected independently by two researchers considering the following categories, when available: first author, date of publication, type of study, participants (number, age, gender, nationality), length of follow-up, progression, outcome/losses.

Below (Figure 1), the flowchart of the selection and inclusion of the study can be observed

Figure 1 - Flowchart of paper selection and inclusion for this review



3 RESULTS

Altogether, 547 articles were found, 450 were excluded and 3 studies were added to the existing ones, totalizing 100 articles that composed the analyzed data. The strength points are a compilation of several studies about the analyzed subject and the limitations are the extremely variable results of the included studies.

Eight clinical manifestations were very frequent and reported more than 10% of the time. In order of frequency there were, respectively, unproductive (dry) cough, with almost 35%, fever, with 34%, headache, around 18%, fatigue, with 16%, diarrhea, with 13.5%, dyspnea, with approximately 13%, urticaria, with 11%, and erythematous rash, with just over 10%. These manifestations should be considered as alarm signs/symptoms of the Covid-19 disease. On the other hand, many symptoms reported, such as loss of smell (anosmia) and taste (ageusia), were seen in only 5.08% and 2.54% of cases, respectively.

It was observed that the most prevalent manifestations were, respectively, in the respiratory system (pulmonary) with 52.5%, followed by 46.6% of gastrointestinal/hepatic tract, 43.2% dermatological, 33.04% neurological, 32.2% ophthalmologic and 29.7% cardiovascular.

4 DISCUSSION

In the present review, it was observed that the five main clinical manifestations were unproductive cough, fever, headache, fatigue, and diarrhea. This agrees with other studies carried out by Chen N et al.[3], Liu L et al.[4], Cespedes MS et al.[5], Kang S[6], Zheng Q et al.[7], Wiersinga WJ et al.[8], Wang L et al.[9], Zhu J. et al.[10], Mesquita R. R. et al.[11], Neto A et al[12], Islam A et al.[13] and Giri M et al[14]. These aspects are important and serve as a warning for professionals who care for patients initially presenting with such manifestations which can change the natural history of the disease by enabling intervention in a timely manner[3,4,5,6,7,8].

In the studies by Zhou Y et al.[15] and Abobaker A et al.[16], there are descriptions of the mechanism of D-dimer changes in the disease caused by SARS-CoV-2 being related to the progression of clinical picture, and for this reason, it is considered a prognostic marker.

SARS-CoV-2 acts mainly on the respiratory system, generating abnormalities such as cough and dyspnea[10,11,17,18] and may generate sudden development of pneumonia[19] and, in severe cases, acute respiratory distress syndrome (ARDS)[10]. Baj et al.[20], Abobaker et al.[16], Boukhris et al.[21] found that SARS-CoV-2 infection leads to a state of hypercoagulation which poses an increased risk of developing thromboembolic events such as pulmonary embolism. Oleynick et al.[22] present the first patient with viral pleuritis associated with COVID-19. The 48-year-old male patient initially developed acute pleuritic chest pain and, subsequently, his worsened pain was associated with unproductive cough and dyspnea. He also developed fever and tachycardia.

The most common gastrointestinal symptoms[10,16,20,23,24,25,26,27,28] were, diarrhea, anorexia, nausea or vomiting, loss of appetite. According to Su et al.[24] anorexia can be partially explained by taste dysfunction. Other gastrointestinal symptoms can be explained in a multifactorial way. There may be direct damage to intestinal or gastric cells, microvascular lesion of the small intestine due to diffuse endothelial inflammation, alteration of intestinal flora[29], increased gastrointestinal permeability due to viral invasion of foreign pathogens by malabsorption of infected enterocytes[30]. Case reports by Abdalhadi et al.[31] and by Ahmed et al.[32] presented patients in whom the possibility of acute surgical abdomen masked the diagnosis. In one of them, the patient had abdominal pain as the main complaint in addition to fever, nausea and vomiting, unproductive cough and diarrhea. Diagnostic hypotheses of appendicitis and pancreatitis were ruled out by computerized tomography scans of the abdomen and COVID-19 was confirmed.

The most common hepatic manifestation is the abnormal counting of alanine aminotransferase and aspartate aminotransferase levels [20,24,27,28,29,30,33,34,35]. Other

manifestations were a slight increase in bilirubin count[20,24,26,27,34] in addition to a reduction in albumin level[24,26,34], elevated prothrombin time[26] and a slight increase in cholangiocyte-related enzymes[34].

The hypotheses about the mechanism of the considered liver injury are direct viral infection of liver cells[20,28,29,30,33,34,35], hepatotoxicity due to the drugs used in the treatment[20,24,28,29,34,35] and to cytokine storm[24,28,29,34,35], hypoxia due to pneumonia[28,29] and cytotoxic T cells liver damage by viral particles[20,35].

Cutaneous manifestations include generalized macular or maculopapular rash commonly associated with a more severe course of the disease [20,29,36,37,38,39,40], erythematous and edematous rash, similar to the most common chilblains in mild cases[5,16,29,30,33,37,39,40,41,42,43,44], multiform erythema most commonly seen in mild disease[37,40], urticaria, especially in the initial stage of infection associated with itching[5,16,20,29,30,36,37,38,39,40,41,43,44], petechiae usually in mild cases[16,20,29,36,37,38,40,43], papulovesicular rash similar to chickenpox[16,20,29,30,33,36,37,38,41,43,44], painful acral purple papules with or without vesicles[36], acro-ischemia with cyanosis of the fingers and toes, skin blisters and dry gangrene in critically ill patients[33,37,38,41], erythematous itchy papules[38],purple enanthema or purple flexural or rectiform lesions[39,41], localized pruritic lesions[16,40], macular hemorrhagic rash[36],papulo vesicular pruritic eruption[36,45].The trunk is the main region involved in these manifestations[5,16,20,30,36,40,44].

The hypotheses for the pathophysiological mechanisms include: viral particles in the blood of cutaneous vessels can lead to deposition of microthrombi and lymphocytic vasculitis[29,36,41,45]; immune response to infection can activate Langerhans cells resulting in vasodilation and spongiogenesis, which can lead to a hypersensitivity response to viral RNA[29,36,41]; micro thrombosis in other organs reducing blood flow to the cutaneous microvasculature may cause reticular manifestations[36]; disseminated intravascular coagulation and accumulation of deoxygenated blood due to hypoxia secondary to pulmonary infection[36]; adipocytes can serve as reservoirs for the virus and these may cause direct damage[37,40,41]. Cutaneous manifestations may appear before other symptoms[16,20,29,36,43,45,46]. A case report published by Suter et al.[47] presented a patient with no comorbidities, allergies, or use of medications who had noticed painful skin lesions on the shins and was confirmed with COVID-19. He was diagnosed with erythema nodosum.

According to Nawabi et al.[48,] the infection affects the central nervous system (CNS), the peripheral nervous system (PNS), and skeletal muscles. The coronavirus can reach the CNS via the olfactory nerve with nasal infection causing inflammation and demyelination[49,50]. It can

enter via hematogenous[20,50,51], lymphatic routes connected by synapse[20,52,53], through ACE2[52,54,50] or by retrograde neuronal pathways[20,29,30]. The virus was detected in cerebrospinal fluid[20,30,49]. Most common neurological complaints include headache[15,18,49,52,55,56,57,58], dizziness[15,52,59,60], mild cognitive impairment[15,49,60], smell impairment[15,61,62,63,64,65,66],altered taste[15,61,65,66], blurred vision[52], hypogeusia[52], muscle pain[49], sleep disorders[49], nerve pain[52], epilepsy[52] and ataxia[52]. In the later phase of the infection, systemic angiopathy, thrombosis, acute cerebrovascular diseases[52], stroke[52,50], and even acute hemorrhagic necrotizing encephalopathy may appear[15,52]. A case report by Klein et al.[67] presents a 29-year-old patient with neurological symptoms showing that cerebrovascular events can have atypical presentations even in young people. A study by Domenico[68] reported what are believed to be the first three cases of *myasthenia gravis* positive for AChR antibodies related to COVID-19. The three had a high serum level of AChR antibodies and repetitive nerve stimulation showing a decrease. Assini et al.[69] brought the report of two cases of Guillain Barré related to COVID-19. One case of a 55-year-old man was a GBS / MG overlap syndrome. The other, a 60-year-old man with acute motor and sensory axonal neuropathy (AMSAN) with severe vegetative impairment.

Mao et al.[70], in a series of cases with 214 patients infected with SARS-CoV-2, divided the neurological manifestations into 3 categories: Central nervous system manifestations, peripheral nervous system manifestations and skeletal muscular injury manifestations.

In the study by Choi et al.[70], with patients with PNS symptoms, the most common symptoms were impaired taste (5.6%) and impaired smell (5.1%). SARS-CoV-2 can enter the CNS via a retrograde neuronal pathway which may explain the olfactory deficiency[**70,71**]. Costa K. V. T. et al.[72] demonstrate that olfactory and taste dysfunctions can be considered predictors of infection by SARS-CoV-2. According to Biadsee et al.[73] olfactory dysfunction was more common from the third to the fifth day of the disease and nasal congestion was strongly correlated with olfactory dysfunction. Baj et al.[20] reported that olfactory and gustatory dysfunctions can persist in up to 56% of recovered patients and that the average duration of smell and taste disorders by SARS-CoV-2 is 7.5 days.

The main ophthalmological manifestations are conjunctivitis with watery eyes, foreign body sensation, redness, increased secretion[16,20,29,33,74,75,76,77], eye irritation[20], keratoconjunctivitis[20], chemosis[30,33,75], conjunctival injection[30], isolated conjunctival congestion[29,75], conjunctive hyperemia[33,75,78,**79**], retinal changes[29,**78**], epiphora[16,33,75]. Such manifestations can appear as the first symptoms[16,20,75,77,78,80]. A study by Latalska et al.[77]

brought the possibility of a new route of entry through interactions with CD147 present in tears, in the conjunctiva and in the corneal epithelium.

Costa et al.[75] brought a theory of ocular transmission to the respiratory tract by draining viral particles in tears through the nasolacrimal duct. Chen et al.[74] presented a patient with ocular symptoms and COVID-19 was confirmed. RT-PCR performed with conjunctival samples taken on days 13, 14, 17 and 19 of the disease showed a tendency to reduce viral RNA.

The most cited cardiac manifestations were acute myocardial injury with elevation of troponin above the upper limit of 99° percentiles in addition to other cardiac biomarkers such as creatine kinase, lactate dehydrogenase, α-hydroxybutyrate dehydrogenase[19,20,29,21,30,33,68,81]; myocarditis or myocardial inflammation without an ischemic cause, mainly related to the activation of interleukin-6 triggering cytokine storm[79] and, thus, direct myocardial injury which can lead to reduced systolic function[18,20,21,29,68,81]; arrhythmias, especially sinus tachycardia[17,20,21,29,33,81,82], sinus bradycardia with sudden death[83]; abnormalities in blood pressure, hypotension being a risk factor for poor prognosis and caused mainly by septic shock or inadequate intake, fever and sweating[20,82]; heart failure / cardiogenic shock[19,20,21,29,81]; acute pericarditis[16,20]; left ventricular dysfunction[20]; acute coronary syndromes[21,29]; right ventricular dysfunction secondary to ARDS and mild pericardial effusion[82].

The pathophysiological mechanisms for that are multifactorial and include sub-regulation of the ACE2 receptor related to blood pressure control and cardiac contractility leading to direct tissue injury[17,20,21,29,30,33,81,82,84], systemic inflammation due to "cytokine storm" leading to inflammatory cell infiltrates which can cause cardiomyocyte damage, apoptosis and atherosclerotic plaque instability resulting in acute myocardial infarction[17,18,20,21,29,33,68,81,82,84], hypoxia generating atrial fibrillation[18,20,21,26,82,84], increased production of catecholamines[33,82], pulmonary hypertension[82] in addition to pharmacological interventions that can often be pro-arrhythmic[20,33].

Miesbach et al.[85] found that Angiotensin 2 and "cytokine storm" are strongly linked to hypercoagulation. Thus, coagulopathy is common in COVID-19 patients[5] with a prevalence of 50% in severe cases[85]. According to Moores et al.[86] when severe, coagulopathy usually manifests as disseminated intravascular coagulation, a prothrombotic state. Behzad et al.[30] state that the main vascular changes in COVID-19 are dilation of vessels lumen and thickening of pulmonary vessels.

Boukhriset al.[21], Klein et al.[67], and Shawkat et al.[87] reported cases of para infectious effusion secondary to COVID-19 coagulopathy. Coagulopathy can cause complications, especially due to intravascular microthrombi and thrombi[20,21,87]. Hanny Al-Samkari et al.[88],

evaluated thrombotic and hemorrhagic complications of COVID-19 and found an overall prevalence of 9.5% for thrombotic and 4.8% for hemorrhagic in a population using a standard dose of prophylactic anticoagulation.

According to a recent review published by Behzad et al.[30], acute renal failure is caused by a virus-induced cytopathic effect and acute kidney injury (AKI) in COVID-19 patients which may generate some degree of acute renal dysfunction[30]. Gupta et al.[29] reported that AKI can occur in an average of 7-14 days after admission[29].

AKI mechanisms in COVID-19 are multifactorial with cytokine damage, cardio renal crosstalk, hypoxia, intra-abdominal hypertension, fluid imbalance, hypoperfusion, tubular toxicity related to rhabdomyolysis and endotoxin[33]. Histopathological findings indicate prominent acute tubular lesion and diffuse erythrocyte aggregation in addition to obstruction in the peritubular and capillary glomerular loops. In addition, another possible mechanism is the presence of lymphocytic endotheliosis in the kidney and viral particles inclusion in endothelial cells of glomerular capillaries, findings that suggest microvascular dysfunction secondary to endothelial damage[29]. In general, studies show a low AKI prevalence, however, the risk may increase with the severity of COVID-19[33].

Behzad et al.[30], Gupta et al.[29] and Słomka et al.[89] attest to lymphocytopenia[90] presented by many of the patients and less frequent leukocytosis[10] especially with neutrophilia. Furthermore, the hypothesis raised is that lymphocytopenia may be triggered or intensified by the direct invasion of lymphocytes by the virus[29,89], by apoptosis[29] or by the action of drugs used in the treatment[89]. Słomka et al.[89] attested changes in the erythrocyte sedimentation rate, which were high in severe cases of the disease. Thrombocytopenia[29,30,33] was related to a worse prognosis. Studies[19,29,33,89] highlight the presence of high levels of D-dimer and fibrinogen products[19,29] related to coagulopathy and worse outcomes[29,33].

A meta-analysis by Abdullahi et al.[63] reported the possible frequency of musculoskeletal symptoms: 80% myalgia, 6.67% back pain, 1.67% muscle weakness, 1.67% musculoskeletal injury, 1.67% arthralgia. COVID-19 late musculoskeletal complications are possible due to prolonged immobilization. It is proposed that myalgia and arthralgia are caused by a high amount of pro-inflammatory interleukins 6.

Rodriguez et al.[91] reported three cases showing oral manifestations: aphthous lesions, burning sensation and tongue depapilation**,** burning sensation of the mouth and unilateral fissures and very intense feeling of dry mouth. All were related to a certain state of immunosuppression. A study by Biadsee et al.[73] reported oral manifestations among patients. 72 reported dry mouth feeling with a strong burning sensation in the mouth and a change in

flavor, 20 reported changes in tongue sensation, nine reported changes like plaques on the tongue, ten reported swelling in the oral cavity, and six reported oral bleeding.

There is a high expression of ACE2 in the human testicles[16,30] and uterus[30]. It is believed that SARS-CoV-2 can cause direct testicular damage through connection with testicular receptors and indirect damage by inducing an inflammatory response[16]. Abobaker et al.[16] stated that semen analysis studies after COVID-19 infection report low concentration of sperm with little motility for up to three months post-infection, indicating that the effect of COVID-19 on this organ may be temporary. Furthermore, Behzad et al.[36] found orchitis as a rare complication of COVID-19.

Behzad et al.[30] reported an increase in mediastinal lymph nodes as a relatively common manifestation. Thus, lymphadenopathy, a phenomenon reactive to viral disease and inflammation, should not be ruled out as an atypical symptom of COVID-19.

According to Gupta et al.[29], hospitalized patients exhibited abnormalities in glucose metabolism including severe hyperglycemia, euglycemic ketosis and diabetic ketoacidosis. Infection by SARS-CoV-2 is related to high levels of cytokines which can impair pancreatic function of β cells and apoptosis causing reduced insulin production and ketoacidosis. ACE2 expression has been reported in the endocrine pancreas[29]. Therefore, diabetes mellitus was reported as a complication of Covid-19[92,93].

The relationship between SARS-CoV-2 infection and the thyroid gland is studied. In a case report by Ruggeri et al.[94], a 43-year-old woman with no history of developing thyroid disease, about one month after SARS-CoV-2 infection, felt anterior cervical pain, fatigue, tremors, fluttering and anxiety. Thyroid function tests that indicated subacute thyroiditis were required. After steroid therapy, functional thyroid tests went back to normal.

Li et al.[95] described the case of a 59-year-old woman with EDTA dependent pseudo thrombocytopenia secondary to COVID-19. When admitted, the platelet count was normal, but two days later, it became low (91 × 109 / L). Subsequently, COVID-19 and the platelet count returned to normal.

5 CONCLUSION

The clinical manifestations in adult COVID-19 patients are diverse and occur in different proportions according to age, comorbidities, and disease stage.

Given the findings, the complexity of the clinical presentation of the infection is demonstrated, with numerous differential diagnoses that must be considered.

The contents presented in this study could be applied in improving care since the knowledge of the variety of clinical presentations of Covid-19 can help in earlier diagnosis. Besides that, the description developed of the signs, symptoms, anatomopathological manifestations and laboratory findings and their physiopathology can be useful for other researchers to continue the investigation of the Covid-19 disease.

Conflict of interest

The authors declare that there is no conflict of interest.

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