Results and effects of patients who have recovered from COVID-19: identifying the relationship with risk factors and comorbidities

Resultados e efeitos dos pacientes que se recuperaram da COVID-19: identificação da relação com fatores de risco e comorbilidades

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Abstract *The number of deaths from COVID-19 is closely associated with multimorbidities. This study aimed to review the clinical and functional conditions of patients who recovered from COVID-19. Additionally, identify the relationship with risk factors and comorbidities.* Systemic arterial hypertension *(SAH) was more frequently observed in patients with severe COVID-19. Diabetes mellitus (DM) is one of the comorbidities that has contributed the most to the increase in the number of hospitalizations due to complications and the number of deaths due to infection by COVID-19. Obesity has been shown to be a risk factor for hospitalization in patients with COVID-19 under 60 years of age. Most survivors of COVID-19 suffer primarily from muscle fatigue or weakness. In addition, patients who were more seriously ill during their hospital stay have greater impairment of functional capacity, pulmonary diffusion and fatigue symptoms, and are the main target population for long-term recovery interventions. To optimize the post-hospitalization rehabilitation of patients after discharge from COVID-19, the need for multidisciplinary work in rehabilitation, the reinforcement of public policies to ensure equity in access to the public health system and training should be considered of the health team in view of the new demands and realities generated by COVID-19.*

Key words *COVID-19, Diabetes mellitus, Hypertension, Functionality*

Resumo *O número de mortes por COVID-19 está intimamente associado a multimorbidades. O presente estudo teve como objetivo revisar as condições clínicas e funcionais de pacientes que se recuperaram da COVID-19. Adicionalmente, identificar a relação com fatores de risco e comorbidades. A hipertensão arterial sistêmica (HAS) foi observada com mais frequência em pacientes com COVID-19 grave. O diabetes mellitus (DM) é uma das comorbidades que mais tem contribuído para o aumento do número de internações por complicações e do número de óbitos por infecção por COVID-19. A obesidade demonstrou ser um fator de risco para hospitalização em pacientes com COVID-19 com menos de 60 anos. A maioria dos sobreviventes da COVID-19 sofre principalmente de fadiga ou fraqueza muscular. Além disso, os pacientes que estiveram mais gravemente enfermos durante sua internação hospitalar apresentam maior prejuízo da capacidade funcional, pior difusão pulmonar e sintomas de fadiga, sendo assim a população-alvo para intervenções de recuperação a longo prazo.. Para otimizar a reabilitação pós-hospitalização de pacientes após alta por COVID-19, deve-se considerar a necessidade de trabalho multiprofissional na reabilitação, o reforço das políticas públicas para garantir a equidade no acesso ao sistema público de saúde e o treinamento da equipe de saúde frente às novas demandas e realidades geradas pelo COVID-19.*

Palavras-chave *COVID-19, Diabetes mellitus, Hipertensão, Funcionalidade*

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Background

The COVID-19 pandemic, which began in China in November 2019, had its first confirmed case in Brazil in March 2020, and by April 2021 it had already killed more than 500,000 nodes in Brazil[1]. The disease is transmitted in the air through respiratory secretions. The symptoms include fever, malaise, dry cough, dyspnea, myalgia, nausea, diarrhea, hyposmia, dysgeusia, lethargy, and muscle weakness[2], with findings of ground-glass opacities in chest tomography[3]. Severe conditions with hypoxemia refractory to oxygen therapy mean some patients face a long period of hospitalization.

In view of the large number of infected individuals, there is also a large number of recovered individuals. After the acute phase, the exact time that the damage caused by the disease continues to affect the individual, especially lung function, functionality, and muscle strength, is still unknown. Individuals who struggle with the chronic effects of COVID-19 will persist. The literature has shown that one of the main consequences seen after the acute phase of COVID-19 infection is peripheral muscle weakness and elevated serum creatine kinase (CK) levels, which occurred in more than 30% of individuals diagnosed with a respiratory syndrome acute caused by COVID-19[4] and cardiovascular damage by different mechanisms, ultimately leading to cardiomyopathies. Likewise, the reduced functional capacity and ability to perform activities of daily living in patients who had been hospitalized with COVID-19 is striking[5].

There is an even worse situation when these patients already had underlying cardiovascular comorbidities, such as systemic arterial hypertension (SAH) and coronary artery disease: They are more likely to suffer from a serious infection by COVID-19, requiring intensive care[6]. Hypertensive individuals as well as those with diabetes mellitus (DM) are the main targets of the deleterious effects and have more severe and sometimes fatal complications of COVID-19[7,8]. In this context, there is still much to be explored about the potential clinical and functional impairments that can persist after COVID-19 due to these aforementioned comorbidities, which can directly affect the functional capacity and quality of life of these individuals. Hence, rehabilitation plays a prominent role in this recovery scenario.

Risk factors and comorbidities

Risk factors for COVID-19 as well as its aggravation should be considered: age ≥ 65 years, smoking, a sedentary lifestyle, pre-existing cardiomyopathies, decompensated respiratory and pulmonary diseases, immunodeficiency, chronic kidney diseases, chromosomal diseases with a state of immunological weakness, malignant neoplasm, some hematological diseases, and pregnancy[3,9,10]. However, of the comorbidities, those that seem to generate the greatest repercussions are SAH, DM, and obesity[9].

Recent studies point to risk factors and comorbidities as predictors of more severe complications in individuals with COVID-19[11,12].

Apparently, SARS-CoV-2 infection is associated with the pathophysiology of comorbidities in line with these predisposing factors, aggravating the symptoms and resulting in a worse prognosis. Hence, these individuals have an increased probability of hospitalization and the need for intensive care and, consequently, a greater risk of in-hospital death[13].

The elderly population is more susceptible to infection by COVID-19 and has a higher percentage of death due to the ease of developing more severe complications[14]. The higher mortality rate in older individuals may be related to decreased immunity and increased frailty due to aging[15,16]. Interferon type 1 (IFN1) is one factor responsible for activating adaptive immunity. Although SARS-CoV-2 is sensitive to IFN1, the virus is capable of affecting the production of this protein, thus delaying and weakening the body's defenses to the virus[17-19]. There is an even greater chance of symptom worsening in cases of infections in this group when associated with risk factors such as chronic diseases[9,11].

Furthermore, DM is one of the comorbidities that has contributed to the increase in the number of hospitalizations for complications and the number of deaths due to COVID-19 infection[20]. The probability of contagion between individuals with DM and without DM does not differ; however, the first group is at greater risk of experiencing more severe complications, especially when concomitant with other comorbidities such as pneumonia[21].

Hussain et al.[22] pointed out possible mechanisms that may be associated with negative manifestations in individuals with DM affected by COVID-19. According to these authors, exacerbated inflammatory responses, changes in immune and platelet responses, and a possible relationship be-

tween SARS-CoV-2 and glycemic regulation and interference in insulin production have been observed. The lack of glycemic control in individuals with DM favors the creation of an inflammatory environment, making them prone to serious injuries in cases of infection[21]. Finally, it is noteworthy that individuals with DM who develop pneumonia tend to have a poor prognosis and more complications than those without DM[23].

COVID-19 and systemic arterial hypertension

SAH has been more frequently observed in patients with severe COVID-19 compared with non-severe patients[24,25] reported that the prevalence of hypertension was significantly higher among patients with COVID-19 who required care in the intensive care unit (ICU) than among those not admitted to the ICU. Patients with COVID-19 with co-existing SAH, high mean systolic blood pressure, and high systolic/diastolic blood pressure variability during hospitalization were independently associated with hospital mortality and ICU admission, suggesting that lower and stable blood pressure values are predictive of a better prognosis.

Early epidemiological studies suggested that cardiovascular diseases (CVD), including SAH, are associated with mortality or severity in patients affected by COVID-19[26] This possibility is worrisome, given that SAH is very common: It affects about 1.39 billion individuals worldwide and the prevalence increases with age, affecting approximately 70% of older adults[27].

COVID-19 and obesity

The situation in Brazil regarding obesity and overweight rates and the pandemic requires special attention. The prevalence of obesity and overweight is high in the country and has increased significantly over the years[24]. Obese patients with COVID-19 and/or with metabolic-associated fatty liver disease had a higher risk of a severe outcome after adjustment for age, sex, smoking, diabetes, hypertension, and dyslipidemia[28].

Obesity has been shown to be a risk factor for hospitalization in patients with COVID-19 who are < 60 years old. However, younger patients with a body mass index (BMI) ≥ 40 kg/m^2 are at a fivefold greater risk of mortality from COVID-19. Severe obesity has also been associated with intubation and mechanical ventilation, impaired chest wall elastance, and reduced respiratory system compliance leading to impaired lung function[29]. It is noteworthy that obese individuals have a more pronounced pro-inflammatory state, with higher levels of cytokines such as interleukin (IL)-6. A higher risk of thrombosis, once conjugated, contributed to the increased risk of severe COVID-19 in obese patients[30].

COVID-19 and respiratory system

Respiratory viruses can adapt quickly and cross the species barrier. Some of these pathogens, such as SARS-CoV-2, occasionally cause epidemics or pandemics and are associated with more serious clinical illness and even mortality. In addition to all these respiratory problems, accumulated evidence from the clinical/medical world strongly suggests that, being opportunistic pathogens, these viruses are able to escape the immune response and cause more severe respiratory complication or even spread to extra-respiratory organs, including the central nervous system[8], where they could infect resident cells and potentially induce other types of pathology. In this scenario, the need of patients with pulmonary complications for ICU admission has been prevalent since the beginning of the COVID-19 pandemic. Individuals with pre-existing respiratory diseases or comorbidities that reduce the full functionality of the lungs tend to progress to a severe condition.

Smoking and chronic obstructive pulmonary disease (COPD) are associated with increased expression of angiotensin II-converting enzyme (ACE-2), increasing the possibility of SARS-CoV-2 entering epithelial cells, taking into account the role of ACE-2 functioning as the main determinant of infection by this virus[31]. Hence, people who smoke and/or have COPD are also more susceptible to more severe forms of COVID-19[31]. Indeed, a document issued by the CDC in 2020 reported that there is an association between smoking and the negative progression of the disease. According to observed results, the chances of progression to severe cases are 1.91-times higher compared with individuals who have never smoked[32]. It is known that smoking poses risks to the respiratory system, increasing damage to the lungs; thus, it can be hypothesized that COVID-19 causes damage to an already weakened endothelium, and consequently generates more complications.

Chronic lung disease has also appeared as one of the comorbidities with a high rate of hospital admissions of patients with COVID-19[3]. As

mentioned above, the explanation for this phenomenon is related to the high amount of ACE2 receptors found in airways, a phenomenon also observed in smokers. The role of ACE2 in the respiratory system is unknown, however, its high expression may be related precisely to the fact that the pulmonary structures are already compromised by COPD and the current use of tobacco[33,34].

The literature contains many reports showing that respiratory tract diseases are important causes of illnesses and hospitalizations and a potential cause of reduced quality of life. Indeed, these conditions often cause functional incapacities in individuals, and in more critical cases, they can lead to death. Based on the above fact, it is essential to develop prevention and care strategies, considering the current pandemic context. Finally, although the effects of COVID-19 on the respiratory system are known, there is still a lot to understand about the long-term effects.

COVID-19 and the cardiovascular system

Several studies have shown that the cardiovascular system can also be negatively impacted by COVID-19[28,35,36]. There is evidence of various impairments in this system, such as findings of myocardial damage, myocarditis, arrhythmias and conduction blocks, vascular dysfunction, and cardiac death[35]. Additionally, the presence of previous diseases of the cardiovascular system, as well as their risk factors, have been described as potential aggravators of multimorbidity in COVID-19[35,37]. The mechanisms of this relationship are being unveiled. The infection caused by SARS-CoV-2 can worsen chronic cardiac pathologies due to decompensation and can lead to cardiac complications that did not exist before infection[37].

Guo et al.[37] identified a greater susceptibility to cardiac tissue damage, assessed by the elevation of troponin T levels, as well as a higher mortality rate in these patients compared with those without previous cardiovascular impairment. In addition, Wang *et al.*[25] demonstrated greater myocardial damage, denoted by the elevation of biomarkers such as creatine kinase MB (CK-MB) and ultra-sensitive troponin I in patients with severe symptoms compared with those who did not require ICU admission. The damage to the myocardium resulting from COVID-19, as well as in other systems, is also dependent on the interaction of the virus with ACE-2 receptors, which promotes a disruption of the protective functions of these receptors to the heart, allowing greater inflammation and consequent damage to the myocardium[38]. Based on this same rationale, the expression of ACE-2 receptors is increased in diseases such as SAH and DM. Individuals with SAH[39], type II DM[40] or chronic heart failure are more likely to evolve severe conditions due to COVID-19 infection and thus require intensive care[6]. They also have higher morbidity and mortality after COVID-19 infection[41].

It is noteworthy that in these patients there is a basal inflammation arising from the pre-existing disease itself, which adds to the inflammatory process caused by SARS-CoV-2, with an imbalance between the increased metabolic demand induced by the infection and the reduction in cardiac reserve. Additionally, both disease courses lead to an imbalance in the performance of the autonomic nervous system (ANS), with pronounced activation of the sympathetic nervous system[41,42] and reduction of the parasympathetic nervous system[41]. Faced with SARS-CoV-2 infection and a pronounced systemic inflammatory response, ANS dysfunction becomes evident and is mainly related to cytokine release and sympathetic activation[43,44]. Another hypothesis is that the ANS is a direct target of the virus, which can also trigger autonomic dysfunction[45]. As a consequence, after the acute phase of infection by SARS-Cov2, these patients who already had autonomic dysfunction will go through a process of more pronounced ANS imbalance[46].

The vascular endothelium has also been highlighted in discussions about the pathophysiology of COVID-19. This organ has primary functions for the maintenance of hemostasis and defense of the body and does so through several important actions such as vasomotor control, anti-inflammation, antioxidation, vascular permeability, and acting as a protective barrier[46]. However, infection with SARS-CoV-2 causes notable endothelial dysfunction with a direct relation to worse outcomes by inciting pro-thrombotic and pro-inflammatory processes[46].

The elevation of pro-inflammatory cytokines (IL1β, IL-6, and tumor necrosis factor alpha [TNFα]) in patients with COVID-19 induces the loss of antithrombotic and anti-inflammatory function of endothelial cells, leading to dysregulation of coagulation, platelet activation, and recruitment of leukocytes in the microvasculature. Histopathological evidence of direct viral infection of endothelial cells, diffuse endothelitis, and micro- and macrovascular thrombosis in the circulation have been found in patients with COVID-19[47].

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In a pattern similar to other systems, it has been suggested that this endothelial dysfunction is directly related to ACE-2 receptors expressed in endothelial cells due to a reduction in their expression or an indirect relationship to potentiate immunothrombosis and to impair the antiviral response[48]. In this scenario, the presence of previous comorbidities such as hypertension, DM, and obesity – in which there is evidence of pre-existing endothelial dysfunction[48] associated with dysfunction induced by SARS-CoV-2 – will contribute to the worsened clinical presentation of the disease with deleterious pulmonary and extrapulmonary complications.

A striking feature in the progression of severe COVID-19 is marked hypoxemia. The combination of pre-existing ANS and endothelial diseases and alterations with hypoxemia and inflammation makes the individual more prone to have fatal cardiac arrhythmias and dysfunctions[41]. Electrolyte imbalances and adverse drug effects can also be potential stressors to previously impaired systems, as well as immune dysregulation, recognized as an important factor in the pathogenesis of vascular disease.

Finally, it has been noted that there is a clear increase in morbidity and mortality due to COVID-19 in individuals with a previous diagnosis of CVD or its risk factors. Some plausible mechanisms of this association translate into a possible worse ability of this already impaired system to respond to the increased demand of a severe viral disease alongside reduced systemic oxygenation[49-51].

Impact of COVID-19 on exercise/functional capacity

Most COVID-19 survivors are mainly troubled by fatigue or muscle weakness, sleep difficulties, and anxiety or depression after discharge from the hospital. In addition, patients who were more severely ill during their hospital stay present more severely impaired functional capacity, lung diffusion, and fatigue symptoms, and they are the main target population for long-term recovery interventions[52]. An elegant study published by Huang et al.[53] demonstrated the COVID-19 consequences 6 months after discharge from the hospital: The proportion of median 6-min walking distances less than the lower limit of the normal range was 24% for those at severity scale 3, 22% for severity scale 4, and 29% for severity scale 5-6.

Interestingly, a previous study of Ong et al.[54] investigating the combination of pulmonary function and exercise capacity in a group of SARS survivors showed that although residual mild pulmonary function defects were detected in over half of recovered SARS patients three months after hospital discharge, 41% presented impaired exercise capacity that could not be explained by pulmonary limitation. In fact, the high use of corticosteroids during hospitalization, nutritional status, bioenergetic changes, as well as myopathy due to disuse due to prolonged hospitalization[55] were factors to explain the important peripheral muscle weakness of these patients.

Many derangements of the musculoskeletal have been described in critically ill patients with COVID-19 that presented prolonged hospitalization[56,57]. Prolonged immobilization associated with malnutrition could explain the marked reduction in muscle strength in intensive care unit-acquired weakness (ICU-AW)[56] In addition, muscle shortening, contractures, deformities, and decubitus ulcers[58] compromise and in most of cases delay early rehabilitation. Most importantly, the excessive, long-term use of steroids and neuromuscular blocking agents during hospitalization leads to polyneuropathy and myopathy[59].

In the hospitalization phase, the patient's functional performance for active or active-assisted mobilization in bed, as well as the patient's ability to understand the task, must be evaluated early in the ICU. As soon as the patient is able to cooperate, evaluations should begin. Peripheral muscle strength, respiratory muscle strength, cooperation for changes in decubitus, and functional independence measure (FIM) scores should be evaluated[60]. The ability to cooperate, especially in postural changes, may be noted and passed on from shift to shift for physiotherapy professionals. The Medical Research Council Sum Score (MRCSS) and functional outcomes – including the Physical Function in Intensive Care Test (PFIT) score, the De Morton Mobility Index (DEMMI), and the Modified Barthel Index (MBI) – may be measured on the first day the patient received the physical therapy intervention and at discharge[61]. In addition, it is of fundamental importance that the therapist assesses the trunk balance and tolerance time in the sitting posture and from the first time the patient stands with support. The first ambulation should be recorded, especially the patient's limit tolerance time (TTlim), desaturation, and symptoms, using a subjective effort scale. These parameters will be used to guide patients to hospital discharge. If possible, ladder tests will allow clinicians to

assess whether the patient is able to move up one flight of stairs when they are discharged from the hospital. Mobility status using the Activity Measure for Post-Acute Care 6-Clicks basic mobility (6-Clicks mobility) and the Johns Hopkins Highest Level of Mobility scales can be considered[62]. The Perme Score can be considered to evaluate the barriers to mobilization[63]. Moreover, a walking test can be applied to some patients before they are discharged.

After discharge, patients may be assessed for functional performance of Activities of Daily Living (ADLs), as well as for tolerance to submaximal exercise and respiratory and peripheral muscle strength. The standing balance, 4-meter gait speed, 5-repetition sit-to-stand motion[64], Glittre ADL[65], and timed up-and-go tests can represent objectives and global forms of evaluation of COVID-19 patients, because they are based on the International Classification model of Functionality, Disability and Health. Furthermore, the 6-minute walking[60], shuttle walking, and step tests[66] may identify exercise intolerance, signals, and symptoms when monitored by a oximeter and dyspnea and muscle fatigue scores. On the other hand, a symptom-limited cardiopulmonary exercise test (CPET) with breath-by-breath gas-exchange monitoring, electrocardiogram registration, and blood pressure and saturation monitoring constitutes a gold standard method to analyze the primary limitation to physical exercise (whether cardiovascular, ventilatory or peripheral muscle)[67]. However, this functional assessment and can only be applied to a subgroup of patients, due to its high cost and the need for a specialized team.

Muscle strength tests with handheld dynamometers can be useful for measuring muscle strength[68]. The one repetition maximum (1RM) tests can also accurately assess peripheral muscle strength in these patients during formal rehabilitation programmes[69]. In addition, inspiratory muscle strength can be measured by maximal inspiratory pressure and endurance tests. All strength tests can be compared with predicted values and are also important parameters for the progression of exercise intensity, as well as for assessing the effects of numerous rehabilitation interventions[70].

In this context, Figure 1 illustrates a functional flowchart for physiotherapists with targets during the hospitalization phase, at discharge, and for the beginning of the rehabilitation program. The proposal aims to guide professionals regarding the importance of functional assessment, considering simple, viable, and inexpensive outcomes, which can be applied in the physiotherapist's daily routine.

Challenges for patient rehabilitation due to the functional repercussions generated by COVID-19

In general, the rehabilitation of patients who have recovered from COVID-19 involves a multidisciplinary health care team, composed of physicians, physiotherapists, speech therapists, psychologists, nutritionists, and physical education professionals. The primary objective is to improve the health and functionality of the affected individuals, whether through the restoration of capacities, minimization of incapacities, or adaptations to carry out daily and professional activities.

Due to recent demands for post-hospitalization rehabilitation of patients who have recovered from COVID-19, many treatment programs lack clinical trials investigating the effectiveness of the interventions used. Furthermore, and similarly, the reliability and validity of various assessment methods are unknown to date in this population. Another challenge for post-hospitalization rehabilitation is related to the large number of professionals working within the hospital environment due to the high demand of those infected with COVID-19. Thus, there is a need to reorganize the health system in order to direct the flow of professionals, equalizing possible discrepancies in care.

The inequality in the health system in developing countries, such as Brazil, is a crucial point that challenges the full assistance of rehabilitation professionals to these patients. To exemplify this condition, we can consider telerehabilitation, an important strategy in times of social isolation for access to health care without the need for personal contact with the professional who assists you. However, for the full implementation of telerehabilitation, it is necessary for several aspects to work, especially infrastructure and socioeconomic determinants. In other words, how will a patient have access to telerehabilitation if the place where they live does not have access to the Internet or if they do not have a connection device (cell phone or computer)?

The example of telerehabilitation is particular due to the need for social isolation, but the distortion in access to health systems in Brazil is chronic. In terms of reflection, how many public health services have teams with all the professionals listed here? Despite the legal and normati-

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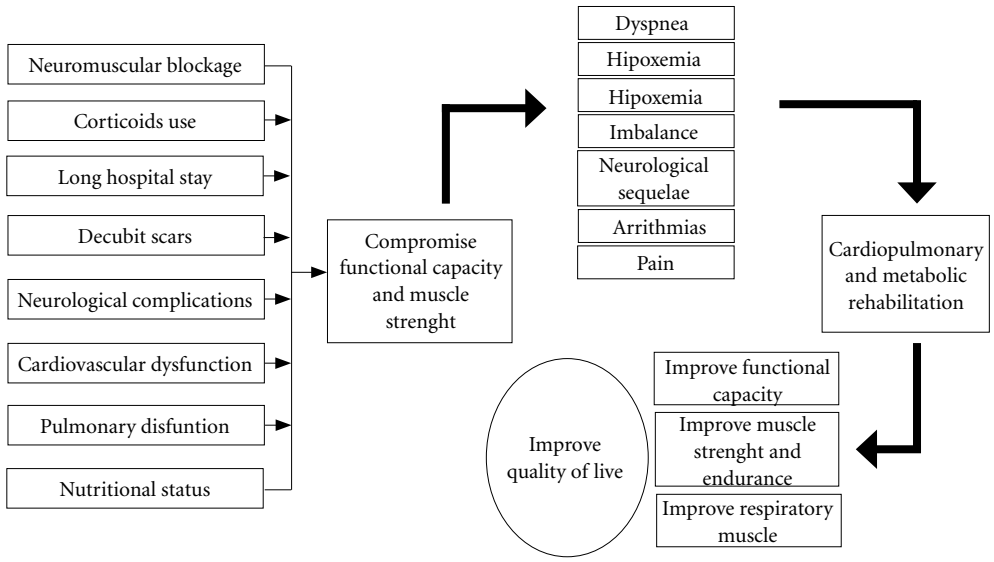

Figure 1. Functional flowchart for physiotherapists with targets during the hospitalization phase.

Source: Authors.

ve support for the creation and maintenance of rehabilitation services in the public health system, they still face difficulties with integrality and equity, with numerous challenges regarding articulation with the whole of health care and with the implementation of expected results of rehabilitation. Based on this complex scenario, some points should be considered to optimize the post-hospitalization rehabilitation of patients who had COVID-19: (i) the need for multidisciplinary work in rehabilitation; ii) the reinforcement of public policies to guarantee equity in access to the public health system; and (iii) the training of the health team in view of the new demands and realities generated by COVID-19 regarding the functionality of patients.

Collaborations

All authors participated equally in all stages of the work.

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