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COVID-19: Beyond the Acute Phase

COVID-19: Para Além da Fase Aguda



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At the beginning of the COVID-19 pandemic, in March 2020, the scientific community's focus was centred on the knowledge of the new coronavirus (SARS-CoV-2), its mode of transmission, the acute manifestations of the disease and its respective treatment. Policymakers were forced to create measures to mitigate its spread in a non-immune world population, trying to minimize public health's impact and avoid the collapse of health services. Despite this collective effort, the number of severe and critical cases was overwhelming, with a very strong repercussion in hospitals and, in particular, in intensive care units (ICU), where attention was and has been concentrated during the initial months and in the various pandemic waves that followed.
In August 2021, the total number of people infected with SARS-CoV-2 exceeded 200 million worldwide, about 1 million in Portugal.[1] An unknown number of infected people has always remained asymptomatic and, among those who became ill, the majority has developed mild to moderate symptoms, 10-15% severe illness and 5% critical illness.[2]

Initially, it was thought that mild cases and those followed up in the community would recover from the infection without sequelae. However, in the very first wave of the pandemic, many of the infected people, some asymptomatic or with mild cases, described, for extended periods of time, a wide range of symptoms, sometimes unpredictable and cyclical, with an important compromise in their quality of life. During these first months, groups of patients were formed, particularly on social networks, to share information and create mutual help. In May 2020, the concept gained prominence through an opinion article written by a professor of infectious diseases, describing a "roller coaster of symptoms" in the seven weeks after his infection.[3] That month, the term #LongCovid was used for the first time by a patient on Twitter, to alert the remaining population, the scientific community and the various institutions involved in the management of the pandemic, to a problem that went unnoticed for a long time, but which was expected to have important long-term consequences.[3,4]
In August 2020, the World Health Organization (WHO) met representatives of the LongCovidSOS group and agreed on the need to recognize this new entity and to promote dedicated research. Based on this intention, the U09 code in the ICD-10 (International Classification of Diseases - 10th revision), has been established as Post-COVID-19 Condition.[5] To date, there is no unanimous and consensual designation for this new clinical entity, that is recognized as a set of physical and mental symptoms, existing four weeks or more after SARS-CoV-2 infection, that is, after the acute stage, knowing that, depending on the severity of the initial clinical picture, the mean recovery time from the disease is usually two to three weeks. It appears that there is no association between the severity of the acute illness and the subsequent symptoms.[2,5,6] According to the British National Institute of Statistics, about 20% of people who test positive for COVID-19, have symptoms for five or more weeks, and 10% have symptoms for twelve or more weeks.[2,7]
Under this comprehensive concept, there are different clinical contexts, essential to consider: cases of asymptomatic infection and mild or moderate acute illness, without hospital admission and cases of severe or critical acute illness with hospital admission, often in the ICU.[5]
A protracted post-viral clinical picture may develop in all cases, with variable symptoms among patients and in the same patient, sometimes after initial recovery, recurrently or persistently, for an indefinite period.[5,6] The manifestations described are multiple, the most common being: fatigue, dyspnea, myalgia, arthralgia, headache, cough, chest pain, anosmia, dysgeusia, diarrhoea, palpitations, cognitive alterations, often described as brain fog.[2] Some cases have diagnostic criteria for Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome, a condition that usually starts after viral infection, with debilitating symptoms such as intense fatigue and musculoskeletal pain, with worsening of symptoms following exertion.[8]
Patients who had a severe or critical acute illness, namely with pneumonia that progressed to Acute Respiratory Distress Syndrome (ARDS), with hospitalization in the ICU, may suffer from organ sequelae, mainly pulmonary and cardiac and from the Post-Intensive Care Syndrome, resulting from long periods of mechanical ventilation, neuromuscular blockade and sedation, including cognitive, psychiatric and physical complications, such as intensive care neuromyopathy.[9,10]

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Given the obvious need to follow-up these patients in highly variable clinical contexts, Post-COVID-19 assessment clinics have been set up worldwide, whose main characteristic is the flexible aggregation of specialities, designed according to each clinical condition. Multidisciplinarity is, therefore, indispensable and the most requested clinical specialities are general medicine, internal medicine, paediatrics, infectious diseases, pulmonology, cardiology, neurology, psychiatry, physical and rehabilitation medicine. Since many cases are of little clinical relevance and self-limited, a conservative approach is advised for the first four to twelve weeks.[6]

As an integral part of the multidisciplinary evaluation, Radiology stands out in the study of various clinical pictures associated with the Post-COVID-19 condition, namely cardiac and neurological, through echocardiogram, computed tomography (CT) and magnetic resonance (MRI).[5] However, as pneumonia is the primary and most frequent complication of SARS-CoV-2 infection, the most significant contribution of Radiology in the follow-up of these patients, is the assessment of pulmonary and respiratory complications. Given the potential severity of SARS-CoV-2 pneumonia in some patients, with progression to ARDS, the need for high-output oxygen therapy, non-invasive and invasive ventilation, the hypothesis of pulmonary sequelae, particularly of the fibrosing type, is questioned. Several possible etiologies can contribute to the development of lung fibrosis in these cases, emphasising viral pneumonia itself, post-ARDS fibrosis and direct trauma caused by mechanical ventilation.[11]

It should be noted that, in addition to pneumonia and possible residual fibrosis, there is another important cause of pulmonary morbidity in COVID-19, resulting from the high prevalence of thromboembolic events, with pulmonary thromboembolism, mainly in the segmental and sub-segmental vessels and thrombotic microangiopathy *in situ* in the pulmonary vascular bed. Thus, it is essential to investigate other possible late complications, such as chronic thromboembolic disease and pulmonary arterial hypertension.[10,12,13,14]

The primary purpose of follow-up the patients who remain with respiratory symptoms after the acute phase, is the timely detection of residual changes that may indicate chronic complications, susceptible to a therapeutic approach but, simultaneously, avoid excessive research and complementary diagnostic tests, allowing spontaneous resolution of cases with a better prognosis.[10] Based on previous studies of other coronavirus epidemics, such as SARS (Severe Acute Respiratory Syndrome) in 2003 and MERS (Middle East Respiratory Syndrome) in 2012, it is known that most infected patients have pulmonary radiological abnormalities at discharge but that about two-thirds are resolved in twelve weeks.[10] Regarding patients with SARS who developed parenchymal lesions and functional decline, most of them improved two years after the onset of the disease.[11] Therefore, routine radiological evaluation or respiratory follow-up is not recommended in patients without pneumonia with radiographic expression or those who have demonstrated complete resolution on chest X-ray during hospitalisation.[10]

For patients who have had more severe pneumonia, there are several follow-up protocols, which have to be adapted to the availability of each centre. As an example, the British Thoracic Society (BTS) adopted two algorithms, depending on the severity in the acute phase and the clinical condition at the time of discharge, which defines the temporal onset of follow-up.[10] Patients who had severe to critical disease have a general evaluation consultation in 4-6 weeks and a face-to-face consultation, with respiratory evaluation and chest X-ray in 12 weeks. If radiological changes have regressed and there are no symptoms, it is unnecessary to proceed with the follow-up. If radiological and/or clinical changes persist, a complimentary assessment with pulmonary function tests, walk test with oximetry and echocardiogram, volumetric high-resolution chest CT (HRCT) without contrast, and eventual CT pulmonary angiogram (CTPA) is suggested. Patients with mild to moderate disease, predominantly followed up on an outpatient basis, undergo a chest X-ray for comparative analysis in 12 weeks. If the radiological changes have resolved and there are no persistent or new symptoms, follow-up ends, expected to happen in most cases. If significant radiological changes persist, it is crucial to assess the accompanying symptoms and perform pulmonary function tests. Further investigation should be considered, based on the results, including walk test with oximetry, echocardiogram, volumetric HRCT without contrast and eventual CTPA. In all cases, depending on the manifestations, whether clinically or in the various complementary diagnostic tests, patients should be referred to the corresponding dedicated clinics of pulmonology, internal medicine and cardiology.[10]

Follow-up thoracic CT protocols should include volumetric HRCT without contrast and CTPA, when there is a need to evaluate the pulmonary arteries in the context of thromboembolism. Considering that CTPA underestimates microvascular peripheral thrombotic disease, which is common in COVID-19, further investigation with dual-energy CT angiography with an assessment of pulmonary perfusion may be helpful in this context.[12] When reading the exams, it is essential to highlight the signs of organizing pneumonia, incipient fibrosis, evaluating the presence of ancillary findings such as reduced lower lobe volume in sagittal planes, residual thromboembolism, perfusional abnormalities and indirect signs of pulmonary hypertension, such as the diameter of the pulmonary artery above 30-31 mm or a ratio of the pulmonary artery to the ascending aorta greater than 1.1, being this a most reliable criterion with established pulmonary fibrosis.[13]

There are many studies carried out and published on the radiological follow-up of these patients, mostly performed at 3 months and in smaller numbers beyond that time, some up to 6 months. Most studies describe chest CT assessment, usually integrating symptoms and functional changes found in pulmonary function tests. The findings are relatively uniform, being the most frequently described, ground-glass opacities, irregular interfaces, coarse reticulation, bronchial dilatations and parenchymal bands.[15] All studies conclude that have inconclusive results regarding the significance of these findings, given the fact that the assessments have been performed too early and some with a small number of participants, with the need for longer follow-up of cases that did not resolve. Furthermore, it is important to stress that some abnormalities found in follow-up exams, even if they suggest a fibrosing component, may only reflect irrelevant reversible residual changes or, even if permanent, with little clinical significance. To assess the clinical relevance of these imaging findings, which is the ultimate goal of their interpretation, it is essential to always

integrate them with the clinical picture and pulmonary function tests.[16]

It is now understood that the expression of the Post-COVID-19 condition is very significant, impacting on patients, society and health services, which will have to deal, for a long time, with the follow-up of these cases. Being no exception, the Radiology Departments must be prepared for an increase in the number of exams arising from this new context.

According to the WHO, it is fundamental to give priority to the clinical characterisation of affected patients in order to diagnose and adopt an appropriate treatment.[3] Part of this task involves carry out long-term follow-up studies with large series of patients, to conclude on the clinical and functional implications of the abnormal findings and define the best approach, trying to minimise their impact in the future and avoid irreversible sequelae.

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