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LETTER TO THE EDITOR

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Hematological predictors of novel Coronavirus infection

Gulali Aktas[1]*

Dear Editor,

I read the article titled *Can the neutrophil/lymphocyte ratio (NLR) have a role in the diagnosis of coronavirus 2019 disease (COVID-19)?* by Nalbant et al.[1], which was published in your journal's May 2020 issue. Neutrophil/lymphocyte ratio (NLR), Platelet /lymphocyte ratio (PLR), and c-reactive protein (CRP), three important inflammatory markers, were found to be higher in Covid-19 positive patients than Covid-19 negative subjects[1]. CRP is a universal inflammatory marker and increases in many infectious and inflammatory conditions. Despite that the correlation between NLR and CRP or PLR and CRP was not evaluated in the study, the authors found that an NLR level greater than 2.4% has an odds ratio of 20.3 for positive Covid-19 test result[1].

Hemogram indexes are considered novel inflammatory markers in many recent studies in the literature. Of these, elevated NLR is suggested as a predictor of poor outcome in patients with Covid-19 infection[2,3]. Covid-19 patients with high NLR levels were reported to have increased interleukin-6 and tumor necrosis factor-alpha and appeared to recover more difficultly than those with lower NLR levels[4].

Mean platelet volume (MPV) is another inflammatory marker derived from the hemogram test. Despite MPV values of Covid-19 positive and negative subjects were not statistically different in Nalbant et al.'s study[1], it was suggested as a useful tool in the prediction of the Covid-19 infection in diabetic subjects[5].

The PLR was also studied in Covid-19 disease in the literature. Authors showed that high PLR levels indicate poorer prognosis and longer hospital stay in covid-19 positive patients[6]. In addition, patients with severe Covid-19 infection have greater PLR levels than those of non-severe Covid-19 infection[2]. According to the data in the literature, not only NLR but also PLR was introduced as an independent prognostic marker of disease severity in patients with Covid-19 infection[7].

Other hemogram indices studied in Covid-19 infection are red cell distribution width (RDW) and monocyte to lymphocyte ratio (MLR). Elevated RDW levels in patients with Covid-19 infection were reported compared to the healthy control subjects[8]. Moreover, it has been reported that increased MLR in patients with Covid-19 infection compared to healthy controls[9].

In conclusion, both NLR, MPV, PLR, RDW, and MLR are useful tools in the prediction of the disease, its severity, and the mortality of Covid-19 infection. Cost-effective and easy-to-assess nature of these tests may contribute to their utility in clinical practice.

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LETTER TO THE EDITOR

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Conflicts of interest in the coronavirus (sars-cov-2) context: banalization of life-death or disinformation?

Bruno Massayuki Makimoto Monteiro[1]*, José Carlos Rosa Pires de Souza[1]

Dear Editor,

The website El País[1] reported that there were more than 116,000 deaths and almost 3.6 million infected in Brazil by August 25, 2020. Nevertheless, the frequent non-compliance with quarantine indicates that part of the population is resistant to the idea that it is impossible to return to normal life[2]. Thus, a debate is raised as to whether this innocent desire is a trivialization of life and death (even if it does not present it as such) or a lack of information.

When looking to the past, it is clear that the population, in general, was led to agree to absurd practices on many occasions, such as in World War II or during the eugenics movements that also took place in Brazil. For example, in Nazi Germany, a considerable part of the German society was in favor of concentration camps, torture, death, and other barbarities, although a greater emphasis is placed on the evil figure of Hitler[3]. Another example was seen in Brazil at the end of the nineteenth and early twentieth centuries when the ruling class (including the middle class which also provided theoretical argumentative support) reproduced racist discourses that defended the whitening of the population because, in their view and from part of the world at the time, economic backwardness was caused by the color of the citizens' skin[4]. It is important to say that although such ways of thinking were accepted as logical during these historical periods, they are no longer considered as such. Therefore, it is essential to be careful before making moral judgments.

Today, history repeats itself. It is observed that part of society is against social distancing and isolation, and even with studies confirming that such measures are essential to mitigate the spread of COVID-19, these people continue gathering every day, going to malls, bars, and nightclubs, among other places. Now, the issue of the return of face-to-face classes has been raised. The other day, in informal academic discussions, it was argued that certain professionals need to be not only on the front line but also to be better prepared to face crises like this; for this reason, face-to-face classes should resume. This argument would be valid for those in their final years of health programs and even for those that are about to graduate (with caveats), if it were not for the fact that many students come from various corners of Brazil and will return to their everyday university life when they arrive at their respective universities whether they are ill or not (whether they are asymptomatic or not). However, the counterargument offered was that it is up to each one to know what to do since they are of age. Is this really true? If it were not for the awareness campaigns of some government agencies in raising the awareness of the population of the need to stay at home to contain the contagion (we say some because the Executive is not too concerned about the prevention of the increase in the number of sick nor dead people), the people's neglect to wear masks, practice distancing, and avoid social gatherings would probably be much worse.

They could say that the rate of recoveries is high and that the need is for Intensive Care Unit (ICU) beds. One of the positions was that, in many states and cities, the ICUs are not full[5]. This is questionable because this is not a necessary and sufficient condition to conclude that everything is okay; after all, if they are not operating at their full capacity at the moment, it does not necessarily mean that this will remain the case in the future. One of the reasons for the lockdown is to reduce the rate of accidents, such as those involving automobiles, so as not to overload such hospital units[6].

Moreover, although the death rate is not high compared to other diseases (such as Ebola, Swine Flu, and Avian Flu), this disease causes sequelae, which affect the quality of life and bring organic damage. According to the study by the State University of Campinas (Unicamp), the chances of cardiovascular, neurological, and digestive repercussions perpetuating even after the patient is cured are real[7]. Moreover, studies show that people who had COVID-19 and were cured were later reinfected, suggesting possible mutations of the SARS-CoV-2 virus[8,9].

Such a scenario has often been highlighted by the authorities and the mainstream media. However, the population does not seem to understand the national and international magnitude of the disease.

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Emphatically, the concern with their private lives is understandable (students, in particular, believe they already could return to regular life and that everything is okay as their relatives work in hospitals where there are no cases of COVID-19 among employees).

No, it is not okay. There are more than 116,000 dead, in addition to those living with sequelae, those whose lives are at risk, and families who have lost their loved ones. The return of classes does not affect these families directly, nor those who might still lose relatives and friends. However, they may be indirectly affected because when face-to-face classes return, several professionals will return to their occupations in person, thus, many people will move from their homes, putting other people at risk. It should be noted that students will also visit other places such as restaurants, malls, laboratories, and the like.

Therefore, in the future, as we look at the past, we will be able to analyze more clearly what happened. For now, people do not seem to be concerned about each other as they would be with their interests. For them, the most important thing is that they can return to their regular "lives," ignoring the facts reported and the lost lives. Citizens today are acting similarly to the Nazi Eichmann who was unable to analyze and question his actions when he led thousands of Jewish people to death[3], to the extent that their actions directly or indirectly impact the life-death of people.

When answering the question in the title of the paper —whether this is a trivialization of life-death or misinformation— it could be said that it is a bit of both and that it is the result of the worsening or development of some emotional problems, which emerged again in a large part of the population or was even triggered by the current situation. However, most people do not admit that they have emotional problems, which causes a progressive increase in these disorders, thus compromising social relationships even more. More arguments can be raised to explain such positions; however, a large number of deaths nationwide (116,000)[1], which is here purposely emphasized, and worldwide (around 820,000)[10] is self-explanatory. If these arguments are not enough, you may want to read the paper again and think more about your life and the life of others.

AUTHORS' CONTRIBUTIONS

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LETTER TO THE EDITOR
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SARS-CoV-2 transmission by aerosols: an underestimated question?

Luciene Muniz Braga[1]*, Oswaldo Jesus Rodrigues da Motta[1,2], Andréia Patrícia Gomes[1], Pedro Costa Oliveira[2], Mathias Viana Vicari[1], Rodrigo Siqueira-Batista[1,2]

KEYWORDS: Coronavirus infections. Betacoronavirus. Aerosols.

Dear editor,

The actual pandemic caused by SARS-CoV-2 (*Severe Acute Respiratory Syndrome*), an etiological agent of COVID-19 (Coronavirus Disease 2019), has already infected more than 16 million people in the world, causing about 900,000 deaths in September 2020. The pathogen belongs to a group of microorganisms that infect the lower and upper airways and cause respiratory diseases, from milder forms resembling a common cold, to classic cases of influenza syndrome – with the symptoms of cough, fever, and coryza – to more serious situations, with pneumonia and severe acute respiratory syndrome (SARS)[1].

Initially, it was believed that the transmission of the virus occurred mainly through droplets and contact, considering the transmission by aerosols restricted to specific situations of medical practice such as nebulization, orotracheal intubation, cardiorespiratory resuscitation, and bronchoscopy, among others. More recent studies, however, have shown the importance of aerosol transmission outside the health environment, including reports of virus spread in concerts, elevators, and shopping centers[2].

To understand the dynamics of transmission of SARS-CoV-2 it is necessary to differentiate between droplets and aerosols, two vehicles for the respiratory dissemination of microorganisms that are produced especially by speaking, coughing, or sneezing. The droplets are larger than 5 micrometers. Infection may occur when droplets reach the oral, nasal, and/or ocular mucosa of the susceptible. It is also important to comment that when these droplets are deposited on surfaces, they make transmission by contact possible, from fomites or the surface of a body contaminated by the viral agent, taken later to the mucous membranes[1,3]. In objects made of steel and plastic, the virus has been stable for up to 72 hours, with high positivity for SARS-CoV-2 in devices such as garbage cans and bed grids[4]. Considering the size of the droplets and their range, distancing of more than 1.5 meters between people, and frequent sanitization of the hands (minimizing the propagation by contact), are important guidelines in terms of biosafety[1,4].

Aerosols, with a diameter of less than 5 micrometers, are transmitted by air. According to the physical-mathematical foundations of fluid dynamics, such particles are carried inside a cloud of turbulent gas and may remain suspended in the air for long periods. In this case, the description of the phenomenon is based on Brownian Motion behavior, which is explained by the collisions of the particles with the suspended molecules and fluid viscosity. Thus, a chaotic and random movement occurs on the aerosols, which are carried by airflow, distributing themselves in different areas of the environment[5,6,7]. Based on what had been described in the epidemics triggered by other coronaviruses, such as SARS-CoV and MERS-CoV, there already existed suspicion that the spread of SARS-CoV-2 was occurring using aerosols[5,7].

Given the high transmissibility of SARS-CoV-2 – especially due to the possible underestimation of virus dispersion by aerosols[4-8] – it is essential to review individual protection measures, in terms of the recommendation of universal use of the N95 respirator or equivalent (PFF2), especially in situations of health care units treating patients with respiratory symptoms. Furthermore, in the current context of the COVID-19 pandemic, and this is the proposal of the present manuscript, *the universal use of the N95 or PFF2 respirator should be considered for all healthcare professionals who provide direct care to patients in closed environments* – a characteristic of most healthcare

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institutions – due to the possibility of aerosol formation and the low possibility of air exchange.

In addition, a cost-benefit analysis of the medical mask (which should be replaced every three hours at the most, or sooner if it is wet) compared to the N95 respirator is pertinent for health care professionals, considering the time of use of this equipment and the related costs. In fact, the availability of the latter (N95 respirator) may even be less costly – from a purely financial point of view – than the offer of medical masks.

It should also be considered that the number of asymptomatic and pre-symptomatic patients and health professionals, who present SARS-CoV-2 detectable in the secretions of the oropharynx and/or nasopharynx, allows the transmission to those who are in the same environments, both workers and patients. In this situation, it is imprudent to act in a risk establishment logic, limiting the use of N95 respirators or equivalent only when it is believed that there will be an aerosol-generating procedure in the classical ways. The risk of contagion, infection and illness of health professionals is aggravated by these findings and is associated with the time of exposure to the patient, the degree of agglomeration in poorly ventilated places and the quality of air in the environment[1,5]. In fact, the existence of (1) adequate air exchange, (2) filtration with HEPA (High-Efficiency Particulate Arrestance) filter type decontamination unit, (3) exhaust system and rooms with negative pressure and (4) use by the professional of the adequate protective equipment, which in this case, certainly should not be the medical mask but the N95 respirator or equivalent (PFF2) must be taken into consideration[7].

It is worth noting, in this context of increased risk of aerosol transmission, that investment in technologies such as ultraviolet radiation-based air disinfectants such as *UV germicidal upper-room* has shown good results against SARS-CoV-2. For the general population, cloth masks are a viable option, if it is not possible to use medical procedure masks or respirators, and it is necessary to evaluate the type of cloth, the number of layers and the presence of a filter, the change time (every three hours or before in case of humidity), the fitting to the nasal and mento-mandibular anatomy and water resistance[8-10]. The use of a medical mask is currently recommended. To improve performance and to reduce SARS-CoV-2 transmission and exposure, the CDC suggests the combination of the cloth mask covering the medical procedure mask, double mask, or the use of respirators[10].

To have good results in the control of SARS-CoV-2, (inter) national health policymakers and administrators of health institutions must ensure the necessary working conditions – in primary, secondary, and tertiary health care – with (1) the application of protocols to verify the existence of symptoms, in the health unit workers, before the beginning of the working day and (2) the guarantee of personal protection equipment for the performance of care activities and high levels of vaccine for all. In addition, it is essential to allocate resources to inform the population about prevention measures, the effectiveness of the mask and the importance of wearing it – even in the absence of symptoms – and the correct way to sanitize hands, clothes, and other surfaces[9]. The duration of vaccine protection is not yet known and widespread vaccination to reach an appropriate level of population-level immunity (60–70%) will take some time. Therefore, the use of masks will have to continue until the cessation of the pandemic. The victory over COVID-19 will depend on these efforts.

AUTHORS' CONTRIBUTIONS

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LETTER TO THE EDITOR

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Anticoagulation as prophylaxis of severe forms of COVID 19? A perspective

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COVID-19 leads to the involvement of the respiratory tract causing a severe acute respiratory syndrome, SARs-Cov-2[1,2]. This can predispose to thrombotic diseases, both arterial and venous, due to the excess of inflammatory reaction, platelet activation, endothelial dysfunction, and stasis[1,3]. Thrombotic events can be diverse: venous thromboembolism[4,5], pulmonary embolism[2,6], and even disseminated intravascular coagulation[2].

Thinking about the pathophysiological importance of these thrombotic events for the appearance of severe forms, we raised the following question: did anticoagulation have a role in the prevention of thrombotic events in SARS-Cov-2? Would this role be greater in patients with countless patients, who generally progress to more severe forms? Are patients who are already using anticoagulants better protected from these severe forms of this disease? The following is a clinical case that illustrates this hypothesis:

- Patient

Male patient, 66 years old, with diarrhea and prostration initially, later evolving with fever, headache, and dry cough. Comorbidities: obesity, systemic arterial hypertension, Diabetes Mellitus, heart failure, sleep apnea, and atrial fibrillation (AF). Using medications including Eliquis 5 mg twice daily to prevent thromboembolic events secondary to AF.

Due to symptoms and the current context of the pandemic, the patient sought emergency care, where an RT-PCR test was performed for COVID 19, which was positive. As the patient was stable from a respiratory and hemodynamic point of view, without the need for oxygen supplementation, symptomatic treatment was prescribed and guided observation at home. The patient evolved uneventfully with complete clinical improvement 15 days after the onset of symptoms.

DISCUSSION

In this clinical case, the patient had numerous comorbidities, which determine a greater predisposition to severe forms of acute respiratory syndrome[1]. However, it evolved well, without any serious hemodynamic, circulatory, or respiratory repercussions of COVID-19. Was this fact related to the use of anticoagulants?

There are still no reports on the use of anticoagulants for the prophylaxis of severe forms in patients with COVID-19. However, as some studies have verified the association between COVID-19 and thromboembolic events in critically ill patients, this hypothesis can be suggested[4,7].

The pathogenesis of thromboembolism in SARs-Cov-2 results from an exacerbated inflammatory response, cytokine storm, and elevation of mediators such as Von Willebrand factor and tissue factor, generating endothelial, hemostatic activation, and consequently the activation of the coagulation cascade[1,3,6]. There is also an increase in prothrombin time, an increase in fibrinogen degradation products, platelet consumption, and an increase in Dimero-D. In addition to these findings, the fact that in autopsies of patients with COVID-19 there is the presence of microthrombi in the pulmonary microvasculature, suggesting that the hypoxemia presented during the severe form may be associated with dissociation between ventilation and local perfusion[8]. Unlike Severe Acute Respiratory Syndrome, patients present good lung compliance in the initial stage, reinforcing the hypothesis of microthrombi[1,3].

Direct oral anticoagulants are an alternative to vitamin k antagonists (Warfarin) in preventing thrombotic events. Unlike warfarin, which prevents the coagulation process by suppressing the synthesis of vitamin k dependent factors, apixaban enters the coagulation cascade directly inhibiting the activated

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factor X, preventing thrombin activation and the consequent development of the thrombus[9].

CONCLUSION

The related patient had several risk factors for an unfavorable outcome, which surprisingly did not occur. Was this fact related to anticoagulation that, as discussed, could prevent the activation of the presented coagulation cascade? We suggested this possibility and suggested that cross-sectional and longitudinal studies be carried out to test this hypothesis. A practical application if this hypothesis is proven, would be the use of these substances in patients at risk who for some reason would not be able to maintain social isolation.

AUTHORS 'CONTRIBUTION

GCFO: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft and Writing – Review & Editing. **BBG:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft and Writing – Review & Editing. **WJM:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft and Writing – Review & Editing.

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LETTER TO THE EDITOR

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Comments on "Kawasaki and COVID-19 disease in children: a systematic review"

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Dear Editor,

Gonçalves et al.[1] presented a systematic review of the association of Kawasaki Disease and COVID-19 in children. While benefiting from an interesting topic, there were some methodological issues that we thought we might address.

This systematic review included only one case report, leading to no further discussion on the topic. Although there is no restriction for the number of included studies in a systematic review, the outcome should add some scientific value to the reviewed topic, which might be of interest for the scientific community[2]. A systematic review, including only one study and one patient, seems to lack any additional scientific value.

The primary goal of a systematic review is to search all sources of evidence in order to find all relevant studies, in response to a clear and formatted research question[3]. In the search strategy of the current study, it would be better if the free keyword "kawasaki syndrome" was accompanied by other terms (i.e., kawasaki disease, kawasaki), along with other equivalent free keywords and MeSH terms like Mucocutaneous Lymph Node Syndrome, in order to prevent unintentional missing of the relevant articles. Also, since most of the cases reported in this field do not entirely fit in the diagnostic criteria of Kawasaki Disease, some new medical terms have been introduced by researchers and clinicians in this state to replace the term "Kawasaki Disease" in order to better define the current inflammatory syndrome, including Multisystem Inflammatory Syndrome in Children (MIS-C), Pediatric Inflammatory Multisystem Syndrome (PIMS), and Kawasaki-like Disease, which should be included in the search strategy to acquire more accurate results[4]. The PICO components, presented in Table 1, are not defined according to the review question. Suppose the study is considered as a systematic review on prevalence/incidence. In that case, the question should follow the CoCoPop format (Condition: Kawasaki disease, Context: COVID-19 infection, and Population: children), if the review is aimed to determine the etiology and risk, the question should follow the PEO format (Population: children, Exposure: infection with SARS-CoV-2, and Outcome: Kawasaki Disease), and if none, the question should follow PICO in the following form: 1. Population: children, Intervention/exposure: COVID-19 infection, Comparator/control: no COVID-19 infection, and Outcome: Kawasaki Disease[5]. "Association" is not an appropriate comparator and "coronavirus" is definitely not an outcome. Additionally, in all questions, the "children" should be defined in exact age ranges. Besides, the authors have mentioned in Table 1 that only "Descriptive/Cross-sectional/Observational studies" will be included, while the "Controlled clinical trials" are in among the inclusion criteria in Table 2, and "randomized controlled trials", "clinical trial", and clinical trial-related terms (e.g., "random allocation", "double-blind method", etc.) are included in the search strategy. Again, in contrast, the PRISMA[6] Flow Diagram of the study (Figure 1) indicates that some studies have been excluded during the eligibility phase, for being "interventional studies".

Moreover, an exclusion criterion of "Poorly described or inappropriate" studies has been mentioned in Table 2 of the study. The criteria for considering a study "inappropriate" should be clearly defined to prevent further misinterpretations. Also, assessing the quality of the studies is not something that could be performed during the screening phase of a study; this is the exact reason that there is a quality assessment (critical appraisal or risk of bias assessment) step in conduction of systematic reviews. Speaking of

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the risk of bias assessment, the authors addressed that the quality of the studies was assessed using the Pithon et al.[7] protocol. We believe that the protocol that the authors are addressing is not compatible with the quality assessment of the current study, and the authors might have made mistakes in choosing and also use of this protocol due to the following reasons: 1. The protocol is developed for dental studies (several items related to mouth wash are mentioned in the checklist), 2. The case studies were clearly excluded from the Pithon et al.[7] study, therefore, the protocol is not compatible with quality assessment of the case studies, 3. The authors claim that any study with less than six scores was excluded, where the only included study obtains hardly four points from the protocol.

The Figure 1, representing the PRISMA Flow Diagram of the study, is completely different from what the article text represents; the authors have mentioned that "Initially, 840 articles were identified, of which three qualified and passed to the stage of abstract assessment. Of these, two were excluded because they did not answer the guiding question.", while the PRISMA Flow Diagram indicates that from 840 studies (837 without duplicates), 6 studies were selected after abstract assessment, where four of them did not pass the full-text assessment.

We believe that the addressed issues might have drawn the study away from the PRISMA statement[6] and clearly affected the quality of the systematic review.

AUTHORS' CONTRIBUTIONS

MSH: Conceptualization, Data Curation, Writing – Original Draft. **MAA:** Writing – Review & Editing.

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POINT OF VIEW
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Training in healthcare during and after COVID-19: proposal for simulation training

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SUMMARY

INTRODUCTION: The challenge of facing COVID-19 falls under all health care structures, and without specific training to health care professionals they are probably the professionals with the highest level of exposure. Regardless of the level of health care, the training of professionals aims to optimize resources and attend patients while assuring quality and security.

POINT OF VIEW: This report proposes simulation training for health care professionals to update professionals for attending patients during the pandemic. This training was built with five simulated stations, considering different stages of a patient with COVID-19. This report takes advantage of different simulation techniques, such as skills training, standardized patient, medium- and high-fidelity simulator, rapid cycle of deliberate practice, and *in situ* simulation.

DISCUSSION: Medical procedures for COVID-19 patients offer additional risk for health care professionals, especially considering exposure to procedures that generate aerosols, such as compression, mask ventilation, and orotracheal intubation. Thus, finding educational strategies that allow training is essential to simulate the evolution of COVID-19 patients in a safe manner.

CONCLUSION: Simulation has proven to be a useful and effective form of training around the world for training health teams on the front lines for patient care in COVID-19.

KEYWORDS: Coronavirus infections. Simulation technique. High-fidelity simulation training. Simulation training.

The challenge of the COVID-19 pandemic is felt in all health care spheres and will certainly persist after the pandemic. There is no doubt that, without specific training, medical professionals will be among those most exposed to illnesses and, consequently, to sick leave, with loss to the team and society. Regardless of the health care level at which professionals work, training aims to optimize resources and promote quality care while ensuring the safety of the professionals and the population.

In this study, we propose a continuing education model for professional development related to the treatment of patients with suspected or confirmed COVID-19 cases. This model is based on simulation training that aims to educate health professionals on COVID-19 protocols.

In general, simulations can be contextualized as educational strategies that range form practicing basic skills to the actual professional treatment of a clinical case. In the latter, technical

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and nontechnical skills (soft skills) are practiced simultaneously. One of the most widespread definitions of simulation states it should be seen as a technique, and not exclusively a technology, which aims to replace or amplify a real experience with supervision, but substantially evokes aspects of the real world in an interactive environment[1]. The use of simulations is no longer considered an innovative activity, given there are reports and records dating back to more than 100 years of technical skills training, using straw-filled dummies[2]. In recent decades, simulations have been updated from both a pedagogical and a technological point of view, such as with robots that confer high fidelity in real time to the actions performed with the relevant hemodynamics, enabling the creation of scenarios more similar to real-world practice.

This technological advance has allowed the training of competencies, such as decision-making, leadership, teamwork, and other determinant actions for better patient care. This strategy can simultaneously work from several aspects desirable to health professionals, and can be included in curricula and in continuing education, according to the available time and financial resources and the target audience to be trained. Training that addresses the management of patients with COVID-19 has been conducted worldwide. Among the main strategies used, simulation stands out, because it ensures a safe environment and prepares for care under situations with the potential risk of contagion[3].

The novel coronavirus (SARS-CoV-2), which causes COVID-19, belongs to the family of betacoronaviruses, RNA viruses that adapt to various hosts and spread rapidly among humans. There are many uncertainties about the management of the disease, but it is known that the contamination of professionals through aerosols and fomites is highly likely, and a high incidence of fecal transmission has been described among professionals responsible for direct patient care[4]. The clinical presentation of this disease is mostly mild, with approximately 80% of infected patients not needing any special care, and the symptoms are similar to those of the common flu; however, a portion of patients can progress to a more severe disease from, with respiratory failure as one of the most important clinical signs[5].

The big question is how to train these professionals to effectively cope with the ongoing pandemic and how to maintain this standard after this situation is under control. Additionally, considering that many health professionals are inexperienced with this disease is important, making it necessary to focus their training on specific changes for the care of patients with suspected COVID-19. In this context, many videos using simulated patients have been employed as a practical strategy to disseminate at least the minimum content and requirements for care. However, these isolated activities may garner too little participant engagement and do not promote the hands-on experience needed by professionals who perform numerous procedures, such as medical professionals, especially on the front line and in intensive care units (ICUs).

The COVID-19 pandemic caused many institutions to take a new perspective on simulation training, which ceased to be just another strategy and became the strategy of choice, as institutions made the necessary adjustments to adapt to the pandemic[6]. Simulation programs were adjusted to meet health needs in order to ensure that teams would adapt to the crisis, since this teaching strategy enables improvements in individual and team learning[6].

Procedures including endotracheal intubation, collection of laboratory samples[7], collection of tracheal secretions[8], and cardiopulmonary resuscitation (CPR)[9,10] have been used in training to develop skills and ensure the safety of teams[7] with respect to COVID-19. Training in donning and doffing in the context of COVID-19 using rapid cycle deliberate practice has also been planned in the pandemic[11]. Training using simulation improves the perceived confidence and preparation of professionals with regard to patients diagnosed with COVID-19[7].

To design an adequate simulation training program, understanding three fundamental concepts is required: fidelity, realism, and complexity. The concept of fidelity refers to the amount of technology used in robots or manikins and can be classified as low, medium, and high[12-14]. With low-fidelity simulators, it is possible to train a motor skill; medium-fidelity simulators combine part of the manikin with software to train on a specific procedure; and high-fidelity simulators are those with spontaneous breathing and real-time hemodynamic changes, allowing training for advanced clinical situations using a simulator, in which different procedural interventions are possible simultaneously. Whereas fidelity refers to the manikin or simulator, realism is related to how close the scenario or clinical case is to reality. Realism is traditionally divided into four domains: conceptual, physical, functional, and psychological[15-19]. The concept of complexity is related to the degree of difficulty of the scenario, recalling that the same scenario can be complex for a group of professionals (e.g., undergraduate students) and less complex for another group (experienced professionals). To develop a simulation training program, considering all available resources is of utmost importance, as well as the learning objectives in order to optimize the simulation usefulness[20].

The aim of this report is to propose a simulation-based training program focused on patient and professional safety during and after the COVID-19 pandemic. This proposal is based on the combination of the fundamental concepts of simulation with the learning objectives of each training exercise.

SIMULATION TRAINING FOR COVID-19

The goal of the training program involves different types of simulation that may or may not occur simultaneously in the rotation scheme, depending on the number of professionals to be trained and on instructors trained in the method and subject, as well as on room availability. Eight to 12 professionals are expected to participate in each station. The duration includes the scenario time and the time that will be used for feedback/debriefing; for the proposed program, approximately 30 minutes is suggested for each case. If the program is performed with only one group of participants and sequential stations, the time at each station may vary depending on its difficulty to the group. When the program is performed with more groups and stations occurring simultaneously in a rotation model, it is important to keep the activity time equal for all.

The proposal considers five stations, starting with basic procedures and gradually evolving with the patient's complexity (see Table 1). The stations start with the donning, doffing, and use of personal protective equipment (PPE). After that, groups proceed to the screening of the patient with suspected COVID-19, followed by critically ill patient care and CPR, and ending with the pronation of the critically ill patient.

The first station aims to practice fundamental technical skills during and after the COVID-19 pandemic: donning, doffing, and use of PPE. For this activity, the use of the skills training model can fulfill the proposal. At this point, the objective is the procedural process, and there is no need for a particular description of a clinical case. The facilitator of this activity should accurately know the resources available in the routine of these professionals and master the care practices of the institution. All participants must perform the complete technical procedure individually so that they can receive immediate feedback and repeat the activity until correct – essential to ensure the effectiveness of the activity. A simple room and a table containing the material to be used (alcohol gel, goggles, mask, procedure glove, apron, hazardous waste bag or container for disposal of the material used) are the necessary materials. A clipboard, paper, and pen can be made available to participants to take notes at this and other stations.

For the second station, we considered the moment of triage of a patient with suspected COVID-19, a situation commonly faced in health services. The use of a standardized patient ensures the fidelity of the scenario and allows the participant to perform a rapid anamnesis, ask the right focused questions, identify signs and symptoms, and engage in clinical reasoning and decision-making. The construction of a clinical case with all the patient's previous and current data and information is mandatory for this activity. The performance of a pilot exercise with an actor who will represent the standardized patient is essential to emphasize the objective of the activity and the attitudes to be taken during the scenario to ensure that the representation is homogeneous between all the groups being trained. This type of simulation is widely used when the objective is to learn technical content and practice interaction and communication between provider and patient. In this model, it is suggested that only one participant act as a volunteer for care, while the others act as observers. Considering good triage practices, a 5-minute scenario may be considered, and at the end, everyone should participate in the debriefing. In times of the pandemic and even after the acute phase of COVID-19, developing scenarios that foster discussion of clinical reasoning and decision-making is essential, in addition to the use of PPE and aspects of patient/professional safety. The clinical history may

Table 1. Simulation training stations for technical and non-technical skills, focused on patient safety during and after the COVID-19 pandemic.

	Learning objectives	Method	Resources
Station 1	Donning, doffing, and use of PPE*	Technical skills training	Materials for specific training (PPE)
Station 2	Screening of suspected patient with COVID-19	Clinical reasoning and technical skills training	Standardized patient
Station 3	Triage of critically ill patient with COVID-19	Clinical reasoning and technical and non-technical skills training	Medium- or high-fidelity simulator combined with standardized patient
Station 4	CPR of the COVID-19patient	Clinical reasoning and technical skills training	Medium- or high-fidelity simulator
Station 5	Care of critically ill patient with COVID-19 – Patient pronation in critical care	Clinical reasoning and technical skills training	Medium- or high-fidelity simulator in the ICU of the institution

*PPE: personal protective equipment

change according to the level of knowledge of the team to be trained, as well as the expected behaviors. A room containing a table, chairs, material for checking vital signs, PPE, alcohol gel, and garbage for disposal of contaminated material are the necessary resources.

The third station aims to simulate critical patient care. In this context, a medium- or high-fidelity simulator is suggested, in which the interventions performed by the health team should be discussed, such as proper donning of equipment; identification of the patient with signs and symptoms of clinical decompensation; checking and administering medications, the permeability of venous access, and medical records; clinical interpretation of laboratory and imaging findings, checking hemodynamic signs; and requesting intervention by other professionals. The construction of a clinical case and the performance of the pilot exercise are necessary to verify whether the information and clues offered in the case align with what is expected during the real scenario. This type of scenario allows participants to be trained in the knowledge of signs of clinical worsening, the application of care protocols, and the practicing of teamwork. It is suggested that two or more participants be volunteers in the scenario, according to the objective defined in the case. The scenario may last 10 minutes or more. At the end of care, volunteers and observers will participate in the debriefing. Creating a checklist to direct the observation of participants and conduct the debriefing is recommended. In this scenario, there is the possibility of including an actor to simulate a companion, providing the participants with an opportunity to discuss technical and attitudinal knowledge. To train the actor who will represent the companion, it is important to make it clear that this actor should avoid caricatured or exacerbated actions that do not contribute to teaching and that push the professionals away from the objective of the scenario. For this type of scenario, it is necessary to establish an inpatient unit containing a stretcher, material for care, and a complete emergency cart.

The fourth station aims to improve the identification and management of cardiac arrest and the performance of CPR maneuvers. We suggest using the rapid cycle deliberate practice educational strategy, which uses the concepts of simulation-based mastery learning, a strategy widely validated in the literature that is based on the need for demonstration of the student's proficiency in a competency before moving to the next educational objective, aiming at mastering a given competency[6]. A medium- or high-fidelity simulator is suggested herein so that resuscitation interventions can be performed. The group of participants can be divided into three or four small groups that will perform the identification of cardiac arrest and CPR maneuvers. All groups should perform the activities, rotating between practice and observation. In this station, there will be no debriefing after care; however, it is up to the facilitator to interrupt care, provide feedback, and direct the proper performance of the techniques. This is an intentional strategy that works well for this type of scenario in which there are many demands (compression, ventilation, rhythm identification, others). All participants must practice compression and ventilation during the time scheduled for this station. Few resources are used; they should include a room for care, simulator, rigid board, bag-mask valve, defibrillator, PPE, alcohol gel, and garbage for disposal of material.

The fifth station aims to train the participants in the care provided for pronation of the critically ill patient with COVID-19. Critically ill patients with COVID-19 may require placement in the prone position to improve ventilation[8]. Professionals should be carefully trained in this procedure because it can cause numerous serious adverse events, such as extubating and loss of central venous access. Our proposal suggests the *in situ* simulation, which is more complex, given the logistics of care and the many material resources needed. Figure 1 shows an example of a ward to be set up for this type of simulation. This type of simulation occurs in the actual care environment and can train the entire team as long as they are staggered in their work shifts. It is undoubtedly a motivating format because the training takes place using real resources and with the routine staff. Debriefing in this proposed method is essential for better knowledge retention. For this activity, it is essential to construct a clinical scenario and conduct the pilot exercise to assess whether the case and the clues provided direct the participants to the expected goal. The simulation scenario is suggested to last for 10 minutes on average, and the debriefing should happen afterward, using a checklist. Regarding the number of

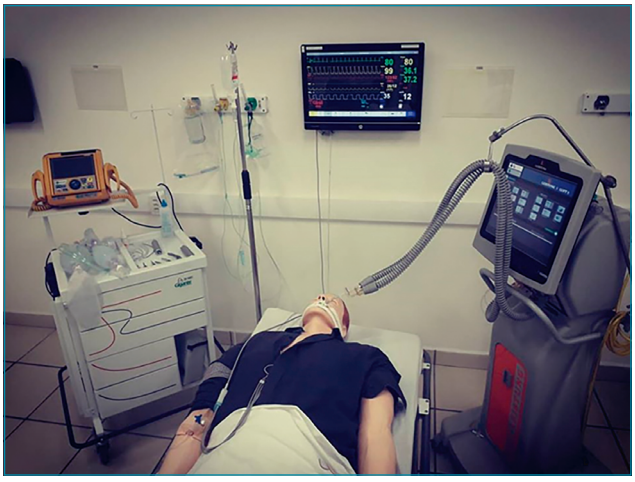

Figure 1. Example of a simulation of critical care for COVID-19 patients.

participants, each institution should consider the number of professionals who will participate in the routine. The *in situ* simulation can be performed with a medium or high fidelity simulator or a standardized patient.

The five training stations proposed can be adapted according to the infrastructure of each service. We suggest constructing the cases and discussing them with colleagues to identify the fundamental objectives to be addressed in each activity. Checklists can help participants and facilitators during the activities, direct the debriefing, and serve as a reference material to be used at later times. Training the facilitator to conduct the debriefing is fundamental for knowledge retention. Audio-visual resources to record the sessions and incorporate them into the discussion is desirable, but their lack should not be an obstacle to the performance of the training exercises.

DISCUSSION

COVID-19 is a highly transmissible disease that directly affects health professionals, especially doctors and nurses working in direct patient care. A 20% contamination rate has been found in health professionals in several countries, and it is higher when they have not been prepared or did not use PPE properly[21]. Different educational strategies have been put to the test during the COVID-19 pandemic, since it is necessary to consider educational measures that minimize biopsychosocial impacts but entail hands-on training performed in a controlled environment so that they, in fact, have a transformative and multiplier effect on patient and provider safety.

The growing demand of the population for access to health services requires new ways of organizing work processes so that the social demand for quality services can be met and the limitations imposed by the COVID-19 pandemic be overcome. Therefore, health becomes an essential arena for human development, with a greater awareness of its importance in the social and economic context.

The use of different simulation strategies can effectively contribute to the training of health professionals, especially physicians, at all health care levels. Educational institutions should offer, as much as possible, specific training to their care partners. Developing training programs in situations such as the COVID-19 pandemic promotes safety not only for patients but also for the professionals involved. Institutions that do not have simulation environments can adapt other ways of disseminating information in a didactic way, which will help health professionals in this difficult time that has impacted the entire world.

The simulation training program proposed in this study considered the progression of patients with COVID-19 and was concerned with training professionals in safe and adequate care. Training of basic activities such as donning, doffing, and using PPE, although simple, is essential for the safety of professionals and the prevention of cross-contamination. Training on CPR maneuvers was included in our program because these maneuvers for patients with COVID-19 pose additional risks to health professionals, especially if we consider the exposure to aerosols generated by procedures such as compression, mask ventilation, and orotracheal intubation. Training procedures to avoid the contamination of professionals are of vital importance at this time, and simulations consistently contribute to training in this pandemic times. Some studies have even used fluorescent powder to visually represent the virus in training on orotracheal intubation[22].

The perception of professionals regarding safety in the care of patients with COVID-19 may increase after conducting simulation training; professionals may feel more confident and willing to care for patients with COVID-19 or other infectious diseases that require isolation[7]. A study that used *in situ* simulation to train ICU/critical-care doctors and nurses on the scenario of a patient with COVID-19 who started with respiratory distress, progressed to pulseless electrical activity secondary to hypoxemia, and ended with a code blue, concluding that there was improvement in the speed of the main events of the CPR maneuvers after the simulation sessions[10]. The authors also reported that observations of the *in situ* simulation allowed them to make changes to procedure as well as adjustments to the flow of care and infection prevention measures[10].

FINAL CONSIDERATIONS

Simulation is a strategy that promotes reflection in a controlled environment that closely resembles the real-world environment. It is not a strategy to be used alone, but as a practical tool, since it helps exponentially in the development of health professionals, such as doctors and nurses. The improvement of the knowledge and skills of these professionals requires strategies that are not fragmented but consider the clinical reasoning and connection with the whole.

In the COVID-19 pandemic, providing professionals with training to develop analytical and reflective critical thinking is mandatory, focusing on not only technical aspects but also attitudinal and social aspects at different health care levels. Simulation is useful and effective in all parts of the world for the training of front-line healthcare teams to care for patients with COVID-19.

Building and implementing a training program that includes the basic aspects of donning PPE to the care of critically ill patients can help in the care of COVID-19 patients, improve the performance of professionals, and lead to better clinical outcomes.

AUTHORS' CONTRIBUTION

CFSB: Conceptualization, Methodology, Formal Analysis, Supervision, Writing – Original Draft, Writing – Review & Editing. **ECB:** Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing. **GFV:** Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing. **MLFB:** Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing. **EFMA:** Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing. **DCF:** Conceptualization, Funding Acquisition, Methodology, Writing – Original Draft, Writing – Review & Editing.

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POINT OF VIEW

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Possible role of exogenous melatonin in preventing more serious COVID-19 infection in patients with type 2 diabetes mellitus

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SUMMARY

COVID-19 infection is more severe in patients with type 2 diabetes mellitus (DM2). The severity of this viral infection is associated with an intense inflammatory activity. DM2 is a disease that also determines a greater degree of systemic inflammation. This is due to hyperglycemia, the higher prevalence of sleep disorders and also the low levels of melatonin, a substance with anti-inflammatory actions, in these patients. In this article, we suggest that exogenous melatonin may have an important anti-inflammatory role in preventing severe forms of COVID -19 in patients with DM2.

KEYWORDS: Diabetes mellitus. Melatonin. Sleep. Coronavirus Infections. COVID-19.

INTRODUCTION

The COVID-19 pandemic manifests itself with particularly adverse outcomes for some groups. Patients with heart disease, lung disease, senility, obesity, and DM2 frequently evolve to severer forms of COVID-19, with respiratory failure and death[1]. Understanding such vulnerability can be an important step to improve the knowledge about the Covid pathophysiology. COVID-19 presents an initial infectious phase, which later evolves into a second phase inflammatory, with greater repercussion and severity. The risk groups present pathologies that bear a common link. They exhibit a previous significant increase in inflammatory activity, which combined with the inflammation generated by COVID-19, could result in a worsening evolution[2].

In diabetes mellitus, systemic inflammation is well known as it results in chronic complications of the disease. Part of this inflammation is due to hyperglycemia[3]. Another significant part of this inflammation is secondary to sleep disorders (sleep deprivation, insomnia, sleep-related breathing disorders, and circadian rhythm sleep-wake disorders) very prevalent in these patients[4]. In addition to a greater circulation of inflammatory agents, both DM2 and sleep disorders determine a lower amount of an important anti-inflammatory agent: melatonin[5-7]. The patient with DM2, therefore, has two reasons for presenting with higher inflammatory status: more inflammatory agents and less anti-inflammatory agents. This can justify the development more likely of severe acute inflammatory reactions in the second phase of COVID-19. In this context, melatonin with its anti-inflammatory properties can be a promising drug. In addition to its direct anti-inflammatory activity[7,8], melatonin can treat sleep disorders common in these patients[9-12] which would further contribute to reducing baseline inflammation. In this article, we will discuss the pathophysiological basis and perspectives for the prophylactic use of melatonin to prevent severe forms of COVID-19 in patients with DM2. We hypothesized that the use of melatonin even before infection can protect patients with diabetes from severe forms of the disease.

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COVID-19 AND INFLAMMATION: PATHOPHYSIOLOGY

The most severe manifestations of COVID-19, such as acute respiratory syndrome, appear to be associated with an exacerbated inflammatory response, which occurs after an initial phase of mild symptoms, such as cough and fever[13,14]. This response has been called a cytokine storm. In vitro, it was shown that initially there is a delay in the production of cytokines, such as interferons, and recruitment of CD8 T cells, responsible for immune response to infections. These mechanisms allow greater initial viral replication and could explain the paucity of symptoms at the initial phase, with low inflammatory activity. Subsequently, there is a rapid increase in cytokines and inflammatory cells in tissues, leading suddenly to acute and intense clinical manifestations. Interferon alpha/beta, interleukins 1, 6, 8, reactive oxygen species (ROS), oxidative enzymes, and tumor necrosis factors, produced by macrophages, take part in this immune response[15]. The acute inflammatory storm is responsible for the multiple organ failure seen in COVID-19. Inflammatory markers, such as ferritin and D-dimer, and a drop in the number of platelets appear as capable of predicting this intense inflammatory activity[16]. Currently, no medications were competent to prevent serious forms of COVID-19 infection. A recent study, for example, showed that hydroxychloroquine – one of the most discussed medications in scientific and political circles ¾ did not show benefits for the prevention of COVID-19[17]. Finding a drug that reduces the chance of severe infection seems particularly vital in groups at risk, such as those composed of patients with greater previous baseline inflammatory activity: DM2, sleep disorders, or both conditions.

DIABETES MELLITUS, SLEEP AND INFLAMMATION

DM2 is a disease characterized by chronic hyperglycemia. This hyperglycemia leads to an inflammatory and also an immune imbalance. The inflammation occurs by activation of the polyol pathway, increased formation of end products of advanced glycosylation and protein C kinase isoforms, and increased influx of ROS into cells. ROS induces epigenetic changes by altering pro-inflammatory genes, thus perpetuating the inflammatory process even after hyperglycemia is resolved. Immunological imbalance can be observed by helper T cells 1 and 2 which produce an excess of anti and pro-inflammatory factors[18]. Similar imbalances are present in severe forms of COVID-19, where there is excessive inflammatory activity and anomalous immunomodulation sometimes inhibits and other times over-activates inflammatory mechanisms[19].

In DM2, in addition to hyperglycemia, frequent sleep disorders contribute to a chronic elevation of the basal inflammatory status. Previous studies found that sleeping fewer hours per night can lead to activation of interleukins and tumor necrosis factors. Not only shorter sleep duration, but poor sleep quality can increase inflammatory status. Finally, sleep apnea, through intermittent nocturnal hypoxemia, can lead to the exacerbation of chronic systemic inflammation[5-7]. Therefore, as sleep disorders are frequent in DM2 is reasonable to think that this fact may contribute to severe forms of COVID-19 that are related to a higher inflammatory status.

MELATONIN AND COVID 19 PREVENTION: WHAT WOULD BE THE RATIONALE?

Some data suggest a possible protective and preventive role of melatonin in DM2 against COVID-19[19-22]. Microbats of the genus *Rhinolophus* are natural carriers of coronaviruses. These animals act as hosts and can transmit coronaviruses that are highly pathogenic to humans and livestock. Despite carrying coronavirus for long periods, these bats normally do not suffer from clinical symptoms and consequences of the infection[23]. Because they rest in ill-illuminated caves during the day and are active in the darkness of the night, they are constantly protected against sunlight. The available data indicate that their melatonin is kept at much higher levels in comparison to those in humans, throughout day and night[23]. The improved immunological ability against coronavirus pathology observed in these bats might bear relationships to this continuously higher level of melatonin in these nocturnal mammals.

The most serious forms of COVID-19 occurred in older people and melatonin levels tend to reduce importantly as age advances[21]. Previous studies have shown that low levels of melatonin are associated with an increased risk of DM2[24,25]. This data is reinforced by studies that showed a higher risk of DM2 related to the presence of melatonin receptor 2 (MTR2), a polymorphism present in the pancreatic beta cell[26]. Would be lower levels of melatonin associated with a higher prevalence of severe symptoms in DM2?

One of the consequences of COVID-19 infection is the inability of macrophage mitochondria to produce melatonin. These cells adopt aerobic glycolysis, becoming highly inflammatory and hindering the production of coenzyme A from pyruvate. Melatonin absence at mitochondrial level prevents neutralization of free radicals and inflammatory cytokines capable of tissue damage[19]. In addition, melatonin has vasodilator activity-dependent and independent of nitric oxide. This latter effect would be associated with activation of the prostaglandin

pathway. This mechanism would also be associated with the antioxidant and anti-inflammatory activities of melatonin and would prevent lesions in pulmonary vasculature at endothelial level, thus avoiding progression to pulmonary hypertension and cardiac injury[27]. Some authors suggest that melatonin could be used in sleep-deprived, inflamed patients to prevent lung injuries in the case of infection by COVID-19[15]. In advanced stages of infection by COVID-19, it is also postulated that melatonin has an effect to suppress the NOD-like receptor 3, a receptor capable of amplifying inflammation[20]. Thus, there would be suppression of cytokine storm in the second phase of the disease. In elderly DM2 sleep-deprived patients, melatonin levels are lower, NOD-like receptor 3 (NLRP3) is not inhibited, and greater COVID-19 severity is expected. Melatonin has a mild profile of side-effects and drug interactions and is not unrecommended in the 2019 edition of the American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults[28]. Future clinical trials could determine its therapeutic role here.

CONCLUSION

We conclude that melatonin modulates protective mechanisms against COVID-19. Melatonin can be safely administered to DM2 sleep-deprived elderly patients. It is not listed in the 2019 edition of the American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. It has good tolerability and the incidence of side effects is low. Melatonin can be part of preventive interventions to avoid the progression from mild to severe forms of COVID-19 in association with other health measures. Randomized clinical trials are needed to assess whether such actions of exogenous melatonin would be similar to the paracrine actions of these substances.

AUTHOR'S CONTRIBUTION

AT: Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing. WJM: Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing.

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POINT OF VIEW
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Reflections on passive smoking and COVID-19

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SUMMARY

Despite substantial evidence on the negative effect of active smoking to Covid-19, the impact of passive smoking in the course of disease remains largely unclear. Our aim was to reflect passive smoking as a risk factor in the current pandemic. Studies are needed to increase our knowledge on passive smoking and Covid-19 implications. The reflections current findings strongly support interventions and policies to curb the tobacco epidemic.

KEYWORDS: Tobacco Smoke Pollution. Coronavirus Infections. Smoking Prevention.

Active smoking has been a global concern and is considered an ancient pandemic with long and chronic progression[1,2]. Currently, the number of deaths due to smoking is estimated at 8 million, including 157,000 in Brazil[2].

Although underestimated, passive smoking, that is, the inhalation of second-hand smoke from tobacco derivatives, is also an important public health concern as it exposes non-smokers to the same carcinogens[3]. Thus, it is an important risk factor for chronic noncommunicable diseases, especially lung cancer[1,4].

According to the World Health Organization (WHO), 900,000 passive smokers die annaully[2]. In Brazil, a survey conducted in the 26 state capitals and the Federal District reported that 6.8% of household members were passive smokers, including 7.0% of women and 6.6% of men. The percentage of passive smokers in the workplace was 6.6% and was higher for men (10.0%) than for women (3.7%)[5].

The harmful effect of tobacco was first reported in 1928[6]. Since then, efforts have been made to establish coping strategies. However, the United States Department of Health demonstrated the causal relationship between passive smoking and lung cancer only in the year 1964. In 2005, the WHO Framework Convention on Tobacco Control (FCTC/WHO) provided tools and guidelines to be implemented by more than 192 member countries[7].

Even with most countries implementing anti-smoking policies, approximately 80% of people remain vulnerable to harmful effects resulting from passive smoking[8]. Cigarette burning produces smoke that contains more than 7,000 chemical compounds. Of which 250 are proved to be harmful, and nearly 70 of these compounds and substances cause cancer[9]. Oral and nasal inhalation of cigarette smoke is believed to profoundly decrease *in vivo* mucociliary transport, making the person susceptible to respiratory diseases[9].

At the beginning of the coronavirus disease (COVID-19) outbreak in late December 2019 in Wuhan, China, the tropism of lung epithelial cells was identified, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[10,11]. Smokers are considered among the vulnerable groups to health complications resulting from COVID-19[11].

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Smoking increases the expression of angiotensin-converting enzyme 2 (ACE2), a known SARS-CoV-2 receptor. While some studies have proposed the higher ACE2 expression in smokers as a possible link between smoking and COVID-19, these mechanisms have not yet been fully elucidated[12,13]. Although this relationship remains controversial, there are large investments in research on this topic. However, studies on passive smoking and COVID-19 remain scarce; thus, this condition may be an important risk factor that has not been considered in the recommendations for pandemic control.

A study by Vázquez and Redolar-Ripoll[11] conducted in Spain showed that, although the percentage of men (50.4%) and women (49.6%) infected by SARS-CoV-2 was similar, the mortality rate was significantly higher in men (4.7%) than in women (2.6%). These authors suggested that these discrepancies could be owing to differences in smoking patterns and prevalence between the sexes, as corroborated by statistical data on the prevalence of male smokers (25.6%) and female smokers (18.8%) in Spain.

A recent meta-analysis including data of 11,322 COVID-19 patients published in the International Prospective Register of Systematic Reviews (PROSPERO) has shown an association between smoking history and severe COVID-19 disease (OR 2.17, 95%CI 1.37–3.46, p<0.001) as well as current smoking and severe COVID-19 disease (OR 1.51, 95%CI 1.12–2.05, p<0.008)[14].

Additionally, some studies have shown that smoking cessation, over time, leads to normalization of a part of the respiratory epithelium architecture, with decreased hyperplasia and downregulation of ACE2 levels. It also significantly improves endothelial function[15]. However, this relationship has not been established in passive smokers.

Although there is no robust evidence of this association, the WHO strongly advises that smokers to quit smoking to minimize its direct risks[2]. In this context, it is necessary to consider the limited discussion of passive smoking, which is so common in society, as a risk factor for COVID-19. This discussion encourages the disclosure of warnings on tobacco product packaging and media campaigns that inform the dangers of passive smoking[2,16].

In the past, respiratory virus epidemics and pandemics demonstrated the significant role of multifaceted approaches to smoking cessation through behavioral, cultural, and pharmacological interventions[17]. These approaches may also be useful to decrease passive smoking in the current pandemic.

Considering the high viral transmissibility, severity in most vulnerable groups, and, above all, current lack of a proven vaccine and treatment, social isolation has always been the transversal axis of COVID-19 prevention and control measures. However, aspects related to prevention practices and attitudes toward risk factors, such as passive smoking, have not been adequately addressed.

A Chinese study showed a higher proportion of lung cancers attributable to passive smoking in the household (19.5%) than in the workplace (7.2%) among women. The main explanation was the greater number of women exposed to passive smoking in the household (66.0%) than at work (19.6%)[18].

According to a survey conducted on adults aged ≥40 years in China, 37.7% of people who never smoked and reported exposure to passive smoking were usually exposed at home and only 7.1% were exposed at work. Therefore, the household is the predominant place of exposure to passive smoking, mainly for women and children. This may cause a displacement effect owing to smoke-free legislation, with a net effect of people increasingly smoking at home to avoid restrictions in public places, and owing to the social isolation caused by the COVID-19 pandemic. The main recommendation is to establish public health policies to reduce passive smoking in the household in times of pandemic[18] and to invest in studies that analyze the impact of active smoking on SARS-CoV-2 infection.

The potential smoking-related COVID-19 disseminators require reviewing. Hookahs, popular among younger population owing to their reduced damage, produce much more smoke than commercial cigarettes[19], directly interfering with the air quality and the health of nearby people. Additionally, the mouthpieces are shared, facilitating SARS-CoV-2 transmission[2,20].

The transmission of diseases such as influenza, cold sores, and tuberculosis through hookah mouthpieces has also been reported[21]. Sharing electronic smoke devices also increase the risk of SARS-CoV-2 transmission[2,19].

Thus, people who are exposed daily to thousands of toxic substances from tobacco smoke are at risk of developing serious disorders[22]. such as cardiovascular diseases, chronic obstructive pulmonary disease, and cancer, and may additionally be more susceptible to SARS-CoV-2.

This review concludes with the idea that passive smoking may be an important risk factor for COVID-19 and provides reflections on the associated factors and processes that involve respiratory diseases, as well as their significance. It is important for the population to be aware of these risks of passive smoking, since the use of tobacco in certain forms discussed above may increase the risk of developing COVID-19, leading to more serious and potentially fatal conditions.

The possible relationship of government finance with the tobacco industry should also be considered, with these data informing potential tobacco control measures in Brazil. It is important to increase the awareness of the dangers of smoking

cigarettes, as well as the importance of reducing their use, regardless of their harm[1,23,24].

The current COVID-19 pandemic is the right time to pass on these recommendations, mainly to non-active smokers, as well as to the users of tobacco, who should be greatly concerned about their health. Increased smoking cessation rates could positively impact the community transmission of SARS-CoV-2 and decrease the risks and concerns of passive smokers.

Thus, campaign practices and concepts should be reviewed, with a focus on the results of populations who are currently experiencing social isolation in enclosed environments. An increased understanding of the impact of these factors on the daily lives of smokers, informed by established theoretical tools, will allow the modification of pedagogical strategies.

The current situation reinforces the need to increase awareness about the risks of passive smoking. There is a critical window of opportunity to help individuals quit smoking and increase surveillance in both the active and passive smoking population to prevent, detect, and quickly treat COVID-19.

Reflection on these findings indicates the need for greater instrumentalization from everyone involved in this process to guarantee the quality of the interventions. Reviews of these concepts, how they are presented to the public, and how they are related to the primary objective of health campaigns, namely, health promotion and the effects of the quality of life of population are needed.

This review may contribute to the proposed reflection process and expanded discussions on this topic to strengthen strategies and expand their scope not only quantitatively but also qualitatively. Studies and healthcare practices related to the current pandemic are needed to increase our knowledge on passive smoking and COVID-19 implications.

Finally, the SARS-CoV-2 epidemic should be an impetus for patients and people at risk to maintain good health practices and to quit smoking not only because of the current situation but also permanently.

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AUTHORS' CONTRIBUTION

LPRRG: Conceptualization, Supervision, Writing – Original Draft. **CCSA:** Conceptualization, Writing – Original Draft. **AHMA:** Conceptualization, Writing – Original Draft. **MAM:** Conceptualization, Supervision, Writing – Original Draft, Writing – Review & Editing.

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SHORT COMMUNICATION

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Bundle for pediatric COVID-19 sepsis

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SUMMARY

COVID-19 infection can progress to severe respiratory infection and have high mortality rates. Several pathophysiological factors are observed in fatal cases, with mortality related to multiple organ failure, in addition to the evolution with high levels of serum ferritin, D-dimer, and C-reactive protein. These severe cases often meet the criteria for macrophage activation syndrome with changes in the host's inflammatory response and an inadequate resolution phase. In the present study, the bundle for COVID-19 sepsis is proposed, including early recognition; protection, handwashing and isolation measures; oxygen therapy; early invasive mechanical ventilation; treatment aimed at modifying the clinical course. This strategy may be useful in the control of children with severe COVID-19 cases, as already demonstrated with the implementation of bundles in sepsis and other etiologies.

KEYWORDS: COVID-19. Sepsis. Infections. Respiratory Distress Syndrome. Respiratory tract infections.

INTRODUCTION

Several pathophysiological factors have been found in COVID-19 fatal cases, which may explain its severe behavior[1]. People with greater comorbidities[4,5], such as heart disease, diabetes, hypertension, or obesity have been noted to present a greater risk of death. Mortality has been related to multiple organ failure as the common final pathway of pneumonia, sepsis, and acute respiratory distress syndrome (ARDS) (Figure 1).

Patients with this outcome have been found to have higher serum ferritin, D-dimer, and C-reactive protein (CRP) levels than those who survive[5]. These findings have been seen in other severe viral infections, especially in children, due to the activation of some signaling pathways by increased interleukin 6 (IL-6), interleukin 1 (IL-1), and tumor necrosis factor alpha (TNF-α)[6]. These severe cases often meet the criteria for macrophage activation syndrome (MAS), which is characterized by a disorderly inflammatory response in the host with an inadequate resolution phase. One of the defining criteria for MAS has been ferritin >500 mg/dL, which has also been seen in patients with severe COVID-19 infection[5,7,8]. This virus, in a septic patient scenario, can release damage-associated molecular patterns (DAMP) and pathogen-associated molecular proteins (PAMPs), which lead to severe inflammation with microcirculation injury, thrombosis, and fibrinogen consumption, coinciding with the increased D-dimer seen in patients who die from COVID-19[5,9]. If this inflammation could be modulated, the microcirculation damage (especially endothelial cell damage) would stabilize, which would stop the apoptotic and pyroptotic cascade, allowing recovery of innate immunity and lung function (the lung being one of the most severely affected organs)[10].

Accordingly, the implementation of a rapid approach has been a determining factor in many of the outcomes seen in this pandemic[1], as proposed in the paper by Al-Hajjar and McIntosh[5], the disease manifestation is less serious than so in the pediatric population than in adults. Thus, a sepsis bundle is proposed for patients with COVID-19 infection, which we believe could be useful in modifying the clinical course of the disease, just as it has proven useful in sepsis from other etiologies[11] (Figure 2).

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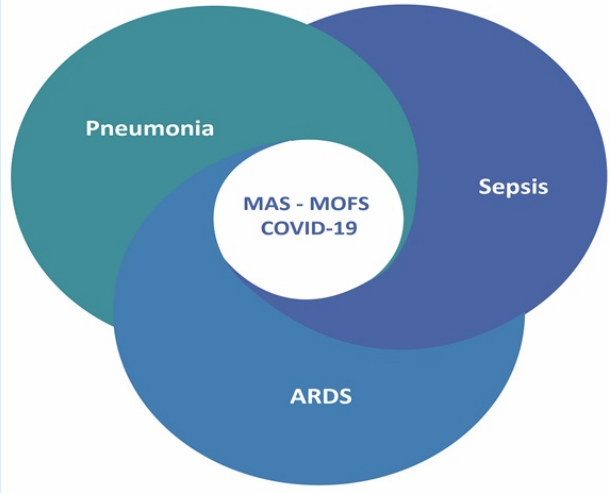
The bundle components for COVID-19 sepsis should include:

1. ***Early recognition:*** The recent sepsis guidelines for both adults and children, as well as the recommendations for management of COVID-19 sepsis, indicate that this measure is key in modifying the clinical course. It should be adhered to fulfill the case definition proposed by WHO, adapted to each center[1]. Keep in mind that fever associated with rapidly developing respiratory symptoms and deterioration have been the most important characteristic of this pandemic.
2. ***Protection, handwashing, and isolation measures:*** These measures are what have helped lower the pandemic's peak. Personal protection for health care personnel who care for these patients is essential. Countries like Spain have described up to 12% contagion of the health care team[1]. Universal isolation measures will avoid nosocomial contagion and dissemination of the virus (SARS-CoV-2).
3. ***Oxygen therapy:*** Given that the lung is the main organ affected, oxygen delivery systems should be offered quickly, according to the patient's needs. Consider using non-rebreather masks with high-efficiency face masks (N95 or FFP) over them[1]. This technique has also been described with the use of high-flow nasal cannulas (HFNCs) to avoid aerosol dissemination[2,10]. The non-invasive ventilation (NIV) should be limited and recommended only if adequate levels of staff protective equipment is available.
4. ***Early invasive mechanical ventilation:*** In the experience of the most severely affected countries (China, Italy, and Spain, given their greater number of cases), rapid initiation of mechanical ventilation has been essential for those who have survived[1,2]. Delaying intubation and ventilatory support has been associated with greater mortality[5]. Adequate preparation for intubation, pre-oxygenation without positive pressure ventilation, and rapid sequence of intubation using videolaryngoscope should be considered[1,2]. The presenting pathophysiological pattern will guide the ventilatory support which will cause the least alveolar damage. It may be useful to establish an "*optimal*" PEEP graphically, numerically or using an esophageal balloon with monitoring with volumetric capnography[12]. The hypoxic pulmonary vasoconstriction phenomenon may be leading to severe pulmonary hypertension, right heart failure, and death. Therefore, reports have indicated that the early use of nitric oxide could be useful. The prone position should be considered when Pa02/Fi02 is <150[12].
5. ***Treatment aimed at modifying the clinical course***: The studies published to date have not described a specific treatment which could be universally recommended. The use of hydroxychloroquine, azithromycin, and ritonavir, among others, has been reported with inconsistent results[13]. In this respect, the presenting immunophenotype in the disease's severe phase could help guide treatment. If we posit that the scenario meets the MAS criteria with immunoparalysis



MAS: macrophage activation syndrome; MOFS: multiple organ failure syndrome; ARDS: acute respiratory distress syndrome.

Figure 1. Various pathways leading to MAS and MOFS in COVID-19 infection.

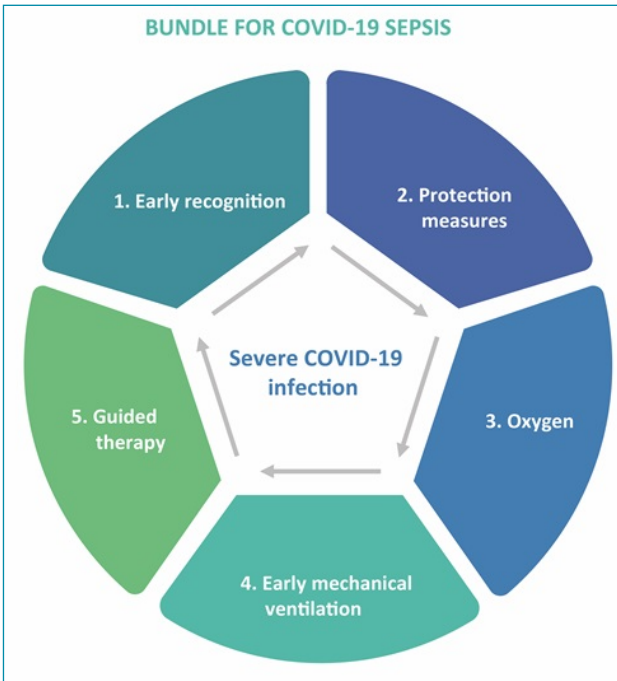


Figure 2. *Bundle* for COVID-19 sepsis

related to MOF (TNF-alpha <200pg / ml), immunoglobulins or colony stimulating factor could be useful[8,9]. Likewise, in patients with TAMOF (<57% ADAMTS-13 activity), plasmapheresis, or eculizumab could be considered[9].

CONCLUSION

The bundle for COVID-19 sepsis can be a useful strategy for the control of the disease, as it has been demonstrated in sepsis of another etiology. Studies are needed to confirm its utility and its potential to modify the clinical course in this disease.

TO EDITOR

In December 2019, for the first time in history, a new viral infection was reported, causing severe respiratory infection and extremely high mortality rates[1]. The virus, which based on its genetic sequence belongs to the *Betacoronavirus* genus, has been found to be highly related to the SARS virus and is known as SARS-CoV-2 (COVID 19)[2]. We have observed its epidemiological behavior with concern, noting that its main characteristic has been its high transmissibility, severity, and lethality, particularly in people over the age of 60[3,4]. We have read with great interest the article published in your magazine entitled: "*Pediatric COVID-19: An Update on the Expanding Pandemic*" by Al-Hajjar and McIntosh[5]. It is with great interest we see that this pandemic is progressing rapidly, and these papers updates are necessary in pathophysiological, diagnostic, and treatment aspects.

AUTHORS' CONTRIBUTION

JFS: Conceptualization, Writing – Original Draft, Writing – Review & Editing. **WBC:** Conceptualization, Writing – Original Draft, Writing – Review & Editing

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SHORT COMMUNICATION

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Obesity and the COVID-19: Analysis of the clinical and epidemiological profiles of 138 individuals

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SUMMARY

INTRODUCTION: Coronavirus disease 2019 (COVID-19) is the disease caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In the ongoing obesity pandemic, its coexistence with COVID-19 becomes worrying and has a less favorable outcome.

OBJECTIVE: This study aimed to describe the clinical and epidemiological profiles of confirmed cases of COVID-19 in individuals with obesity in the state of Alagoas.

METHODS: The observational cross-sectional study involving 138 confirmed cases of COVID-19 who had obesity as a comorbidity reported at the time of notification of the disease. The data were collected from the COVID-19 database in the state of Alagoas, and the variables analyzed were sex, age (and age group), race/color, outcome, clinical manifestations, and associated comorbidities. The Kolmogorov–Smirnov, Mann-Whitney *U*, χ^2, or Fisher's exact tests were performed as appropriate. The significance was set at 5 and 95% confidence intervals.

RESULTS: There was a predominance of females (55.1%; n=76), aged <60 years (70.3%; n=97) and brown race/color (n=76; 55.1%). The most prevalent symptoms were cough (n=84; 60.9%), fever (n=78; 56.5%), headache (n=36; 26.1%), and adynamia (n=28; 20.3%). The median age was 49 years, with no difference between genders (p=0.340). The lethality rate was 17.4% (n=24), being higher in the male population (22.6% in males and 13.2% in females). Of the 24 deaths, 13 (54.2%) were recorded in the elderly people. In addition to obesity, 54.3% (n=75) had systemic arterial hypertension and 30.4% (n=42) had diabetes mellitus. There was no difference in the prevalence of comorbidity between genders.

CONCLUSIONS: The profile studied demonstrates that obesity represents a challenge for coping with COVID-19.

KEYWORDS: Obesity. Epidemiology. Coronavirus Infections.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a disease caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first recorded in December 2019 in the city of Wuhan, China[1]. On March 11, 2020, the World Health Organization (WHO) declared pandemic status[2].

On August 17, 2020, the countries had already registered 21,809,170 cases and 772,479 deaths due to COVID-19 globally. Among the 188 countries analyzed, the United States,

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Brazil, and India are ranked top three countries with 5.4, 3.3, and 2.6 million confirmed cases, respectively[3].

Obesity has been associated with a worse prognosis of viral infections, as in Asian influenza in 1957–1960, H1N1 in 2009, and currently, COVID-19[4]. The unfavorable effects can be attributed to the metabolic and immunological breakdown, due to the chronic inflammation that accompanies obesity and the metabolic syndrome, with abnormal production of cytokines and increased acute phase reagents. Other factors, such as insulin resistance, dyslipidemia, atherosclerosis, type 2 diabetes, hypertension, and asthma, are comorbidities that adversely affect COVID-19 patients[5,6].

The coexistence of an ongoing obesity pandemic, which in some Western countries reached up to 40% of the adult population, e.g., the United States[7,6], COVID-19 can become even more dangerous. In Brazil, the number of obese people has increased to 72.03% between 2006 and 2019, according to Surveillance of Risk and Protection Factors for Chronic Diseases by Telephone Survey (Vigitel)[8]. About 55.4% of the population is overweight and 20.3% of them are obese adults, being similar between men and women[8]. Given the above and the need for knowledge production, this study aimed to describe the clinical and epidemiological profiles of confirmed cases of COVID-19 in individuals with obesity reported in Alagoas, Brazil.

METHODS

This is a cross-sectional observational study involving 138 confirmed cases of COVID-19 who had obesity as a comorbidity reported at the time of notification of the disease.

The data were collected from the COVID-19 database in the state of Alagoas available at http://www.dados.al.gov.br/dataset/painel-covid19-alagoas on August 1, 2020. The following variables were analyzed: gender, age (and age group), race/color, outcome, clinical manifestations, and associated comorbidities.

For statistical analysis, the normality of the data was assessed by the Kolmogorov–Smirnov test. Continuous variables were presented by means of measures of central tendency and dispersion, and categorical variables were presented by means of absolute and relative frequencies. The Mann-Whitney *U* test was used for continuous variables and the chi-square or Fisher's exact test was used for categorical variables, as appropriate. The significance was set at 5% and 95% confidence intervals. The analyses were performed using SPSS software (IBM SPSS Statistics for Windows, Version 22.0.IBM Corp., Armonk, NY).

Since these are secondary open access data, in which it is not possible to identify individuals, this study did not require the appreciation of the Research Ethics Committee.

RESULTS

Of the 138 records analyzed, 55.1% (n=76) were females, with a minimum age of 15 and a maximum age of 84 years. The median age was 49 years (interquartile range [IQR] 21), with no difference between genders (p=0.340). The lethality rate was 17.4% (n=24), being higher in the male population (22.6% in males and 13.2% in females). When comparing deaths and survivors, a significant difference in age was observed (p=0.004): the median age of death was 61.5 (IQR 25) and of survivors was 47 (IQR 21). Additionally, the number of deaths increased with aging (p=0.007). Of the 24 deaths, 13 (54.2%) were recorded in the elderly people (Figure 1 and Table 1).

In studying the epidemiological profile, there was a predominance of the population aged <60 years (70.3%; n=97) and brown race (n=76; 55.1%). The most prevalent symptoms were cough (n=84; 60.9%), fever (n=78; 56.5%), headache (n=36; 26.1%), and adynamia (n=28; 20.3%). Only the variables cough and fever showed differences between the sexes (p=0.047 and p=0.004). In addition to obesity, 54.3% (n=75) had systemic arterial hypertension and 30.4% (n=42) had diabetes mellitus. There was no difference in the prevalence of comorbidity between genders (Table 1).

DISCUSSION

The WHO classifies both COVID-19 and obesity as international public health emergencies. The association between the two conditions is not yet fully known, but obesity is known to promote a secretion of proinflammatory cytokines, and obese individuals have an impaired immune response. The angiotensin II-converting enzyme (ACE II) is expressed in quantity in adipose tissue and has a high affinity for SARS-CoV-2, which may explain the less favorable outcomes of COVID-19 in obese patients[9–11].

Global clinical observations indicate that the virus can cause more serious complications in obese individuals or those with related conditions. In a Chinese study with 30 infected patients, those with high body mass index (BMI) (>27), therefore were considered obese, had the disease with more severe symptoms compared with patients with a BMI of 22[12].

In a retrospective cohort of 124 patients from France, obesity (BMI >30 kg/m²) was present in 47.6% of the intensive care unit (ICU) patients, which is associated with the need for invasive mechanical ventilation (IMV)[13]. In a study with 3,615 patients from New York, it is demonstrated that patients with a BMI of 30–34.9 were 2.0 and 1.8 times more likely to be admitted to acute and critical care, respectively, than individuals with a BMI of <30[14]. Additionally, reviews carried out

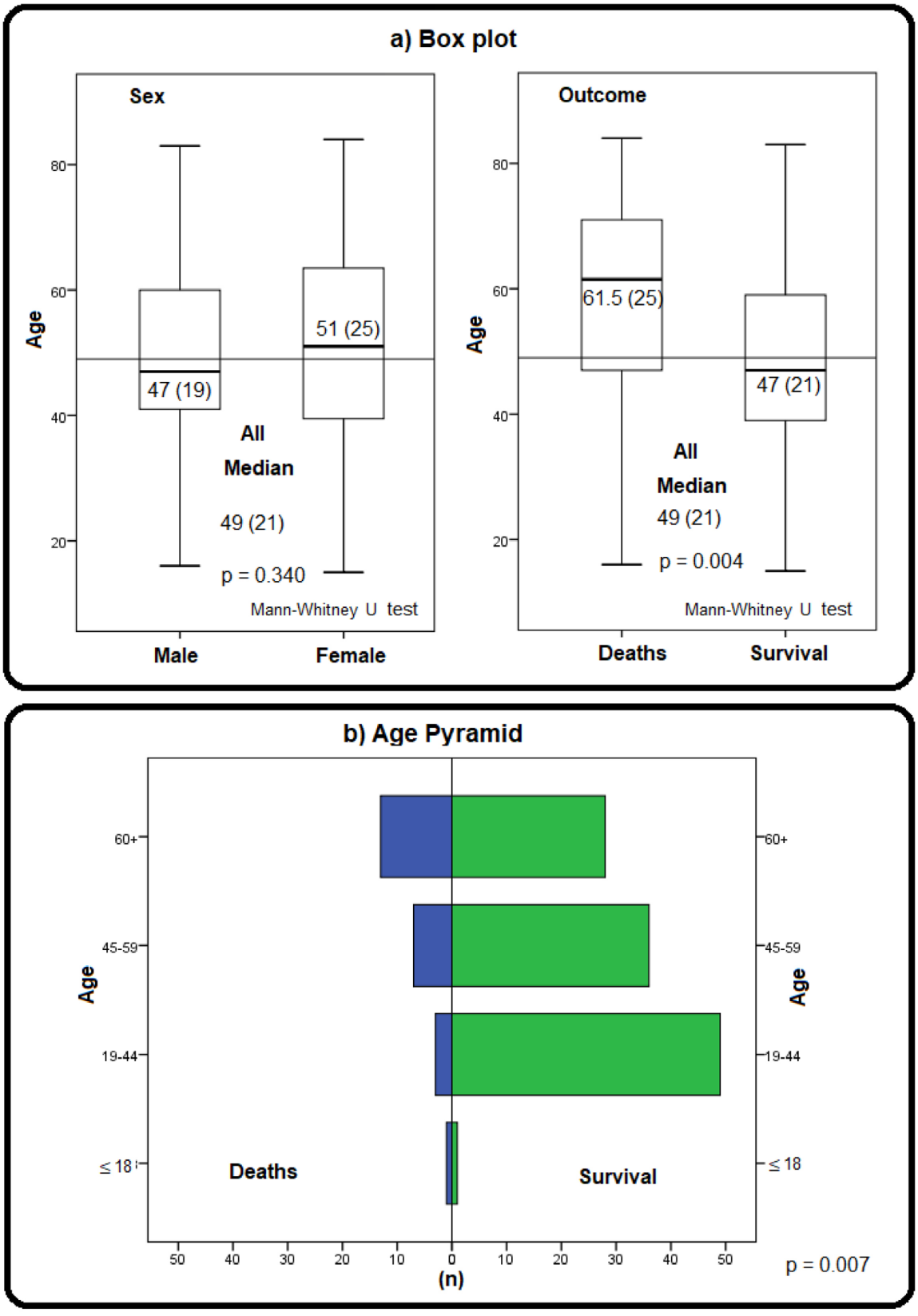

Figure 1. Age distribution of COVID-19 cases in individuals with reported obesity. Alagoas, Brazil (n=138).

Table 1. Clinical and epidemiological characterization of confirmed cases of COVID-19 in individuals with reported obesity. Alagoas, Brazil (n=138).

	Male (n=62; 44.9%)		Female (n=76; 55.1%)		Total (n=138; 100%)		p-value*
	n	%	n	%	n	%	
Age							
≥60	18	29.0	23	30.3	41	29.7	0.513
<60	44	71.0	53	69.7	97	70.3	
Race/color							
East Asian	1	1.6	1	1.3	2	1.4	0.141
White	11	17.7	11	14.5	22	15.9	
Unknown	21	33.9	13	17.1	34	24.6	
Pardo	27	43.5	49	64.5	76	55.1	
Black	2	3.2	2	2.6	4	2.9	
Outcome							
Death	14	22.6	10	13.2	24	17.4	0.110
Survival	48	77.4	66	86.8	114	82.6	
Clinical manifestations							
Fever	37	59.7	41	53.9	78	56.5	0.308
Cough	43	69.4	41	53.9	84	60.9	0.047
Headache	9	14.5	27	35.5	36	26.1	0.004
Loss of strength	9	14.5	19	25.0	28	20.3	0.094
Difficulty breathing	6	9.7	8	10.5	14	10.1	0.55
Dyspnea	11	17.7	6	7.9	17	12.3	0.068
Myalgia	4	6.5	12	15.8	16	11.6	0.073
Odynophagia	6	9.7	7	9.2	13	9.4	0.575
Comorbidities							
Cardiovascular disease	8	12.9	5	6.6	13	9.4	0.166
Diabetes mellitus	18	29.0	24	31.6	42	30.4	0.446
Chronic respiratory disease	3	4.8	2	2.6	5	3.6	0.404
Systemic arterial hypertension	31	50.0	44	57.9	75	54.3	0.225
Chronic renal disease	3	4.8	1	1.3	4	2.9	0.237

*Exact test Fisher.

also ratify the relationship between obesity and worse prognosis for COVID-19[5,15].

A retrospective study of 3,406 patients at a university hospital in the United States showed that morbid obesity is strongly associated with the mortality of individuals hospitalized over 50 years. Of the hospitalized individuals, the lethality in individuals above 50 years old reached 38%, while in the young population it was 10.5%[9]. In our investigation, the median age of individuals who died was substantially higher than the age observed in survivors (61.5 and 47, respectively). In addition, the age pyramid shows the concentration of deaths in the elderly population.

Several studies have already reported the advanced age as a risk factor for COVID-19 mortality, in addition to being associated with longer hospital stay and high viral load. The factors, such as immunosenescence (i.e., reduced efficiency of

natural immune cells in the elderly), chronic subclinical systemic inflammation of old age, and accumulation of comorbidities, are related to the worst prognosis of the disease in this group[16]. The retrospective cohort study with 200 patients in New York identified 46 obese (BMI ≥35 kg/m²), among which 20.4% were 65 years old or more[17]. The study also observed that, among the elderly, both malnutrition and obesity were linked to an unfavorable outcome for patients[17]. In Brazil, about 20.9% of the elderly population is obese (BMI ≥30 kg/m²)[8].

In addition to age and obesity, other comorbidities and underlying risk factors can act together, increasing the risk of complications and mortality due to COVID-19. Diabetes mellitus, arterial hypertension, cardiovascular disease, chronic kidney disease, chronic lung disease, cancer, immunosuppression, and smoking are among the most common risk factors[18]. In an investigation carried out in Pernambuco, the presence of cardiovascular diseases accelerated mortality from COVID-19 in 4 days[19]. In our study, 54.3% of individuals with obesity had systemic arterial hypertension and 30.4% had diabetes mellitus.

The prevalence of multiple comorbidities in individuals hospitalized with COVID-19 has been widely reported. In a study with 103 patients hospitalized with COVID-19 in the state of Rhode Island (the United States), the most common comorbidity was arterial hypertension, followed by diabetes mellitus and heart disease (64.0, 36.8, and 24.2%, respectively)[2]. A study carried out in Pernambuco, involving 197 deaths due to COVID-19 who had underlying cardiovascular diseases, 78.7% of them had two or more comorbidities, the most common being diabetes mellitus and obesity[20]. The overlap of multiple risk factors should be the subject of scientific investigations to estimate the importance of each one in COVID-19 severity and mortality.

Even considering the methodological care adopted, this study has following limitations. Secondary data are subject to the influence of collection procedures, such as filling in the notification form and typing, which may result in inconsistent records. Obesity reported in this study had no precise specification of the classification method, such as BMI or weight and height. The inclusion of weight and height variables in the notification forms could have reduced this bias and allowed a more accurate analysis of the relationship between obesity and COVID-19 in Brazil.

CONCLUSION

Based on the observed profile, this study showed that obesity represents an additional challenge in coping with the COVID-19 pandemic, mainly due to the high lethality and the overlapping of comorbidities in the same individual. We emphasize the importance of protecting the obese population from contamination by SARS-CoV-2 and of establishing measures that make the diagnosis possible and ensure adequate clinical monitoring for those who are infected by the virus. In addition, the need to strengthen public policies that have an effect on risk factors becomes an urgency.

AUTHORS' CONTRIBUTIONS

KCM: Conceptualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft, Writing – Review & Editing. JLSL: Conceptualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft, Writing – Review & Editing. AGSJ: Conceptualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft, Writing – Review & Editing. RFC: Conceptualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft, Writing – Review & Editing. CDFS: Conceptualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft, Writing – Review & Editing.

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SHORT COMMUNICATION
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Physical activity practice during COVID-19 pandemic in patients with intermittent claudication

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SUMMARY

OBJECTIVE: To describe physical activity habits and barriers for physical activity practice in patients with peripheral artery disease and claudication symptoms during Coronavirus 2019 (COVID-19) pandemic.

METHODS: In this cross-sectional survey study, 127 patients with peripheral artery disease (59.8% men; 68±9 years old; and 81.9% had the peripheral artery disease diagnosis ≥5 years old) were included. The physical activity habits and barriers for physical activity practice were assessed through telephone interview using a questionnaire with questions related to: (a) COVID-19 personal care; (b) overall health; (c) physical activity habits; (d) for those who were inactive, the barriers for physical activity practice.

RESULTS: Only 26.8% of patients reported practicing physical activity during the COVID-19 pandemic. Exercise characteristics more common among these patients include walking, performed at least 5 days a week, during 31–60 min at light intensity. In contrast, among physically inactive patients, pain, injury or disability (55%), the COVID-19 pandemic (50%), the need to rest due to leg pain (29%), and lack of energy (27%) were the most frequent barriers to physical activity practice.

CONCLUSION: The physical activity level of patients with peripheral artery disease is impacted by the COVID-19 pandemic.

KEYWORDS: Coronavirus infections. Social isolation. Intermittent claudication. Exercise.

INTRODUCTION

Peripheral artery disease (PAD) is a prevalent condition in the elderly population[1] and that frequently is associated with several comorbid conditions, including hypertension, diabetes, coronary artery disease, and obesity[2]. In patients with PAD and claudication symptoms, function capacity is reduced, bringing aggravating the symptomatology and other comorbid conditons[3,4].

Physical activity practice is considered a cornerstone of clinical treatment in patients with PAD and claudication symptoms. However, most of the patients do not achieve the minimum of physical activity levels recommended by general and specific guidelines (i.e. 150 min/wk of moderate-vigorous physical activities)[5]. Most of the reasons for physical inactivity in these patients include claudication symptoms, difficulty in having

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places to physical activity practice, fatigue, and the presence of other diseases[6-8]. In the early of 2020, the world faced an outbreak of the novel coronavirus disease, later called COVID-19, and on the 11th of March 2020, COVID-19 was characterized by World Health Organization as a pandemic[9,10]. The social isolation and mobility restrictions adopted to reduce the virus spread have reduced physical activity levels in all age groups. This is even worse in high-risk groups for COVID-19, which includes elderly patients and people with chronic diseases[11,12].

In patients with PAD, the impact of COVID-19 on the practice of physical activity was not described, which limits the understanding of the magnitude of the problem and proposes strategies to cope with physical inactivity in these patients. This study aimed to describe physical activity habits and barriers to physical activity in patients with PAD and claudication symptoms during the COVID-19 pandemic.

METHODS

Study design and patients

This observational, descriptive cross-sectional survey study involved patients with PAD and claudication symptoms recruited from the database of researches previously developed by our group. This current study was approved by the local ethical committee before data collection (CAAE #31529220.8.0000.5511). Participants did not identify themselves and their answers were only included in the sample if they authorized it before the protocol started. All procedures follow the national legislation and the Declaration of Helsinki.

Patients were included if they met the following criteria:

a) agreed to participate and respond to all questions of the survey;
b) the previous diagnosis of PAD;
c) age ≥45 years old;
d) had ankle-brachial index (ABI) ≤0.90 in one or both legs, and;
e) absence of non-compressible vessels, amputated limbs and/or ulcers.

Patients were only excluded if they presented some disability during the phone call that compromises the answer to the questionnaire (i.e. cognitive, hearing, and speech).

Data collection

Data collection was performed through a phone interview, between May 15 and August 10, 2020, conducted by health professionals with experience in studies with patients with PAD.

The evaluation of the impact of COVID-19 on the practice of physical activity of patients with PAD was assessed through a questionnaire developed by researchers of the study. The questionnaire was composed of the following questions:

Personal information: was accessed by our database including info about sex ("woman" or "man"), date of birth (DD/MM/YYYY), time of PAD diagnosis (in years), body mass index (kg/m^2) and PAD severity (ankle-brachial index).

COVID-19 personal care: involved questions about the recommendations of personal care during the Covid-19 pandemic and about COVID-19 diagnosis. 1. "Are you in social isolation?", 2 – "Were you diagnosed with COVID-19?" If yes, 3 – "Have you recovered?" Possible answers: "Yes" or "No".

Overall health: This domain assesses the presence of diagnosed diseases and health behavior. From the list of diseases, the participant should report all that applied. (possible answers: Hypertension, diabetes, high cholesterol, high triglycerides, cardiopathy, respiratory disease, or other). It was also questioned "Do you smoke" Possible answers: "yes" and "no".

Physical activity: To assess physical activity habits, participants were asked about: 1- "Did you practice physical activity before the pandemic?", 2- "Are you performing some physical activity?" Answers for both questions were "Yes" or "No". If yes, 3 – "How many times are you exercising a week? (possible answers: one to seven days a week), 4 – "For how long are you exercising?" (possible answers: "less than 30 min", "between 30 and 60 minutes", and, "more than 60 minutes"), 5 – "What is the intensity of the physical activity?" (possible answers: low, medium/moderate or high), 6 – "What type of exercise are you doing?" (possible answers: "walking/jogging", "functional exercise", "resistance exercise", "I am not exercising", "others – open question".

Barriers to physical activity: For patients who were not exercising, it was questioned "Which of the following are the main reasons for you NOT to practice physical activity?" From the list of barriers, the participant should report all that applied. (possible answers: "COVID-19 pandemic", "some difficulty in getting to place", "weather unfavorable", "lack of company", "pain", "injury or disability", "needing to rest because of leg pain", "lack of physical energy", "being afraid of hurting", "lack of time", "lack of knowledge", or "other").

Statistical analysis

Data were stored and analyzed using the Statistical Package for the Social Sciences (SPSS Version 20.0). Normality and homogeneity were analyzed, and parametric statistical procedures were employed. Continuous variables were summarized as mean and standard deviation, whereas categorical variables were summarized as relative frequencies.

RESULTS

The sample included 127 patients with PAD (Table 1). Patients were mostly elderly, with comorbid conditions, including hypertension (84%), dyslipidemia (80%), cardiac disease (52.8), and diabetes (46%) The majority of patients were in social isolation (89%) and three of them were infected with full recovery of COVID-19.

Table 2 shown the physical activity habits in patients with PAD. Fifth-four percent of patients reported physical activity practice before the COVID-19 pandemic and during the pandemic the number of patients reporting some physical activity practice reduced to 26.8%. Among patients that remained physically active, the more common modality was walking exercise (58.8%), performed at least 5 days a week, during 31–60 min at light intensity.

Table 3 shown the barriers to physical activity in inactive patients with PAD (n=93; 73%) during the COVID-19 pandemic. The most frequent barrier to physical activity practice was pain, injury or disability (55%), the COVID-19 pandemic (50%), the need to rest due to leg pain (29%), and lack of energy (27%).

Table 1. Clinical characteristics, co-morbidities and COVID-19 conditions of the patients with peripheral artery disease (n=127).

	Values
Gender (male), n (%)	76 (59.8)
Age, years	68±9
Body mass index, kg/m²	27.4±4.2
Ankle-brachial index	0.54±0.17
Time of disease since diagnosis, n (%)	
<5 years	23 (18.1)
5–10 years	55 (43.3)
>10 years	49 (38.6)
Comorbidities and risk factors, n (%)	
Smoker	19 (15.0)
Former smoker	80 (63.0)
Diabetes mellitus	58 (45.7)
Hypertension	106 (83.5)
Dyslipidemia	102 (80.3)
Obesity	29 (22.8)
Cardiac disease	67 (52.8)
Respiratory disease	20 (14.6)
Regarding COVID-19, n (%)	
Social isolation	113 (89.0)
COVID-19 diagnosis	3 (2.4)
Recovered from COVID-19*	3 (100)

Data presented as mean±standard deviation, and as absolute and relative frequency. *n=3

Table 2. Physical activity habits in patients with peripheral artery disease (n=127).

	Values
Physical activity habits (n=127)	
Physical exercise before COVID-19	69 (54.3)
Physical exercise during COVID-19	34 (26.8)
Characteristics of Physical exercise currently (n=34)	
Modalities	
Walking exercise	20 (58.8)
Functional exercise	13 (38.2)
Resistance exercise	3 (8.8)
Frequency (x/week)	
1–2	6 (17.6)
3–4	9 (26.5)
5–7	19 (55.9)
Duration (min)	
≤30	9 (26.5)
31–60	19 (55.9)
≥61	6 (17.6)
Intensity	
Light	17 (50.0)
Moderate	14 (41.2)
Vigorous	3 (8.8)

Table 3. Barriers to physical activity in sedentary patients with peripheral artery disease (n=93). Data presented as absolute and relative frequency.

	Values
COVID-19 pandemic	46 (49.5)
Some difficulty in getting to place	8 (8.6)
Weather unfavorable	3 (3.2)
Lack of company	2 (2.2)
Pain, injury or disability	51 (54.8)
Needing to rest because of leg pain	27 (29.0)
Lack of physical energy	25 (26.9)
Being afraid of hurting	15 (16.1)
Lack of time	6 (6.5)
Lack of knowledge	2 (2.2)
Others	12 (12.9)

DISCUSSION

The main results of this study were:

(i) the number of PAD patients who reported physical activity practice reduced more than half during the COVID-19 pandemic;

(ii) among physically inactive patients, the most reported barrier to physical activity practice were pain, injury or disability, the COVID-19 pandemic, lack of energy and the need to rest because of leg pain;

(iii) among patients that remained active, walking exercise, 5 days a week, during 31–60 min at light intensity were the most frequently reported.

Patients with PAD and symptoms of claudication are less physically active than age-matched controls[5], with few of them achieving the general recommendation to physical activity for the elderly (150 min/wk of moderate-vigorous physical activities). In the current study, 56% of patients reported performing some physical activities before the COVID-19 pandemic, which was reduced to only 27% during the COVID-19 outbreak. Given that physical activity can promote overall health benefits in patients with PAD[13-15], our results raising the attention to highlight the urgent need to stimulate physical activity during periods of mobility restrictions. Among patients who were not practicing physical activity during the COVID-19 outbreak (73%), the main barriers during COVID-19 to physical practice include pain, injury or disability, the COVID-19 pandemic, lack of energy, and the need to rest because of leg pain. Most of these barriers have been frequently reported in patients with PAD claudication[6-8] and are related to the symptoms of the disease, the presence of the comorbid conditions, and lack of motivation and energy. Moreover, the COVID-19 pandemic is now included in this hall, adding a new difficulty to patients become physically active, which was probably caused by the social isolation and mobility restrictions. Adherence to these recommendations is important in patients with PAD since they are considered a high-risk group. In this context, strategies to minimize claudication symptoms and avoid social contact could be useful to overcome the reported barriers.

Among patients who remained physically active during the COVID-19 pandemic, walking was the most frequent mode of exercise, performed at least 5 days a week, during 31-60 min at light intensity. This physical activity pattern of the patients follows the current general and specific recommendations, except for intensity that ha been recommended in moderate to vigorous activity[16]. The preference to not perform moderate and vigorous physical activities have been widely reported in patients with PAD and has been attributed to the anticipation of claudication pain. Interestingly, in the elderly population, light-intensity physical activities have been associated with improvements in several health outcomes[17,18], and the potential health benefits in PAD patients must be investigated in the future.

Previous studies[19,20] have shown the potential of home-based walking programs to improve walking capacity and quality of life in patients with PAD. However, walking in the neighborhood during the COVID-19 pandemic can be problematic for patients, and other alternatives could be necessary. Homebased functional exercises have shown important results in the elderly and can be useful for patients with PAD, especially for promoting less pain during the exercise, which can increase adherence to the practice. The use of mobile apps, videoconferences, and other technologies could also be useful to improve physical activity levels in patients with PAD. However, their feasibility and effectiveness should be tested.

This study presents limitations that should be emphasized, the main one is the use of self-reported assessments that are susceptible to information bias. To avoid direct contact with patients, the assessments were performed using phone calls, which impose additional difficulties in obtaining information. The recruited sample is part of previous studies of our group, and whether the results can be expanded to the general population is unclear.

CONCLUSION

The physical activity level of patients with PAD is impacted by the COVID-19 pandemic. Remote strategies to perform physical activity avoiding claudication symptoms could be useful to increase their physical activity levels during this period.

AUTHORS' CONTRIBUTIONS

RMR: Conceptualization, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **MAC:** Conceptualization, Formal Analysis, Writing – original draft, Writing – Review & Editing. **NW:** Conceptualization, Writing – Original Draft, Writing – Review & Editing. **GGC:** Conceptualization, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **HK:** Conceptualization, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **MDO:** Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **JFC:** Data Curation, Writing – Original Draft, Writing – Review & Editing. **HAB:** Data Curation, Writing – Original Draft, Writing – Review & Editing.

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ORIGINAL ARTICLE

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Comparison of neutrophil lymphocyte ratio, platelet lymphocyte ratio, and mean platelet volume and PCR test in COVID-19 patients

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SUMMARY

OBJECTIVE: The polymerase chain reaction test, used in the diagnosis of COVID-19, can be positive with delay, and thorax tomography is used for the diagnosis of the disease. We aimed to compare the relation between thorax tomography findings, PCR test results, and neutrophil lymphocyte ratio; platelet lymphocyte ratio and mean platelet volume neutrophil lymphocyte ratio; platelet lymphocyte ratio and mean platelet volume in COVID-19 patients.

METHODS: COVID-19 patients were divided into three groups, according to baseline laboratory and thorax tomography findings: Group A: thorax tomography finding positive – polymerase chain reaction test positive; Group B: thorax tomography finding negative – polymerase chain reaction test positive; and Group C: thorax tomography finding positive – polymerase chain reaction test negative. Neutrophil lymphocyte ratio, platelet lymphocyte ratio, and mean platelet volume values were compared between these three groups.

RESULTS: Group C neutrophil lymphocyte ratio level and polymerase chain reaction level were statistically higher than that of group B ($p<0.001$ in both). Mean platelet volume was not statistically significant between groups ($p>0.005$ for all). A positive correlation was detected between neutrophil lymphocyte ratio and C-reactive protein ($r=0.421$, $p<0.001$). Similarly, positive correlation was found with polymerase chain reaction and C-reactive protein ($r=0.243$, $p=0.001$).

CONCLUSION: The thorax tomography finding can be detected earlier in the disease before the polymerase chain reaction test. The sensitivity of the polymerase chain reaction test varies according to the tester, the way of performing it, and the quality of the test. Therefore, especially in patients with polymerase chain reaction negative and thorax tomography findings, neutrophil lymphocyte ratio and platelet lymphocyte ratio levels should be evaluated, and patients should be followed up upon suspicion of COVID-19 diagnosis.

KEYWORDS: Neutrophils. Lymphocytes. Blood platelets. Mean platelet volume. Polymerase chain reaction. Coronavirus infections.

INTRODUCTION

Coronavirus-19 Disease (COVID-19) first appeared in Wuhan, China. The disease spread rapidly from Wuhan to other regions. The World Health Organization (WHO) declared COVID-19 disease as a pandemic on March 11, 2020. COVID-19 cases were also reported in Turkey on the same dates. Typical symptoms of COVID-19 are fever, sore throat, fatigue, cough, and shortness of breath. The incubation period of the virus was from five to 19 days. Based on this, the isolation period was determined as 14 days[1].

Rapid and accurate detection of COVID-19 is essential to control outbreaks in the community and hospitals. Each country has developed unique algorithms for the diagnosis of this epidemic. Based on current diagnostic criteria, laboratory

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examinations, including nasopharyngeal and oropharyngeal swab tests, have become a standard assessment in the diagnosis of COVID-19 infection. Among the current diagnostic tests for coronavirus, reverse transcription polymerase chain reaction (RT-PCR) is performed. In a series of 51 patients with confirmed COVID-19 infection, RT-PCR positivity was demonstrated in the first test of 71% throat swabs or sputum samples[2]. RT-PCR results usually become positive after a few days (2–8 days)[3]. In patients with contact history and fever, sore throat, fatigue, cough, or shortness of breath, COVID-19 infection is diagnosed with typical thorax computed tomography (CT) features despite negative RT-PCR results[4].

OBJECTIVE

Due to inflammation, number of lymphocytes decrease and the number of neutrophils increase in patients with COVID-19. Studies have reported that NLR is a predictive factor for disease progression, poor prognosis, and severe cases of COVID-19[5-8]. Depending on the severity of inflammation, lymphocyte, neutrophil, and platelet counts, besides mean platelet volume (MPV) is varied. Studies have suggested that neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) reflect inflammation more effectively and strongly than the number of lymphocytes, platelets, and neutrophils separately in inflammatory disease[9,10]. Similarly, MPV has been used as an indicator of inflammation in inflammatory diseases[11,12]. Based on this hypothesis, we aimed to compare the relation between CT findings, PCR test results and NLR, PLR, and MPV in COVID-19 patients.

METHODS

The study was performed retrospectively using data from the Public Health Management System, which is the pandemic registration system of the Provincial Health Directorate, Bolu, Turkey. AbantIzzetBaysal University Faculty of Medicine Ethics Committee approval was obtained (Ethics approval number: 2020/140). Patients diagnosed with COVID-19 older than 18 were included in the study. Patients' symptoms, CT findings, PCR test, and white blood cell count (WBC), lymphocyte (LYM), neutrophil (NEU), platelet, MPV, albumin, AST, ALT, ALP, GGT, and urea levels were recorded from the pandemic recording system at the time of diagnosis of COVID-19. NLR was obtained by dividing the neutrophil count by the lymphocyte count. PLR was obtained by dividing platelet count by lymphocyte count. COVID-19 patients were divided into three groups according to baseline laboratory and CT findings: Group A: CT finding positive – PCR test positive; group B: CT finding negative – PCR test positive and group C: CT finding positive – PCR test negative. NLR, PLR, and MPV values were compared between these three groups.

Statistical analysis

IBM Statistics15.0 (SPSS) statistical software was used to evaluate the data. Descriptive statistics are presented as Mean ± SD and Median (min–max). The consistency of continuous variables to normal distribution was examined with Kolmogorov-Smirnov tests. The data were evaluated statistically with one-way ANOVA. *Post hoc* analyzes were evaluated using TUKEY HSD and Tamhane tests. Categorical variables were evaluated with χ^2 analysis. Receiver-operating characteristic (ROC) curve analyzes were performed to determine the cut-off values of NLR, PLR, and MPV (CRP for comparison), area under the curve (AUC), sensitivity and specificity to predict COVID-19 disease. Pearson's correlation test was used for the relation between the continuous variable. Statistical significance value accepted was $p < 0.05$.

RESULTS

A total of 153 patients with COVID-19 were included in the study. There were 38 patients (19%) in group A, 85 patients (41%) in group B, and 80 patients (40%) in group C. The median age of group A was 55.4±15, of group B was 53.1±16.6, and of group C was 54.8±16.6 (p=0.7). WBC levels are as follows: group A., 5.05 (2.5–10.6) uL; group B, 6.3 (2.1–19.8) uL; group C, 7.5 (2.6–28) uL (p<0.001) (Figure 1). In subgroup analysis, WBC level of Group C was statistically higher than that of groups A and B (p<0.001 and p=0.001, respectively). The NEU level was similarly significant among groups, and the NEU level of group C was statistically higher than in groups A and B (p=0.001 and p<0.001, respectively, Table 1). Among hemogram parameters, MPV, lymphocyte, and RDW levels were not statistically significant (p>0.05 for all). CRP level was 21 (0.1–135) mg/L in group A, 4.45 (0.1–292) mg/L in group B, and 43.4 (0.1–450) mg/L in group C (p<0.001, Figure 1). In subgroup analysis, the CRP level of group C was significantly higher than in both groups A and group B (p=0.003 and p<0.001, respectively). AST levels were 28 (11–90) U/L in group A, 29 (14–90) U/L in group B, and 26 (9–130) U/L in group C (p=0.02). When subgroups were compared, the AST level of group B was statistically significantly higher than group C (p=0.02). There was no difference between ALT, GGT, ALP, and total bilirubin levels (p>0.05 for all) (Table 1).

The NLR value was 2.1 (0.45–60) in group A, 1.92 (0.51–17.4) in group B, and 3.5 (0.63–44.8) in group C (p=0.004)

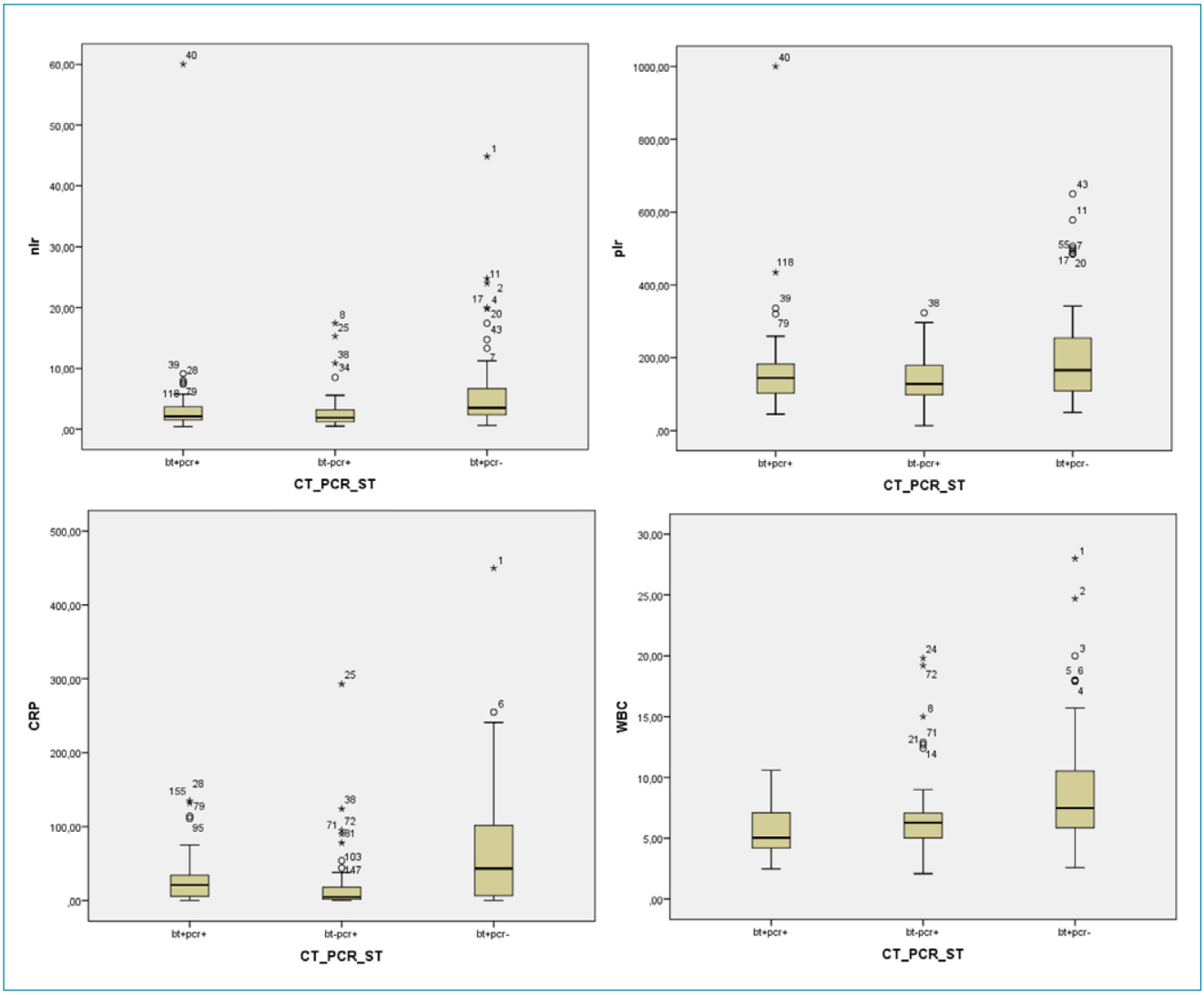

Figure 1. Neutrophil lymphocyte ratio (NLR); Platelet lymphocyte ratio (PLR); C reactive protein (CRP) and white blood cell (WBC) levels in group A (CT +, PCR +), group B (CT-, PCR +), and group C (CT +, PCR-).

(Figure 1). Group C NLR level was statistically higher than that of group B (p<0.001). The PLR level was similarly statistically significant between the groups (p=0.009), and the PLR level of group C was significantly higher than that of group B (p<0.001). In subgroup analysis, NLR and PLR levels were not statistically significantly in Group C than in Group A (p>0.05) (Table 1). Correlation analysis was performed between WBC, NLR, PLR, MPV, AST, and CRP. A positive correlation was detected between NLR and CRP (r=0.421, p<0.001). Similarly, positive correlation was found for PLR and CRP (r=0.243, p=0.001).

A ROC analyze performed to determine sensitivity and specifity of hemogram parameters (WBC, NEU, NLR, PLR) and CRP in detecting early COVİD-19 patients (Figure 2). The best cut-off values in predicting group C were WBC >6.4uL (68% sensitivity, 60% specificity, AUC=0.699, p<0.001), NEU >3.77 (72% sensitivity, 60% specificity, AUC=0.695, p<0.001), NLR >2.33 (75% sensitivity, 60% specificity, AUC=0.723, p=0.037), PLR >140 (60% sensitivity, 55% specificity, AUC=0.599, p<0.017), and CRP >11.8 mg/L (68% sensitivity, 60% specificity, AUC=0.708, p<0.001). With ROC analysis, NLR revealed a more sensitive diagnostic value than CRP, WBC, NEU, and PLR in predicting Group C patients with 75% sensitivity and 60% specificity (Figure 2).

DISCUSSION

In our study, NLR and PLR were significantly higher in the patient's group with CT (+) – PCR (-) (group C) than

Table 1. Laboratory data and demographic characteristics of group A (CT +, PCR +), group B (CT -, PCR +), and group C (CT +, PCR -).

	Group A	Group B	Group C	p
Mean±SD				
Age (years old)	55.4±15	53.1±16.6	54.8±16.6	0.07
Urea (mg/dL)	33.9±1.1	32.2±1.4	44±2.2	<0.001
ALT (U/L)	37.1±3.7	23.8±1.5	38.8±3.7	0.1
GGT (U/L)	42.2±5.6	50±3.2	45±7.3	0.9
Total bilirubin (mg/dL)	0.91±0.25	0.90±0.33	0.97±0.34	0.4
Median (min–max)				
NLR	2.1 (0.45–60)	1.92 (0.51–17.4)	3.5 (0.633–44.8)	0.004
PLR	144 (44–1000)	128 (12.8–323)	165 (49–650)	0.009
WBC (uL)	5.05 (2.5–10.6)	6.3 (2.1–19.8)	7.5 (2.6–28)	<0.001
NEU (uL)	3.25 (1.2–7.6)	3.3 (1.2–8.3)	4.6 (1.1–15.3)	<0.001
Lymp (uL)	1.4 (0.1–4.7)	1.7 (0.5–16)	1.35 (0.4–4.4)	0.06
MPV (fL)	8 (6.7–10)	8.32 (5.4–11)	8.05 (5.9–10)	0.89
RDW (%)	15.3 (12.5–27)	15.05 (11.9–24.5)	15.02 (12–20.1)	0.76
AST (U/L)	28 (11–90)	29 (14–90)	26 (9–130)	0.02
ALP (U/L)	86 (50–140)	76 (23–181)	77 (39–137)	0.76
CRP (mg/L)	21 (0.1–135)	4.45 (0.1–292)	43.4 (0.1–450)	0.001

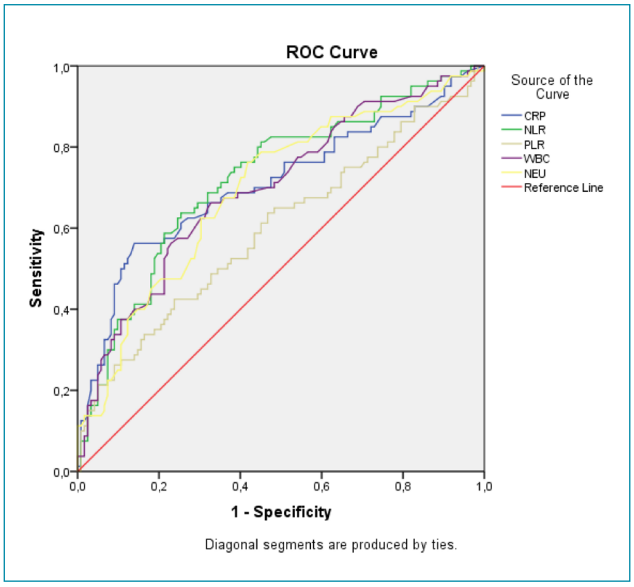

Figure 2. Roc curve of Neutrophil lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR), C reactive protein (CRP), neutrophil (NEU), and white blood cell (WBC) count for the detection of early COVID-19 patients.

those with CT (+) – PCR (+) (group A) and CT (-) – PCR (+) (group B) at the time of initial diagnosis. Significant positive correlation was found with the CRP used as an inflammatory marker and NLR-PLR. Similarly, WBC and NEU were significantly higher in group C. With these results, patients in group C were considered those with the highest inflammation in the early period, thus confirming the hypothesis that inflammation parameters, NLR, and PLR may be high in these patients. It has been reported that the PCR test may take 19 days to become positive[13]. Before PCR became positive, we showed that CT finding and hemogram parameters (WBC, NEU, NLR, PLR, CRP) can be used in the diagnosis of COVID-19. The most important of these parameters was NLR (75% specificity).

Although the COVID-19 median incubation time has been reported as three days[14]. Coronavirus (SARS-CoV-2) is transmitted from person to person with a relatively low mortality rate, causing a rapid epidemic[14]. Fever, cough, and shortness of breath are the dominant symptoms; and gastrointestinal symptoms have been reported to be rare[14-16]. In the first admission, fever developed only in 43.8% of patients, and in 83.4% after

hospitalization[17]. COVID-19 cases can be missed due to the absence of fever. In our study, fever was observed in 88 out of 203 patients (43%), cough in 62 (30%), dyspnea in 34 (17%), and non-respiratory symptoms in 41 patients (20%). Other symptoms in our study were joint pain (1%), sore throat (1%), headache (1%), anosmia (2%), diarrhea (1%), and weakness (4%). Studies have found that lymphopenia is common and severe[15,18]. NLR has been shown to be an independent prognostic biomarker in progressing to pneumonia in COVID-19 patients[19]. NEU releases a large amount of reactive oxygen species that can induce cell DNA damage and expose the virus from the cells. Thus, antibody-induced cell-mediated cytotoxicity (ADCC) can directly kill the virus, expose the virus antigen, and stimulate cell-specific and humoral immunity[20]. In addition, NEU can be triggered by virus-related inflammatory factors[21]. On the other hand, systemic inflammation caused by viral infection significantly reduces the number of lymphocytes[22]. Thus, virus-induced inflammation has been reported to increase NLR. In many studies, it has been found that NLR[9,10] and PLR[23] can show more systemic inflammation than NEU and LYM alone. In our study, NLR and PLR were found high in patients with CT (+) – PCR (-). In patients with CT (+) – PCR (-), high NLR and PLR was considered as the period with the highest inflammation.

There were some limitations in this study. First, the data were obtained from a single clinical research center, not from multiple clinical research centers. Second, the data are limited. In addition, the results of this study may differ from those of other academics and need further improvement in clinical cases.

CONCLUSION

COVID-19 is a rapidly spreading disease. The clinical manifestations of this disease can vary even in patients with the same viral infection; the severity of the condition may be related to the number of immune system cells. The CT finding can be detected earlier in the disease before the PCR test. The sensitivity of the PCR test varies according to the tester, the way of performing it, and the quality of the test. Therefore, especially in patients with PCR negative and CT findings, NLR and PLR levels should be evaluated, and patients should be followed up by suspecting the diagnosis of COVID-19.

AUTHORS' CONTRIBUTION

SO: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft. **EO:** Data Curation, Formal Analysis, Writing – Original Draft. **MED:** Conceptualization.

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ORIGINAL ARTICLE

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Association of ABO blood group and age with COVID-19 positive test

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SUMMARY

OBJECTIVE: The aim of this study is to evaluate the relation between the coronavirus (SARS-CoV-2) disease (COVID-19) and blood groups and the Rh factor.

METHOD: A total of 313 patients hospitalized in the Internal Medicine clinic, at the intensive care unit (ICU) were included in the study. The cases were divided into two groups: those who were COVID-19 positive and those negative, detected with real-time reverse transcription polymerase chain reaction testing. The demographic, clinical, ABO blood groups, and Rh factor data of the cases were obtained from the hospital records retrospectively.

RESULTS: The mean age of COVID-19 positive (+) cases was 57.74±16 years and of COVID-19 negative (-) cases, 66.41±15 years. The difference was significant (p<0.001); there was no difference between the two groups in terms of sex (p=0.634). When age was categorically separated in COVID-19 (+) cases, $\chi 2$ was extremely significant. Among the ABO blood groups of COVID-19 (+) and (-) cases, $\chi 2$ was 4.975 (p=0.174). In the logistic regression, it was 4.1 (p=0.011) in the O blood group. COVID-19 positive test was determined as 13, 4, and 4 times higher in the 31–40, 41–50, and 51–60 age groups, respectively (p=0.001, p=0.010, p=0.003).

CONCLUSION: The incidence of COVID-19 has increased in the younger population and in the O blood group. Our findings support that, in this population, the ABO blood groups can contribute to the early detection of COVID-19.

KEYWORDS: Coronavirus infections. ABO blood-group system. Rh-Hr blood-group system. COVID-19.

INTRODUCTION

The novel coronavirus (SARS-CoV-2), which causes COVID-19, declared as a pandemic by the World Health Organization (WHO), has affected the whole world. Difficulties in its diagnosis and treatment are present. Therefore, individuals at risk should be identified in relation to this disease.

The ABO blood group system is the most researched erythrocyte antigen system due to the easy identification of phenotypes[1]. The distribution of the ABO blood groups and Rh factor differs between ethnicities and nations[2]. Whereas the rate of Rh positivity in people of white skin color is around 85%, it reaches roughly 95% in African Americans, and almost 100% in African descendants[3]. Genetic factors such as blood group antigens may have an impact on the development and severity of some diseases. Many studies have shown that some diseases are associated with some blood groups. Many epithelial cells have blood group antigens on their surfaces. These antigens play a role in various biological processes, such as cell movement, differentiation, inflammation, and bacterial adhesion4.

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Various studies have shown a relation between predisposition to infectious diseases and blood groups5. The relation between various viruses, such as the West Nile6, HIV7, and SARS-CoV-1[8] and ABO blood groups have been identified. There are several speculations and several studies on the relation between ABO blood groups and SARS-CoV-2[9,10].

In this retrospective single-center study, we aimed to investigate whether there is a relation between COVID-19, which is an infectious viral disease, and ABO and the Rh groups.

METHOD

In the study, 313 patients who had been hospitalized in the internal medicine clinic and at the intensive care unit (ICU), who had been tested for COVID-19 with real-time reverse transcription polymerase chain reaction (rRT-PCR), between between 1 April 2020 and 30 May 2020, were included in the study. Out of the 313 cases, 21 died and 38 had been hospitalized at the intensive care unit. Nasal and pharyngeal swabs of all cases were collected. The isolated samples of patients, which had been transported with the VNAT viral transport and delivered to the molecular virology laboratory, had been studied by the Biospedy (Bioeksen, Turkey) rRT-PCR Kit, provided by the Ministry of Health. Those with positive rRT-PCR result were considered as COVID-19 positive (+), and those with 2 negative rRT-PCR results, 48 hours apart, were considered as COVID-19 negative (-). Hospital records (demographic, clinical, ABO blood groups, and Rh factor) of the patients older than 18 were analyzed retrospectively. The cases were divided into two groups: COVID-19 positive (+) and COVID-19 negative (-). The chest computed tomography (CT) reports of all cases were obtained by scanning the hospital data system retrospectively. Ethics committee approval was obtained from the Ministry of Health of the Republic of Turkey and Sakarya University Medical Faculty for the study (No.: 715224737050.01.04/131; April 04, 2020).

Statistical Analysis

Data analysis was performed by using statistical software (SPSS, version 10.0 [SPSS Inc,

Chicago, IL]. Normally distributed data were compared via one-way analysis of variance, and non–normally distributed data were compared via Mann-Whitney U test. Categorical associations were evaluated by using χ^2 test and multiple logistic regression analysis. Statistical significance was defined as $p \leq 0.05$.

RESULTS

A total of 145 (46.3%) out of the 313 cases were female, and 168 (53.7%) were male. COVID-19 was detected (+) in 220 of the 313 cases (70.3%). The mean age in COVID-19 (+) cases was 57.74±16 years; in (-) cases, 66.41±15 years, and this difference was significant (p<0.001); there was no difference between the two groups in terms of sex (χ^2=0.226, p=0.634). Similarly, there was no difference between COVID-19 (+) and (-) cases in terms of the ABO blood groups and Rh factor (χ^2=4.975, p=0.174; χ^2=0.002 p=0.968; respectively). The demographic characteristics of patients infected with SARS-CoV-2 have been demonstrated in Table 1. The age and ABO group in COVİD-19 (+) and (-) cases are displayed in Figure 1. (-) When the thoracic CT findings of the COVID-19 (+) and (-) cases were compared, the difference between the two groups was significant (χ^2=18.139, p=<0.001). The most common symptom of COVID (+) cases was cough. The comorbidities of COVID

Table 1. Demographic characteristics of patients infected with COVID-19.

Characteristics	COVID-19 (+) n 220	COVID-19 (-) n 93	p-value
Age, years old (SD)	57.74 (16)	66.41 (15)	0.001
Men (n)	120	48	0.710
Women (n)			0.362
Blood groups			
A	100	47	
B	32	13	0.174
AB	12	10	
O	76	23	
Rh	%	%	0.968
Positive	196	83	
Negative	24	10	
DM	41	41	0.990
HT	52	60	0.332
CAD	16	22	0.338
COLD	11	16	0.142
CHF	11	22	0.067
Malignity	11	23	0.034
CKD	10	25	0.006
CVD	9	8.5	0.979
Dialysis	8	14	0.190
AKF	5	4	0.431
Exitus	8.6	4.6	0.240

SD: Standard deviation; DM: Diabetes mellitus; HT: Hypertension; CAD: Coronary artery disease; COLD: Chronic obstructive lung disease; CHF: Congestive heart disease; CKD: Chronic kidney failure; CVD: Cerebro vasculary disease; AKF: Acut kidney failure.

(+) cases were hypertension (HT), diabetes mellitus, coronary artery disease (CAD), chronic obstructive lung disease, congestive heart disease, malignancy, chronic renal failure, and acute renal failure, respectively. There was no relation between sex and blood group (χ^2=5.619, p=0.132). The relation between blood groups and CAD was significant (χ^2=10.347, p=0.016), and the relation with HT was nearly significant (χ^2=7.031, p=0.071).

No relation was determined between the ABO group and COVID-19 positivity/negativity with the chi square test. However, there was a significant relation between age and COVID-19. Hence, further analysis was carried out using the logistic regression. We divided the patients into six groups, according to age (21–30, 31–40, 41–50, 51–60, 61–80, and 81–100) in order to explain the specific age range. The percentages of occurrence of COVID in the age ranges were 94%, 83%, 83%, 54%, 65%, and 54%, respectively. A logistic regression model was built, in which COVID-19 status was the independent variable and the AB0 blood group and age categories were the independent categorical covariates. COVID-19 positive AB0 blood type with the lowest prevalence and the age categories with the lowest prevalence were selected as indicator covariates. Our model revealed that patients with 0 blood type and those in the 31–40, 41–50, 51–60-year-old age groups were 4.1 and 13, 4, 4 times more likely to test positive for COVID-19, respectively (Table 2). ABO blood groups distribution among age groups is presented in Figure 2.

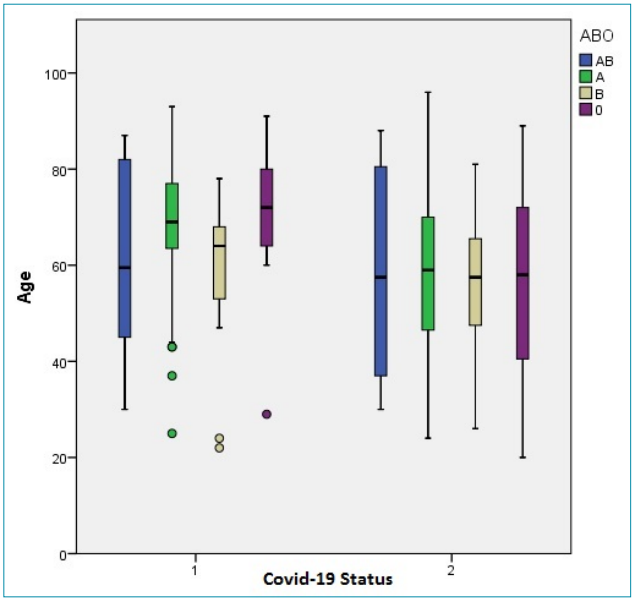

Figure 1. The age and ABO group in cases with and without COVID-19 (+).

There was no relation between the blood group and mortality (χ^2=2.376, p=0.498), and the mortality rate was the highest in group B. There was no relation between blood groups and patients hospitalized at the ICU (χ^2=2.903 p=0.407). The blood group of patients hospitalized at the ICU was O, most frequently.

There was no relation between the blood group and ward/intensive care unit hospitalization (χ^2=3.738, p=0.291).

There was no difference between Rh and sex, COVID, ward/intensive care unit hospitalization (χ^2=2.396, p=0.122; χ^2=0.002, p=0.962; χ^2=0.402, p=0.526, respectively). When rh was evaluated categorically by age, chi-square was 6.013, and p=0.538. Rh blood groups distribution according to age and COVID-19 status is presented in Figure 3. There was no relation

Table 2. Logistic regression model with COVID-19 status is the independent variable; blood group ABO and age categories are independent categorical covariates.

B		S.E	Wald	p	OR
Blood groups					
AB	0.910	0.714	6.940	0.074	2.523
A	0.925	0.527	3.082	0.079	2.555
B	0.979	0.605	2.618	0.106	2.685
O	1.403	0.550	6.575	0.011	4.096
Age cat (year)					
Agecat (21–30)	0.716	0.646	1.230	0.267	2.047
Agecat (31–40)	2.621	0.813	10.384	0.001	13.750
Agecat (41–50)	1.402	0.545	6.622	0.010	4.065
Agecat (51–60)	1.529	0.508	9.053	0.003	4.612
Agecat (61–80)	0.075	0.426	0.031	0.860	0.928
Agecat (81–100)	0.368	0.442	0.694	0.405	1.445

between the Rh factor and mortality (χ^2=2.590, p=0.108) either. There were 34 patients with Rh negativity in total, and three were at the ICU, but no death was seen.

DISCUSSION

The study reported the cohort of COVID-19 (+) 220 and COVID-19 (-) 93 hospitalized patients, confirmed with rRT-PCR. There were significant differences in COVID-19 positive cases in terms of age, compared to negative cases. The age was younger in COVID-19 positive cases. In the logistic regression, the probability of COVID-19 positive test was determined 4.1 times higher in the O blood group, and in the 31–40, 41–50, 51–60 age groups, it was found to be 13, 4, and 4 times higher, respectively. The reason for COVID-19 positivity being higher in these age groups was thought to be related to the fact that this patient group was not subject to curfews and traveling outside their country.

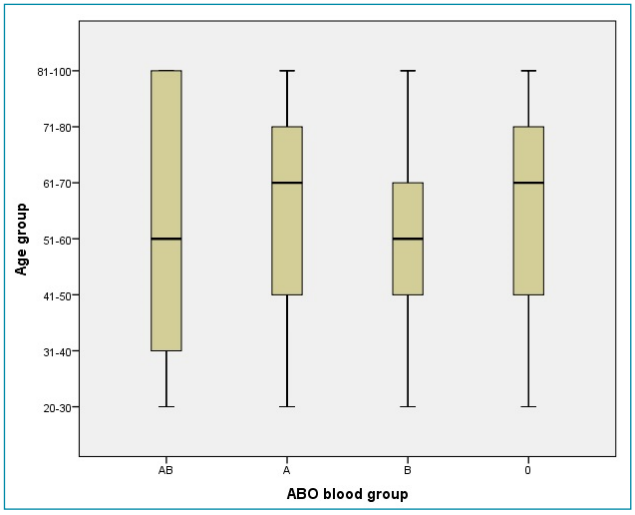

Figure 2. ABO blood group distribution among age groups.

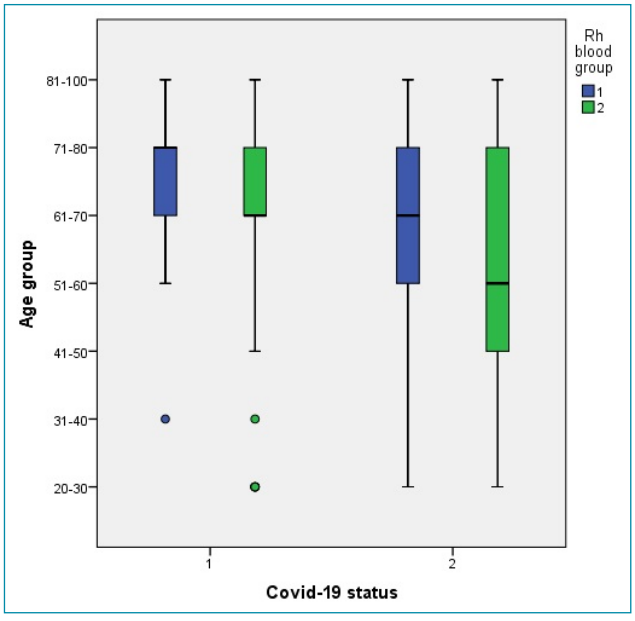

Figure 3. Rh blood group distribution according to age and COVID-19 status.

The ABO blood group system basically contains A and B antigens and their corresponding antibodies. There are 4 genetic forms: A, B, AB, and O[11]. Besides that, ABO gene variants that vary between different ethnic population groups are also known[2,12]. A relation between various viruses (such as the West Nile[6], HIV[7], hepatitis B[13], and SARS-CoV-1[8]) and ABO blood groups has been identified. Considering that there may be a relation between COVID-19 and blood groups, two studies have shown that the blood group A has a higher risk of developing COVID-19, and blood group O has a lower risk[9,10]. In the study by Zhao et al.[9], the control group comprised completely healthy individuals, and the lack of age and sex information of the control group was a disadvantage. In the study conducted by Wu et al.[10], the control group consisted of completely healthy individuals without COVID-19 testing. In our study, all cases were hospitalized and comprised cases with confirmed COVID-19 +/- with rRT-PCR.

In the present study, more COVID-19 positive cases were found within the blood group O. Dzik et al.[14] found a non-significant slightly higher proportion of blood group O's individuals among patients with COVID-19. Increased evidence has shown that the need for hospitalization due to this infection may be disproportionately affected by race and ethnicity in China and the United States, as well as other countries[15,16]. Since the blood group ABO and the Rh factor vary by ethnicity, the distribution of ABO when comparing the infected and the uninfected cohorts may be affected. Our data and those by Sunny Dzik[14] did not support the recommendations of Li et al.[17], that the blood group A's individuals should strengthen protection to reduce the risk of infection. People with blood type O should not underestimate this virus and must take precautions to avoid the risk of infection[17]. The 4.1 times higher frequency of COVID-19 positive test in blood group O found herein and the slight increase of COVID-19 disease found by Dzik et al.[14] in the blood group O in Boston may be related to race and ethni differences in blood group distribution[2]. This can be explained by the fact that the COVID-19 pandemic disproportionately affected those of Latin or Spanish descent in which the O group is more common in Boston[14,15]. Likewise, the increase in COVID-19 cases associated with blood group A in China may be related to the high incidence of blood type A [16]. In Turkey, although blood group A is common, the region in which we are located is an industrial area, which has ethnic origin differences and receives immigrants[18]. This may have affected our results.

There was no relation between blood type ABO and death among individuals hospitalized with COVID-19[9,14,19]. In the present study, no relation between the blood group and mortality consistent with previous studies was found; the mortality rate was the highest in blood group B. Our mortality count (n: 21) was a limiting factor in the statistical analysis.

It has been stated there is a relation between the Rh factor and COVID-19, as a result of a preprint study[19]. We could not find any relation between the Rh factor and mortality. However, there were no Rh (-) cases in patients who died. The Rh (-) case number herein was scarce (n: 34), which complicated the statistical analysis.

Present results emphasize that the populations used to compare blood group ABO distributions should be carefully selected, and further studies are needed.

In summary, people's blood group may be one of the risk factors for COVID-19. Blood groups may be associated with some clinical characteristics of patients with COVID-19.

AUTHORS' CONTRIBUTION

AN: Conceptualization, Data Curation, Formal Analysis, Supervision, Validation, Writing – Original Draft, Writing – Review & Editing. **TK:** Data Curation, Writing – Original Draft. **SY:** Data Curation, Writing – Original Draft. **CLW:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **HC:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

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Correlation between venous blood gas indices and radiological involvements of COVID-19 patients at first admission to emergency department

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SUMMARY

The purpose of this study was to investigate the relation between venous blood gas and chest computerized tomography findings and the clinical conditions of COVID-19 pneumonia.

METHODS: A total of 309 patients admitted to the emergency department and subsequently confirmed COVID-19 cases was examined. Patients with pneumonia symptoms, chest computerized tomography scan, venous blood gas findings, and confirmed COVID-19 on reverse transcription-polymerase chain reaction (PCR) were consecutively enrolled. Multiple linear regression was used to predict computerized tomography and blood gas findings by clinical/laboratory data.

RESULTS: The median age of patients was 51 (interquartile range 39–66), and 51.5% were male. The mortality rate at the end of follow-up was 18.8%. With respect to survival status of patients pCO_2 and HCO_3 levels and total computerized tomography score values were found to be higher in the surviving patients ($p<0.001$ and $p=0.003$, respectively), whereas pH and lactate levels were higher in patients who died ($p=0.022$ and $p=0.001$, respectively). With logistic regression analysis, total tomography score was found to be significantly effective on mortality ($p<0.001$). The diffuse and random involvement of the lungs had a significant effect on mortality ($p<0.001$, 95%CI 3.853–38.769, OR 12.222 and $p=0.027$; 95%CI 1.155–11.640, OR 3.667, respectively). With linear regression analysis, the effect of pH and lactate results were found to have a positive effect on total tomography score ($p=0.003$ and $p<0.001$, respectively), whereas pCO_2 was found to have a negative effect ($p=0.029$).

CONCLUSION: There was correlation between venous blood gas indices and radiologic scores in COVID-19 patients. Venous blood gas taken in emergency department can be a fast, applicable, minor-invasive, and complementary test in terms of diagnosing COVID-19 pneumonia and predicting the prognosis of disease.

KEYWORDS: Coronavirus infections. Blood gas analysis. Thorax. Radiology. Emergencies. Mortality.

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INTRODUCTION

New coronavirus disease (COVID-19) is a serious and mortal infectious disease, causing severe acute respiratory distress syndrome[1,2]. Since there is no curative vaccine or medicine yet, using determined measures and early detection tools serve as the gold standard tools against COVID-19. In the Emergency Department (ED), first-level COVID-19 triaging is performed according to clinical and laboratory results. Later, in case of doubt or severe respiratory failure, non-contrast chest computed tomography (CT) as a second-level triage complementary diagnostic tool is recommended[3-5]. However, a significant proportion of patients admitted to the ED with suspected COVID-19 are reported as COVID-19 negative[6], and the risk of radiological exposure and misdiagnosis should be considered[7,8]. Several point-of-care molecular devices are currently being integrated for fast and accurate diagnosis of SARS-CoV-2 infections[9]. It is valuable with respect to determining lungs involvement patterns of COVID-19 pneumonia and giving information about the disease prognosis through chest CT[10-12]. Evaluation of blood gas parameters is an indispensable approach in the differential diagnosis of respiratory complaints in ED, and venous blood gas (VBG) analysis has been increasingly adopted in those departments as much as arterial blood gas (ABG)[13]. Both chest CT and ABG analysis were evaluated in one study; mild-moderate correlation was found between chest CT findings and ABG indices in patients with COVID-19 pneumonia[14]. In another study, COVID-19 patients presented a positive correlation between increased pulmonary inflammatory volume on CT and low ABG indices[14,15]. Since ABG analysis is a more invasive procedure, VBG analysis as an initial assessment is accepted in the evaluation of acute respiratory complaints; there is no significant difference in many arteriovenous parameters (PH, pCO_2, Bicarbonate)[16,17].

Although there is no recommendation for routine use of venous blood gas assessment in COVID-19 patients, it may be effective in to manage the disease and determine the prognosis, as venous blood gas can be a simple, fast, cheap, and practical method at the first admission in emergency services during the COVID-19 pandemic process. The aim of this study is to investigate whether there is a correlation between the VBG indices and total chest CT scores (TCTS) in patients with COVID-19 pneumonia at admission to ED and whether they will determine the disease prognosis.

METHODS

A retrospective analysis was performed on 309 COVID-19 patients who were admitted to our academic hospital, from March 20, 2020 to May 20, 2020. Patients with pneumonia symptoms, chest CT scan, and confirmed COVID-19 on reverse transcription-polymerase chain reaction (RT-PCR) nasopharyngeal (NP) swabs were consecutively enrolled. The study was conducted in accordance with the Declaration of Helsinki, and after approval of the ethics committee of our university`s Faculty of Medicine (No.: 61522473/050.01.04/282). Patients aged >18 years, with simultaneous RT-PCR, chest CT, and VBG were included in the study. Patients with negative RT-PCR for SARS-CoV-2 with nasopharyngeal swabs, pulmonary edema, chronic obstructive pulmonary diseases, malignancy, congestive heart disease, liver dysfunction, acute/chronic kidney injury, and incomplete clinical data were excluded. During the specified study period, a total of 643 inpatients were examined, and only 309 patients were included considering the exclusion criteria. The demographic characteristics of the patients, such as age, gender, admission complaints, comorbid status, as well as biochemical parameters, venous blood gas indices and chest CT findings were recorded.

CT protocol and scoring

All patients underwent unenhanced CT with a 64-slice multi-detector CT (MDCT) scanner (Toshiba Aquilion) when they came to clinical attention due to pneumonia symptoms. All images reviewed by one radiologist independently blinded to the clinical information. CT visual quantitative evaluation was based on summing up the acute lung inflammatory lesions involving each lobe. Percentage of involvement in each lobe was recorded, as well as the overall lung "total severity score (TSS)". Each of the five lung lobes was assessed for percentage of the lobar involvement and classified as none (0%), minimal (1–25%), mild (26–50%), moderate (51–75%), or severe (76–100%), with corresponded score as 0, 1, 2, 3, or 4. TSS was reached by summing the five lobe scores (range from 0 to 20)[9].

Statistical analysis

Statistical analysis was performed with SPSS Statistics (IBM Corporation, Somers, NY) software, version 22). The normality of the distribution of continuous variables was determined using the Kolmogorov–Smirnov test. The continuous variables were expressed as median and interquartile range, depending on the normality of their distribution. Categorical variables are interpreted as frequency tables. The Mann–Whitney U test was used to compare the variables that were not normally distributed. Categorical features and relations between groups were assessed with an appropriate chi-square test. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated with Spearman`s test. A multiple linear regression model was used to identify independent predictors of total CT scores. The model fit was assessed using appropriate residual and goodness-of-fit statistics. Logistic regression was conducted to assess whether predictor variables, such as some laboratory findings and demographic data, significantly predict mortality. The statistically significant two tailed p-value was considered as <0.05.

RESULTS

The median age of patients was 51 (IQR: 39–66). There were 159 (51.5%) female and 150 (48.5%) male patients. The diagnosis of all patients was confirmed with RT-PCR NP swabs. The most common symptoms at admission to ED were fever (63.8%), cough (54.4%), and shortness of breath (31.1%). Among the chronic concomitant diseases, hypertension, and diabetes mellitus (DM) were recorded the most frequently with 29.4% and 18.1%, respectively. At the end of follow-up, 58 patients died (18.8%). These and other baseline clinical and laboratory findings are summarized in Table 1.

When blood gas indices and TCTS values of patients were evaluated with respect to survival, pCO_2 and HCO_3 levels were found to be higher in the surviving patients (p<0.001 and p=0.003, respectively), whereas PH and lactic acid levels were higher in patients who died (p=0.022 and p=0.001, respectively). TCTS results were significantly higher in the group who died (p<0.001) (Table 2). The logistic regression analysis was done to evaluate the effect of TCTS and distribution pattern of lesions in lung parenchyma on mortality; TCTS was found to be statistically significantly effective on mortality (p<0.001, 95%CI 1.165–1.325; OR 1.243). Whereas no death was observed in the centrally located group of lung lesions (n = 8), the effect of peripherally located lesions on mortality was not significant (p=0.275, 95%CI 0.598–6.072, OR 1.906). However, the diffuse localization of lesions (p<0.001, 95%CI 3.853–38.769, OR 12.222) and random localization (p=0.027, 95%CI 1.155–11.640, OR 3.667) had a significant positive effect on mortality (Table 3).

With correlation analysis, a significant positive correlation was found between pH (Figure 1A) and lactate (Figure 1B)

Table 1. Clinical findings and laboratory features of the study population.

Characteristic	Results (n=309)
Age, years old*	51 (39–66) (range:17–91)
Gender, F/M (%)	159/150 (51.5/48.5)
Initial symptom, positive	
Fever	63.8
Cough	54.4
Dyspnea	31.1
Weakness	24.3
Sore throat	12.0
Diarrhea	3.9
Loss of taste	4.5
Anosmia	7.4
Headache	5.2
Diarrhea	3.9
Chronic diseases, positive	
Diabetes	18.1
Hypertension	29.4
Heart Disease	10
Diagnostic method	
Nasopharyngeal RT-PCR	100%
Pulmonary involvement, n (%)	251 (81.2)
Bilateral involvement	213 (68.9)
Unilateral involvement	38 (12.6)
Diffuse located	52 (18.8)
Peripherally located	115 (37.2)
Random located	76 (24.6)
Centrally located	8 (2.6)
Mortality, n (%)	58 (18.8)

Table 2. Comparison of blood gas results, demographic features, and total CT scores, according to survival conditions

	Results*		*p*-value
	Dead (n=58)	Alive (n=251)	
Age, years old	71.5 (64.0–81.0)	47 (36.0–62.0)	<0.001
Gender, F/M (%)	24/34 (41.4/58.6)	126/125 (50.2/49.8)	0.226
pH	7.40 (7.35–7.45)	7.38 (7.35–7.41)	0.022
pCO_2	40.2 (36.1–45.6)	45.4 (40.5–49.0)	<0.001
HCO_3	23.4 (21.4–25.4)	24.80 (23.3–26.0)	0.003
Lactate	2.10 (1.60–3.05)	1.60 (1.20–2.10)	<0.001

*The results for continuous variables were expressed as median (interquartile ranges), since they are not normally distributed.

Table 3. Logistic regression analysis of the pulmonary involvement pattern on mortality

	OR	95%CI	p-value
Pulmonary involvement pattern			
No involvement, ref* (n=58)	1	–	–
Diffuse involvement (n=51)	112.222	3.853–38.769	<0.001
Peripheral involvement (n=115)	1.1.906	0.598–6.072	0.275
Random involvement (n=76)	3.3.667	1.155–11.640	0.027
Central involvement (n=8)	0 (no death)	–	–

*Accepted as a reference category.

levels of TCTS, whereas a significant negative correlation was found between pCO_2 (Figure 1C) levels ($p<0.001$). No correlation was found between TCTS and other parameters, such as HCO_3 and PO2 ($p>0.05$). In addition, by linear regression analysis; pH and lactate results were found to have a positive effect on TCTS ($p=0.003$ and $p<0.001$, respectively), whereas pCO_2 was found to be negatively effective ($p=0.029$).

DISCUSSION

In the present study, a correlation between simultaneous venous blood gas (VBG) indices taken at the time of first admission to the emergency department and TCTS in patients diagnosed with COVID-19 disease was shown. Besides that, when the first admission VBG and TCTS are evaluated together, they determine and provide significant information about the prognosis of the disease. For the first time, a mild-to-moderate relation between ABG and chest CT findings in COVID-19 patients has been shown[14].

These results may be important in determining the prognosis and hospitalization indicators of the first admitted patients in the EDs. However, since taking ABG is a more invasive procedure, VBG analysis is preferred as an initial procedure to assess acute respiratory failure[16,17].

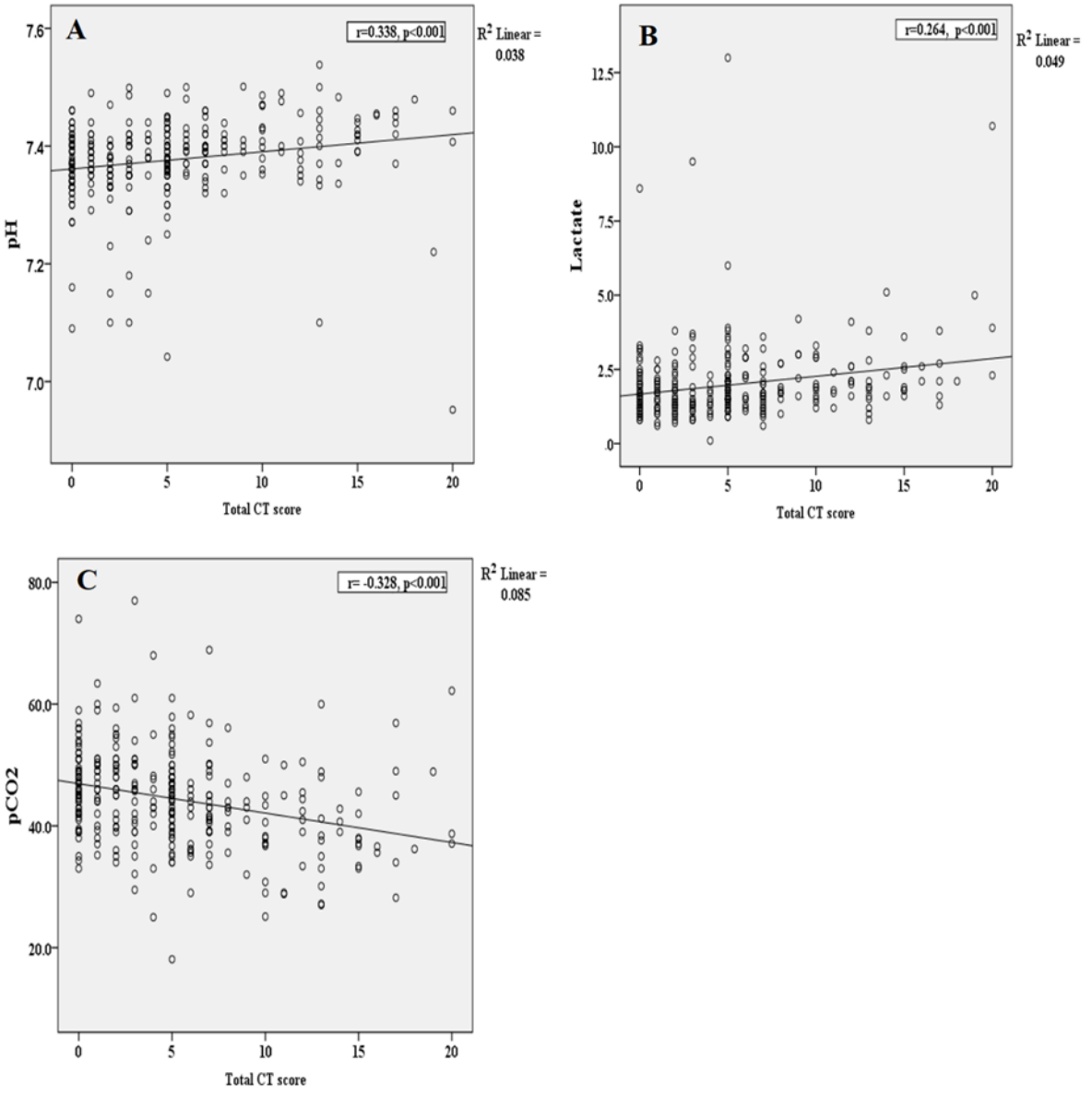

Figure 1. Correlation analysis of pH (A), lactate (B), and pCO_2 (C) with total CT score

Studies have shown that the levels of arteriovenous parameters with respect to power of hydrogen (PH) are very close to each other and interchangeable at about 0.03–0.04[13]. Similarly, there is little difference in pCO_2 and bicarbonate levels and 95% limits of agreement are very wide precluding clinical interchangeability[13].

CT scanning provides important bases for early diagnosis and treatment of COVID-19. CT imaging presentations of COVID-19 pneumonia are mostly patchy ground glass opacities in the peripheral areas under the pleura, with partial consolidation, which will be absorbed with formation of fibrotic stripes if improved[18,19]. In the present study, a significant effect of the distribution pattern of the disease on the lung parenchyma on mortality was found. Radiological lesions, which are in peripheral and of diffuse involvement, were shown to be more prominent in patients who died. A positive correlation between VBG parameters and TCTS parameters was also observed. Whereas a significant positive correlation was detected between pH and lactate levels of TCTS, a significant negative correlation between pCO_2 levels was found ($p<0.001$). To the best of our knowledge, this is the first time a significant relation between VBG indices and radiological findings in COVID-19 patients has been demonstrated. The findings of abnormal VBG detected in COVID-19 patients may be an indicator of the emergence of an inflammation, thus giving an idea about the disease prognosis. To support results herein, Shang et al.[14] reported similar results between ABG indices -but not VBG- and radiological parameters. VBG indices may be more advantageous than ABG, because it is less invasive and has a simple technique acquisition.

The main limitation of this study is not prospective, controlled and randomized study.

In conclusion, COVID-19 pneumonia is still not controlled worldwide. Since the results of RT-PCR nasopharyngeal test taken from suspected patients in ED cannot be obtained very quickly, radiological imaging supplying faster results is frequently used. A correlation between VBG parameters and radiological findings was found in these patients. In the presence of suspected disease in ED, VBG can be a complementary test not only in diagnosing of COVID-19 pneumonia, but also predicting the prognosis of the disease, as it is a cheap, simple, and non-invasive method.

AUTHOR CONTRIBUTIONS

HD: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **AK:** Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **FG:** Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **SS:** Data Curation. **SY:** Data Curation. **AT:** Data Curation, Conceptualization, Software, Validation. **ESC:** Data Curation, Conceptualization, Software, Validation. **NF:** Data Curation, Conceptualization, Software, Validation. **CV:** Data Curation, Conceptualization, Software, Validation. **OK:** Supervision. **TD:** Supervision. **HD:** Validation, Visualization, Writing – Original Draft, Writing – Review & Editing.

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ORIGINAL ARTICLE

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COVID-19 pandemic information on Brazilian websites: credibility, coverage, and agreement with World Health Organization. Quality of COVID-19 online information in Brazil

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SUMMARY

OBJECTIVE: To assess the credibility and the quality content of COVID-19 pandemic information on Brazilian websites.

METHODS: We performed Google searches and screened the first 45 websites. The websites were categorized as academic, commercial, government, hospital, media, nongovernmental organizations, and professionals. The credibility was assessed by JAMA benchmark criteria and HONCODE. A checklist with WHO information about COVID-19 was developed to assess the quality content. For each website, the level of agreement with WHO information was categorized into "total," "partial," or "disagreement".

RESULTS: A total of 20 websites were analyzed. None of the websites had HONCODE certification. Six websites (30%) met none of the four JAMA criteria and only one website (5%) fulfilled all the four criteria. Only 11 out of 20 websites showed overall coverage >50% for the checklist. Overall, 70% (14/20) of the websites had at least 50% total agreement with WHO items. The government websites presented more disagreement with the WHO items than media websites in the overall quality content analysis.

CONCLUSION: The COVID-19 information on Brazilian websites have a moderate-to-low credibility and quality, particularly on the government websites.

KEYWORDS: Coronavirus Infections. Health Information Systems. Internet. World Health Organization. Pandemics.

INTRODUCTION

In December 2019, the Chinese National Council and the World Health Organization (WHO) were both notified about the first cases of patients with pneumonia from an unknown source and shared symptoms in the city of Wuhan, China. It was discovered that these symptoms were caused by the SARS-CoV-2, a novel coronavirus, and the disease developed by this coronavirus was called COVID-19. The accelerated spreading of the COVID-19 outbreak led the WHO to announce that it became pandemic in March 2020[1-3].

The COVID-19 pandemic is one of the biggest concerns of the 21st century. As less information is available about this novel disease, the scientific community is increasingly engaged in understanding the most important parameters to manage the disease and to reduce the spreading of the outbreak. As a result, emerging information is quickly shared by researchers, international organizations, and media[3].

Nowadays, the Internet has been a common source of health information to the population. However, as any Internet user can provide content on the Internet regardless the quality or accuracy of the content, a lot of fake news related to health issues have been shared in the social media, blogs, and websites. During a pandemic, the fake news may impair the prevention,

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spreading, and treatment of the disease[4]. Unfortunately, it is difficult for the population in general to distinguish the reliable information and the fake news on the Internet once people are not critical about the content that is consumed by them.

According to the National Household Sample Survey, the Internet utilization in households increased from 74.9% to 79.1% within 1 year[5]. This increased use of Internet is especially important because the individuals have valued more Internet-based information than the information derived from the elders of the family, as it was in the past[6]. Given that the main sources of online information are websites and blogs and that the most searched content during a global outbreak involves the prevention and the treatment of the new disease, reliable online information is crucial to improve the pandemic-related health outcomes[7,8].

To provide accurate information about the definition, symptoms, spreading, prevention, treatment, and other aspects related to the new disease COVID-19, the WHO has released reports covering public advice, country and technical guidance, frequently asked questions, travel advice, and mythbusters[9]. Considering that part of the Internet-based information is inaccurate, the aim of this study was to assess the quality and credibility of COVID-19-related information available in websites and to verify the agreement of that information with the WHO reports and advices.

METHODS

This qualitative study was conducted between April and May 2020. Online searches were performed by using the advanced Google search engine in the Google Chrome browser with the search terms "coronavirus" and "COVID-19." The searches were limited to Brazilian websites published in Portuguese. All browser caches and cookies were cleared before searching. The first 45 websites were screened for analysis. The website would contain a specific webpage for information related to the COVID-19 aimed to the general population. The websites containing only daily news or information directed toward a specific public, or redirecting to obtain the main information in other websites were excluded. As adopted in the previous studies, up to four webpages of each website were considered for this analysis[10-12]. The searches, the screening for inclusion and exclusion, the categorization of the websites, and the assessment of the outcomes were all performed by two independent researchers. Any discrepancy was resolved by consensus.

Each website was classified into one of the following categories: academic (from universities, schools, or educational channels), commercial (with commercial purposes), governmental (from government agencies), media (from media corporations), professional (from health professionals with or without academic credentials), hospital (from medical centers, clinics, and hospitals), and nongovernmental organizations (from NGOs).

The outcomes were the credibility and the content quality and coverage of the websites. The HONCODE and JAMA benchmark criteria were used to assess the website credibility. The quality and coverage of website contents were evaluated by using a qualitative content analysis.

HONCODE is a system created in 1995 that provides an electronic certification to high-standard websites[13]. To have the HONCODE certification, a website may follow eight ethics principles: authority, complementarity, confidentiality, attribution, justifiability, transparency, financial disclosure, and advertising[4]. We have checked whether the websites were certified by HONCODE through the HON website http://www.healthonnet.org/. Each website was categorized into "yes" (certified) or "no" (not certified).

The JAMA benchmark criteria is one of the most common tools used to assess the quality of Internet-based information. It assesses four components: authorship (whether the website states the authors and contributors), attribution (whether the website states the references and sources), disclosure (whether the website discloses any conflict of interest, sponsorship, advertising, etc.), and currency (whether the website states dates and update dates)[4,14]. Each website was categorized into "yes" or "no" for each criterion.

In order to assess the quality and coverage of the website contents, we developed a 57-item checklist with WHO information related to the COVID-19 pandemic. These 57 items were divided into definition (2/57), symptoms (4/57), spreading (9/57), prevention (17/57), treatment (7/57), and others (18/57). For quality assessment, we measured the agreement between the website information and each item from WHO checklist. The agreement was judged to be "total" when website information exactly matched the WHO information, "partial" when website information were incomplete in comparison with the WHO information, and "disagreement" when website information were totally discordant to the WHO information. For website coverage evaluation, we measured using the 57-item WHO checklist. For each item covered by the website, one point was attributed. If the website contains more content related to WHO information, more points were provided.

RESULTS

From 45 websites screened for eligibility, 25 were excluded. The reasons for exclusion were: not having a specific webpage for COVID-19-related information (19 websites), redirecting to other websites for information (2 websites), having information directed at a specific audience (3 websites), and not a Brazilian website (1 website). From the 20 included websites, 8 websites were authored by media corporations, 6 websites by

governmental agencies, 3 websites by hospitals, 1 website by commercial entities, 1 website by professionals, and 1 website by academic sources.

None of the websites had HONCODE certification. Six websites (30%) met none of the four JAMA benchmark criteria. Three websites (15%) met one JAMA criteria, four websites (20%) met two JAMA criteria, six websites (30%) met three JAMA criteria, and only one website (5%) fulfilled all the four JAMA benchmark criteria (Table 1).

None of the websites covered all the items from the WHO checklist (Table 2). Of note, 11 out of 20 websites showed overall coverage >50% of the checklist. Overall, 70% (14/20) of the websites had at least 50% total agreement with WHO items. Per category, 60% (12/20), 45% (9/20), 60% (12/20), 75% (15/20), 80% (16/20), and 50% (10/20) of the websites exhibited at least 50% total agreement with definition, symptoms, spreading, prevention, treatment, and other WHO items from the checklist, respectively. Overall, 80% (16/20) of the websites had at least one disagreement with WHO items (Table 3).

DISCUSSION

Although Google does not have a strong control of quality content, it is the most used search engine in the world[4,11,15]. For this reason, we have used Google engine to fetch the websites presenting COVID-19 information. As most Internet users do not go beyond the second page of web search, we have only screened the first 45 websites in order to include at least 15 websites for the final analysis[15]. A total of 25 websites were excluded mainly because of reporting only the daily news about the pandemic situation in the country and not having a specific webpage to provide information related to the main aspects of the COVID-19 disease.

The WHO has been crucial to guide governmental actions around the world during the COVID-19 pandemic. This international organization has provided updated, quick, and reliable information to avoid misunderstandings[9]. Our findings show that although 75% of the Brazilian websites had total agreement with at least half of the WHO items related to prevention, none of the websites exhibited agreement with all the WHO prevention items. Many websites had incomplete or

Table 1. Individual website categories, HONCODE certification, and JAMA benchmark criteria analysis.

Websites	Website Category	HONCODE	JAMA Benchmark Criteria			
			Authorship	Attribution	Disclosure	Currency
bbc.com/	Media	No	Yes	Yes	No	Yes
Brazilescola.uol.com.br/	Academic	No	Yes	No	Yes	No
coronavirus.pr.gov.br/	Government	No	No	No	No	No
coronavirus.saude.gov.br/	Government	No	No	No	No	No
dasa.com.br/coronavirus	Commercial	No	No	No	Yes	No
especiais.gazetadopovo.com.br/coronavirus/	Media	No	Yes	Yes	Yes	Yes
especiais.g1.globo.com	Media	No	Yes	Yes	No	Yes
estadao.com.br	Media	No	Yes	Yes	No	Yes
folha.uol.com.br/	Media	No	Yes	Yes	No	Yes
goiania.go.gov.br/	Government	No	No	No	No	No
hospitalsiriolibanes.org.br/	Hospital	No	No	Yes	No	Yes
istoe.com.br/	Media	No	No	Yes	Yes	Yes
metropoles.com/	Media	No	No	Yes	Yes	Yes
portal.anvisa.gov.br/	Government	No	No	No	No	No
prefeitura.pbh.gov.br/	Government	No	No	No	No	Yes
rededorsaoluiz.com.br/	Hospital	No	No	No	No	No
saopaulo.sp.gov.br/	Government	No	No	No	No	No
sergiofranco.com.br/	Professional	No	No	Yes	No	No
unimedpoa.com.br/	Hospital	No	Yes	Yes	No	Yes
uol.com.br/	Media	No	No	Yes	No	Yes

mistaken information related to the minimum recommended distance among people, the need to avoid crowded places and travels, and the recommendation about stay home when people feel unwell. These findings are important because studies have showed that quarantine, social distancing, and isolation are helpful to reduce COVID-19 outbreak[9,16]. Therefore, the websites should provide accurate information to the population about these prevention strategies.

We have found that the government websites presented more disagreement with WHO items than media websites in the overall quality content analysis. Considering that WHO is an international public health agency that provides updated outbreak situation reports, builds research partnerships to accelerate the development of vaccines and drugs, and has handled other pandemics in the past, governments should be aligned with the WHO guidance to ensure a better management of COVID-19 pandemic[17]. The observed disagreement between WHO and government websites (from 8.6% to 33.3%) highlights the need for improvement in health communication. During a pandemic, effective health communication plays an essential role on reducing the fear and anxiety related to the outbreak and increasing the adherence to adequate prevention measures[18]. Positively, Brazilian media websites showed high quality content and less disagreement with WHO information (from 0% to 8.5%). It is especially relevant because media have a large audience on Internet. The major four Brazilian media companies reach approximately 58.7% of the digital population[19]. Therefore, COVID-19 information provided by media websites is expected to have a strong quality as information is quickly disseminated and reaches a huge number of people.

For the JAMA benchmark analysis, out of six websites that met none of the criteria, four websites appeared either on the first or on the second page of Google search, and five of them were authored by government agencies. It is intriguing because the websites with less credibility are located in the most viewed pages of web searches and are created by the government, which should be the most reliable source of information as people tend to follow the government instructions

Table 2. Individual website coverage of WHO items.

Websites	WHO items coverage, n (%)						
	Overall	Definition	Symptoms	Spreading	Prevention	Treatment	Others
bbc.com/	30 (52.6)	0 (0.0)	4 (100.0)	5 (55.5)	10 (58.8)	2 (28.5)	9 (50.0)
Brazilescola.uol.com.br/	25 (43.8)	2 (100.0)	4 (100.0)	3 (33.3)	10 (58.8)	2 (28.5)	4 (22.2)
coronavirus.pr.gov.br/	9 (15.7)	0 (0.0)	2 (50.0)	1 (11.1)	5 (29.4)	0 (0.0)	1 (5.5)
coronavirus.saude.gov.br/	31 (54.3)	2 (100.0)	4 (100.0)	3 (33.3)	12 (70.5)	2 (28.5)	8 (44.4)
dasa.com.br/coronavirus	30 (52.6)	2 (100.0)	4 (100.0)	4 (44.4)	11 (64.7)	2 (28.5)	7 (38.8)
especiais.gazetadopovo.com.br/coronavirus/	32 (56.1)	2 (100.0)	4 (100.0)	5 (55.5)	10 (58.8)	2 (28.5)	9 (50.0)
especiais.g1.globo.com	40 (70.1)	2 (100.0)	3 (75.0)	7 (77.7)	11 (64.7)	4 (57.1)	13 (72.2)
estadao.com.br	32 (56.1)	2 (100.0)	4 (100.0)	6 (66.6)	11 (64.7)	2 (28.5)	7 (38.8)
folha.uol.com.br/	35 (61.4)	2 (100.0)	4 (100.0)	6 (66.6)	10 (58.8)	3 (42.8)	10 (55.5)
goiania.go.gov.br/	18 (31.5)	0 (0.0)	4 (100.0)	2 (22.2)	9 (52.9)	2 (28.5)	1 (5.5)
hospitalsiriolibanes.org.br/	29 (50.8)	2 (100.0)	4 (100.0)	6 (66.6)	11 (64.7)	2 (28.5)	4 (22.2)
istoe.com.br/	21 (36.8)	1 (50.0)	2 (50.0)	3 (33.3)	7 (41.1)	2 (28.5)	6 (33.3)
metropoles.com/	12 (21.0)	2 (100.0)	1 (25.0)	1 (11.1)	5 (29.4)	2 (28.5)	1 (5.5)
portal.anvisa.gov.br/	20 (35.0)	2 (100.0)	4 (100.0)	3 (33.3)	9 (52.9)	0 (0.0)	2 (11.1)
prefeitura.pbh.gov.br/	23 (40.3)	1 (50.0)	3 (75.0)	3 (33.3)	10 (58.8)	1 (14.2)	5 (27.7)
rededorsaoluiz.com.br/	22 (38.5)	2 (100.0)	4 (100.0)	3 (33.3)	9 (52.9)	2 (28.5)	2 (11.1)
saopaulo.sp.gov.br/	21 (36.8)	2 (100.0)	3 (75.0)	3 (33.3)	7 (41.1)	2 (28.5)	4 (22.2)
sergiofranco.com.br/	19 (33.3)	1 (50.0)	2 (50.0)	3 (33.3)	4 (23.5)	3 (42.8)	6 (33.3)
unimedpoa.com.br/	33 (57.8)	2 (100.0)	4 (100.0)	6 (66.6)	9 (52.9)	3 (42.8)	9 (50.0)
uol.com.br/	33 (57.8)	2 (100.0)	4 (100.0)	5 (55.5)	10 (58.8)	3 (42.8)	9 (50.0)

in the crisis management[16]. The most credible websites were authored by media. These findings are similar to the aforementioned quality content analysis, where media websites showed higher quality than the government websites.

Website coverage of WHO information was low. Only half of the websites presented at least 50% coverage of items from WHO checklist. The lack of reliable information can lead to serious negative effects on the population such as the panic, excessive buying of supplies such as food and hygiene items, and unnecessary medications without medical prescription, which affects people especially those suffering from chronic diseases[20]. Therefore, accurate information may be freely and easily available to overall population to stimulate adequate behaviors and to keep population aware of the better ways of preventing and managing the COVID-19 outbreak.

This study has some limitations. First, the assessment of quality content was based on the agreement between website information and WHO guidelines and recommendations. As the Brazilian Ministry of Health has some divergent recommendations from WHO, some websites followed Ministry of Health guidelines and consequently did not agree with the WHO items. Second, the WHO checklist used to verify the agreement with the websites was developed by our research group. Therefore, it may not be considered as a valid tool. Third, information related

Table 3. Quality content analysis of the individual websites.

Content analysis, n (%)	Websites									
	bbc.com/		coronavirus.pr.gov.br/	coronavirus.saude.gov.br/	dasa.com.br/coronavirus	especiais.gazetadopovo.com.br/coronavirus/	especiais.g1.globo.com/	estadao.com.br	folha.uol.com.br/	goiania.go.gov.br/
Overall										
Total	14 (46.7)	18 (72.0)	5 (55.6)	17 (54.9)	18 (60.0)	19 (63.4)	31 (77.5)	18 (56.3)	18 (51.5)	8 (44.5)
Partial	14 (46.7)	7 (28.0)	1 (11.1)	11 (35.5)	10 (33.3)	10 (33.3)	9 (22.5)	12 (37.5)	14 (40.0)	8 (44.4)
Disagreement	2 (6.6)	0 (0.0)	3 (33.3)	3 (9.6)	2 (6.7)	1 (3.3)	0 (0.0)	2 (6.2)	3 (8.5)	2 (11.1)
Definition (0–2)										
Total	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	0 (0.0)
Partial	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disagreement	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Symptoms (0–4)										
Total	1 (25.0)	3 (75.0)	0 (0.0)	2 (50.0)	1 (25.0)	2 (50.0)	2 (66.7)	0 (0.0)	2 (50.0)	1 (25.0)
Partial	3 (75.0)	1 (25.0)	0 (0.0)	1 (25.0)	3 (75.0)	2 (50.0)	1 (33.3)	3 (75.0)	2 (50.0)	1 (25.0)
Disagreement	0 (0.0)	0 (0.0)	2 (100.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (50.0)
Spreading (0–9)										
Total	1 (20.0)	3 (100.0)	1 (100.0)	2 (66.7)	3 (75.0)	2 (66.7)	5 (71.5)	5 (83.4)	1 (16.6)	1 (50.0)
Partial	3 (60.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (25.0)	1 (33.3)	2 (28.5)	0 (0.0)	5 (83.4)	1 (50.0)
Disagreement	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.6)	0 (0.0)	0 (0.0)
Prevention (0–17)										
Total	6 (60.0)	7 (70.0)	4 (80.0)	8 (66.6)	7 (63.7)	6 (60.0)	10 (90.9)	7 (63.7)	4 (40.0)	6 (66.7)
Partial	4 (40.0)	3 (30.0)	1 (20.0)	2 (16.7)	3 (27.3)	4 (40.0)	1 (9.1)	4 (36.3)	4 (40.0)	3 (33.3)
Disagreement	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	1 (9.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)
Treatment (0–7)										
Total	2 (100.0)	1 (50.0)	0 (0.0)	2 (100.0)	2 (100.0)	2 (100.0)	3 (75.0)	2 (100.0)	2 (66.7)	0 (0.0)
Partial	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (33.3)	2 (100.0)
Disagreement	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others (0–18)										
Total	4 (44.4)	2 (50.0)	0 (0.0)	3 (37.5)	3 (42.9)	5 (55.6)	9 (69.3)	2 (28.5)	7 (70.0)	0 (0.0)
Partial	4 (44.4)	2 (50.0)	0 (0.0)	5 (62.5)	3 (42.9)	3 (33.3)	4 (30.7)	5 (71.5)	2 (20.0)	1 (100.0)
Disagreement	1 (11.2)	0 (0.0)	1 (100.0)	0 (0.0)	1 (14.2)	1 (11.1)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)

Note: The level of websites in agreement with the WHO items is expressed overall and per categories.

to a pandemic change quickly, which just allows to assess the information at a specific point in time.

CONCLUSIONS

Our findings showed that Brazilian websites have poor-to-moderate credibility and quality of content regarding the COVID-19 pandemic, while compared with the WHO information items. Furthermore, it was observed that the government websites are less credible and have lower quality content than media websites. These findings highlight the need for increasing the reliability of online health information about COVID-19 pandemic and developing the strategies to turn Internet users able to identify the quality and credibility of the online health information they are consuming.

AUTHORS' CONTRIBUTIONS

LFSF: Conceptualization, Methodology, Writing – Original Draft, Supervision. **MMBS:** Conceptualization, Investigation, Writing – Review & Editing, Visualization. **WMSJ:** Methodology, Project administration, Supervision, Writing – Review & Editing.

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Strategies to keep kidney transplant alive amid the SARS-CoV-2 pandemic

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SUMMARY

OBJECTIVE: This study aims to describe the result of the strategies adopted to maintain the transplant program amid the COVID-19 pandemic.
METHODS: Since March 2020, several measures have been adopted sequentially, including the compulsory use of personal protective equipment and the real-time polymerase chain reaction testing of collaborators, symptomatic patients, potential deceased donors, candidates for recipients, and in-hospital readmissions, regardless of symptoms. The living-donor transplantation was restricted to exceptional cases.
RESULTS: Among 1013 health professionals, 201 cases of COVID-19 were confirmed between March and August 2020, with no severe cases reported. In this period, we observed a 19% institutional increase in the number of transplants from deceased donors compared with that observed in the same period in 2019. There was no donor-derived severe acute respiratory syndrome virus (SARS-CoV-2) infection. Four COVID-19-positive patients underwent transplantation; after 28 days, all were alive and with functioning allograft. Among the 11,875 already transplanted patients being followed up, there were 546 individuals with confirmed diagnosis, 372 who required hospitalization, and 167 on mechanical ventilation, resulting in a 27% mortality rate.
CONCLUSIONS: These data confirm that the adoption of sequential and coordinated measures amid the pandemic was able to successfully maintain the transplant program and ensure the safety of health professionals and transplanted patients who were already in follow-up.
KEYWORDS: Delivery of health care. Chronic kidney disease. Kidney transplantation. Coronavirus infections.

INTRODUCTION

On March 11, 2020, about 3 months after the first confirmed cases in Hubei Province, China, coronavirus disease 2019 (COVID-19), a disease caused by severe acute respiratory syndrome virus (SARS-CoV-2), was declared a pandemic by the World Health Organization[1]. In Brazil, the first confirmed case was registered on February 26 in São Paulo. On March 16, social distancing measures were adopted, with schools and offices closed, followed by bars and restaurants. The first death occurred on March 17.

Currently, Brazil is the second country with the highest number of COVID-19 cases in the world, with infection widespread in all 27 states of the Union[1]. In addition to the direct effects of COVID-19, which include the occupation of infirmary beds and intensive care units by acute respiratory syndrome patients and the high consumption of personal protective equipment, it was possible to anticipate the magnitude of the impact of the pandemic on access to health services. This was especially true for services dedicated to the treatment of chronic and complex diseases, such as chronic kidney disease and kidney transplants.

According to the data from the Brazilian Dialysis Census, there are currently 133,464 patients on chronic dialysis treatment, with an average annual increase of 5587 patients in the

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last 10 years[2]. With the largest number of procedures, Brazil has the largest public kidney transplant system in the world, next only to United States. In the last 10 years, an annual average of 5703 kidney transplants were performed in the country[3].

Hospital do Rim is a tertiary hospital located in the city of Sao Paulo. Since its foundation in 1998, more than 15,000 kidney transplants have been performed, with an average of 70 procedures a month and 70% of these kidney transplants involve a deceased donor[4]. However, there are still more than 9000 patients on the waiting list in this institution, and, in Brazil, approximately 30,000 candidates are waiting for the transplantation procedure[2].

The direct and immediate risks of COVID-19 to the organ donation and transplantation program are numerous. From the risk of infection of the health professionals involved in the organ procurement and transplantation, as well as the risks associated with inadvertent transmission by the donor organ, the more intense immunosuppressive therapy received by the newly transplanted can increase the risk for infection in the context of chronic use of immunosuppressive drugs. Indirect and medium and long-term losses include the collapse of intrahospital organ search committees and transplant teams, the reduction in the number of potential donors, and the accumulation of dialysis patients in a scenario of lack of equipment and supplies.

METHODS

Aiming at maintaining the activity of organ procurement, donation, and transplantation and minimizing the risks to the transplantation program, the first and most decisive actions were taken on January 13, 2020, with the institution of a COVID-19 managing committee and daily pedagogical actions among employees and patients on concepts, forms of contagion, and institutional and community care in relation to the pandemic. The measures for higher impact in containing the spread of COVID-19 were taken by the institution on March 16, 2020, starting with the investigation of SARS-CoV-2 infection using real-time polymerase chain reaction (RT-PCR) tests for all employees and symptomatic transplanted patients, with test results being obtained within a period of 24 h. In parallel, personal protective equipment, including N95 masks and face-shield masks, were made available for compulsory use by all professionals and patients within the institution. The investigation of respiratory symptoms and measurement of temperature and oximetry for all people was also instituted at the hospital.

RESULTS

There were 201 confirmed cases of COVID-19 among the 1013 employees of the institution, but only 125 among the 752 full-time permanent staff. In 56 of the 201 cases, the probable source of contagion was intrahospital interaction, demonstrating the efficiency of the measures adopted. Since this population presents low risk for complications, with an average age of 37 years, having overweight as the only comorbidity (99 employees, 49%), the predominant symptomatology was mild; only 6 required hospitalization in a ward bed. All these 201 employees returned to work without sequelae.

Elective interventional transplant procedures were postponed from March 28, 2020 and performed only in exceptional situations, when the risk of infection of the recipient on dialysis was considered high due to their frequent displacement in the community. Thus, the number of transplants with live kidney donors was reduced from a monthly average of 28 to 4 procedures (Figure 1).

Inadvertent transmission of SARS-CoV-2 infection from the deceased donor to either a health care professional or to organ recipients was a major concern, as potential candidates remain in emergency or intensive care units days before the diagnosis of brain death as well as during the family authorization process for organ donation and extraction. Thus, since April 6, 2020, screening with RT-PCR using nasal swab of all potential donors prior to organ harvesting was instituted, with timely test results for donor exclusion in cases of confirmed infection. Since the beginning of screening until August 28, 2020, 269 deceased donors were tested, and 20 (7.5%) were rejected after confirmation of SARS-CoV-2 infection. There has been no confirmed donor-derived SARS-CoV-2 infection in any transplant recipient.

A similar screening strategy has been applied to potential transplant recipients since April 20, 2020, with nasal swab collection for investigation of SARS-CoV-2 infection just before the surgical procedure. Initially, due to logistic limitations of obtaining the result in time to perform the surgery, the transplantation was performed in asymptomatic recipients screened by normal thoracic tomography, with the result of the RT-PCR test available after the transplantation. Between April 6 and June 12, 2020, 154 transplantations were performed without the result of the RT-PCR SARS-CoV-2 pretransplant test, and 3 of them were confirmed positive. After this period, the results of the RT-PCR were obtained before the surgery, except when the cold ischemia time was prolonged enough to compromise the graft viability. In this condition, another patient was submitted to transplantation without the result of the test due to a critical cold ischemia time of 36 h and was confirmed positive. Between April 6 and August 28, 2020, 20 potential recipients tested positive, with 16 being discarded and 4 of them undergoing transplantation in the conditions described earlier. In 28 days, these four patients were asymptomatic, with functioning renal graft and with the usual immunosuppression regime.

A major issue concerns the decision to reduce the initial immunosuppression intensity of the transplant. The institutional decision was to maintain the protocols, composed of induction with 1 g of methylprednisolone intraoperatively, a single dose of 3 mg/kg of thymoglobulin in the immediate postoperative period, and maintenance with tacrolimus, prednisone, and azathioprine or mycophenolate. The rationale for this decision was the possibility of high risk of acute rejection of the graft associated with an eventual reduction of the immunosuppression intensity. During this period, patients were back to the community and were subjected to with high mobility for follow-up visits and thus were more exposed to the risk of acquiring viral infections. The adoption of this conduct in this 6-month period did not lead to a negative repercussion on the evolution of transplantations performed.

In the follow-up after transplantation, face-to-face elective consultations were limited to patients who underwent transplantation within the last 1 year or for specific medical situations. In other cases, the attending physician continued telephonic visits for follow-up on the previously scheduled date. Since May 6, 2020, the emergency department of the institution was unified into a Care Unit of the Hospital Sao Paulo. Since May 15, 2020, patients with indication for hospitalization for other post-transplantation complications are subjected to RT-PCR collection. Among the 499 patients admitted for other complications, 7 (1.4%) showed positive RT-PCR test results for SARS-CoV-2.

In these circumstances, a telemedicine department was created to educate, guide, and assist symptomatic or COVID-19-positive patients; this was associated with active tracking, through telephone contact, for residents in the regions most affected by SARS-CoV-2 infection. The reference network of each patient was mapped, and clinical resolution was oriented in units closer to their personal residence, respecting the organization of the SUS line of care and using the reference and counter reference mechanisms. Diagnosed COVID-19 patients who remained isolated at home received telephone follow-up periodically, which was based on the severity of their case. Those admitted to other institutions were monitored through regular contact with the local assistant health care team.

Between March 3, 2020, the date on which the first patient with diagnosis of COVID-19 was registered in the institution, and August 28, 2020, there were 237 notifications of potential donors and 70 effectuations (30%) in our Organ Procurement Organization and a total of 375 transplants with deceased donors, as a result of the additional receipt of organs from other organ procurement organizations of the state and the country (Figure 1). When compared with the same period in 2019, there was a maintenance of the number of notifications and an increase of 19% in the number of transplants involving deceased donors. On the other hand, there was a fivefold reduction in the volume of interventional transplants (102 versus 22 procedures). The patient and graft survival within 30 days remained similar when compared with that of the previous year. Among the

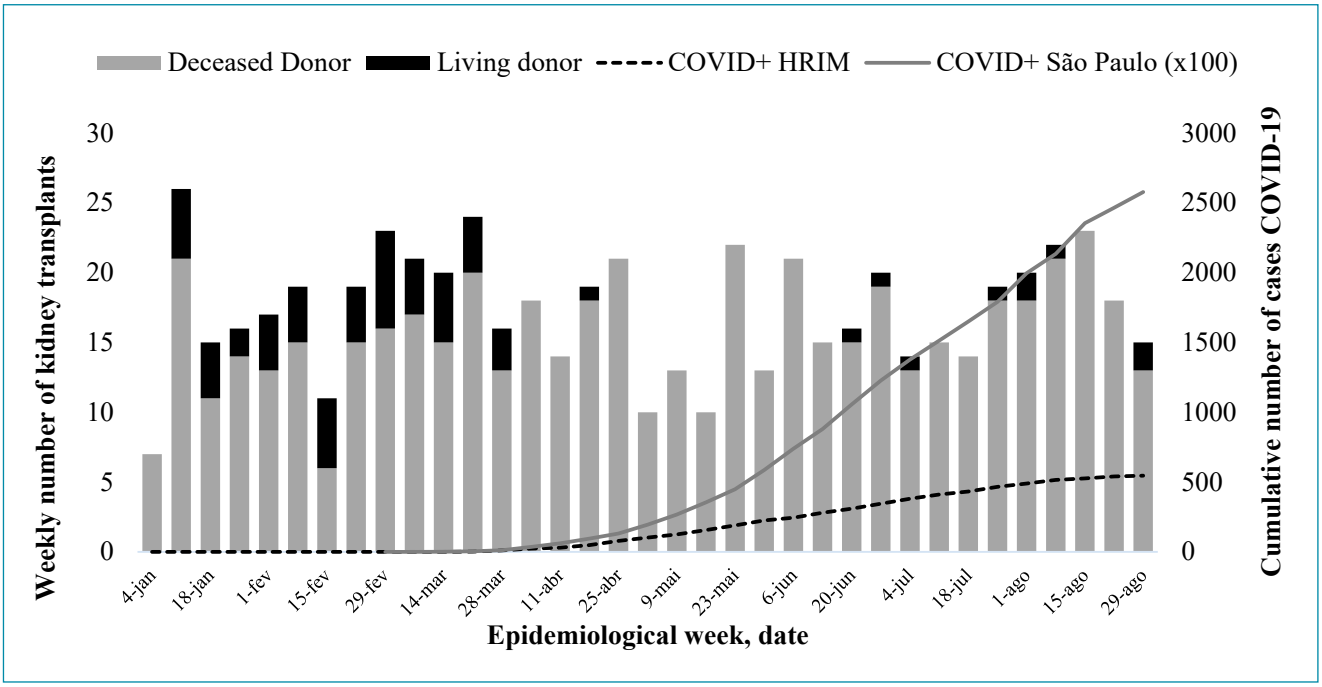

Figure 1. Number of new kidney transplants per epidemiological week during the COVID-19 pandemic among kidney transplant recipients of HRIM and the general population of São Paulo city (100×).

transplanted patients during the pandemic period, 16 developed COVID-19 by acquiring the infection in the local community, 14 readmitted, and 2 died due to the disease.

Among the 11,875 patients transplanted in outpatient follow-up, there were 546 patients with a confirmed diagnosis of COVID-19. Out of these, 372 required hospitalization and 167 required mechanical ventilation. Regarding immunosuppression during hospitalization, there was transient interruption of an antimetabolite in 69 (13%) patients, while interruption of all immunosuppressive drugs except steroids was necessary in 178 (32%) patients. Acute renal graft dysfunction occurred in 286 (52%) of the individuals and 167 (30%) required hemodialysis. There were 148 deaths, resulting in an overall fatality rate of 27%. The mortality rate was 39% among 372 patients who required hospitalization, 84% among those who required mechanical ventilation, and 85% when on mechanical ventilation and hemodialysis.

DISCUSSION

The strategies for confronting the pandemic were discussed and disseminated in all media, with massive participation of the transplant community. This communication network allowed the adoption of similar measures by several organ harvesting and transplant programs, with extensive discussions of alternatives based on the local epidemic of the disease. In the Brazilian Association for Organ Transplantation, we participated in many vital activities exchanging experience in facing the pandemic and creating awareness that the national transplantation program would be partially impacted. However, as the pandemic has a migratory character and the country has a continental dimension, we always understood that it would be possible to keep transplants concentrated in the less affected regions and we coined a phrase: "the soul of transplantation cannot die." Thus, the capillarity of the national transplant activity was kept active. The result was a national number of transplants slightly above 50% in relation to the same period last year, which guarantees all the social achievements of this activity, as well as the maintenance of civil society involvement in organ donation throughout the country. In the state of São Paulo, together with the State Transplant Center and the Regional Organ Procurement Organizations, the teams remained in the front line, making all their energy available, which resulted in the support of the programs with more than 30 years of history in the field of transplantation.

CONCLUSIONS

The COVID-19 pandemic, which is unprecedented in terms of geographic spread, poses a serious threat to overall public health and, specifically, to the solid organ transplant program. Thanks to the coordinated sequence of preventive actions and measures from a network of interprofessional and inter-institutional collaborations, it has been possible, so far, to guarantee safe access for patients with end-stage chronic kidney disease to kidney transplantation and its follow-up. In times of great challenges like COVID-19 pandemic, this initiative represents an example of relative success in maintaining the transplant program without compromising the safety of health professionals and transplanted patients who are in the follow-up.

AUTHORS' CONTRIBUTION

JMP: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. **MPC:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. **LAV:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. **RAF:** Methodology, Data curation, Formal analysis, Writing – original draft. **MRN:** Data curation, Supervision, Formal analysis, Writing – original draft. **RDF:** Conceptualization, Data curation, Formal analysis, Writing – original draft. **SBSM:** Data curation, Supervision, Writing – original draft. **DWCLS:** Validation, Writing – original draft. **WFA:** Writing – original draft. **MLSV:** Conceptualization, Writing – original draft.

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Roles of certain biochemical and hematological parameters in predicting mortality and ICU admission in COVID-19 patients

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SUMMARY

OBJECTIVE: In this study, we aimed to retrospectively analyze the roles of certain hematological and biochemical parameters in predicting mortality and intensive care unit admission in patients diagnosed with coronavirus disease 2019 (COVID-19).

METHODS: We analyzed the complete blood count and biochemical parameters of 186 COVID-19 patients by using the polymerase chain reaction test. Whether these parameters can be used to predict intensive care unit admission and mortality in the COVID-19 patients was investigated.

RESULTS: The complete blood count and biochemical parameters of COVID-19 patients and in those admitted to intensive care unit were compared. The red cell distribution width, ferritin, lactate dehydrogenase, D-dimer, C-reactive protein, prothrombin time, and creatinine levels were found to be the most significant parameters. We found that these parameters are significant for predicting not only intensive care unit admission, but also the mortality of the patients admitted to the intensive care unit.

CONCLUSIONS: We determined that the most effective parameters to predict intensive care unit admission and mortality in COVID-19 patients are ferritin, lactate dehydrogenase, D-dimer, C-reactive protein, red cell distribution width, creatinine, and intensive care unit. Close monitoring of these parameters and early intervention in alterations are of vital importance.

KEYWORDS: Coronavirus infections. Mortality. Intensive care unit. Blood coagulation. International normalized ratio. Fibrin fibrinogen degradation products. Creatinine. C-reactive protein. Erythrocyte indices.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) first appeared in the city of Wuhan, China, spread to the entire world and caused a global pandemic. The virus, which was subsequently named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has become the most serious health problem due to its rapidly increasing mortality[1]. Since much of the data about the clinical outcomes of this disease are yet to be explored, both treatment and follow-up decisions can be challenging. It is crucial to predict which patients will be admitted to intensive care unit (ICU) and which patient has a high risk of mortality.

The relation of certain hematological parameters, including hemoglobin and red cell distribution width (RDW), with both ICU admission and mortality in COVID-19 has been demonstrated in earlier studies[2,3]. It has been reported that the hemoglobin level is significantly decreased and RDW is significantly elevated in patients with severe disease. In another study, the researchers reported that the most distinct determinants for

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the differential diagnosis between community-acquired pneumonia and COVID-19 were hemoglobin and RDW values[4].

Lactate dehydrogenase (LDH) is an enzyme that converts lactate into pyruvate — a reaction that occurs in severe tissue destruction caused by sepsis, malign diseases, and severe infections in many tissues. In a study, the researchers stated that LDH level was an indicator for pneumonia caused by COVID-19, which increases with severe pneumonia and decreases when pneumonia was resolved, but a cutoff value could not be given[5].

In a recent systematic research and meta-analysis reviewing 15 studies, low platelet count, elevated C-reactive protein (CRP), and LDH were found to be associated with mortality in COVID-19 patients[6]. In another meta-analysis reviewing 10 studies, elevated liver enzymes, including alkaline phosphatase (ALP) and alanine aminotransferase (ALT), decreased albumin, elevated creatinine kinase (CK), and most importantly, elevated LDH were pointed out[6]. Another study argued that procalcitonin (PCT), CRP, and LDH levels demonstrated significant elevations in a pooled laboratory analysis of children with mild and severe COVID-19, and the elevation of CK-MB could predict early cardiac injury in children[7]. In a different study, laboratory markers were compared in patients with severe and mild COVID-19 disease and the authors stated that especially low lymphocyte count, ferritin, D-dimer, CRP, cardiac troponin, and LDH were significant parameters with predictive value[8].

Liu et al.[9] reported that CRP and interleukin 6 (IL-6) levels increased in severe stages of the disease, and CRP >41.8 mg/L may be an independent risk factor for progression in the early stage COVID-19 patients. In a recent study, Wang[10] claimed that elevated CRP accompanies lung lesions and therefore reflects the severity of disease. In an article exploring the hematological findings and complications of COVID-19, Terpos et al.[11] reported elevated D-dimer, prolonged prothrombin time (PT), and activated partial thromboplastin time (aPTT), resulting in disseminated intravascular coagulation, in addition to the increase in CRP, IL-6, and LDH levels. Similarly, many recent studies demonstrated neutrophil/lymphocyte ratio as an independent risk factor for the severe COVID-19 disease[12].

It is evident from the studies in the literature that various parameters are used in determining severe and mild COVID-19 infection. However, the parameters that are effective in determining ICU admission and mortality of these patients should be clearly revealed. For these reasons, in this study, we aimed to retrospectively analyze the roles of certain hematological and biochemical parameters in predicting mortality and ICU admission in patients diagnosed with COVID-19 disease.

METHODS

Patients

All the confirmed and hospitalized COVID-19 patients in the University of Health Sciences Izmir Bozyaka Training and Research Hospital between March 2020 and August 2020 were included in this study. Cases were diagnosed according to the interim guidance report of the World Health Organization (WHO)[13] and to the diagnosis and treatment guidelines of COVID-19 of Ministry of Health in Turkey[14]. Patients met all the following conditions:

1. contact history;
2. fever or other respiratory symptoms;
3. typical computed tomography (CT) image findings suggestive of viral pneumonia, and;
4. positive result of real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA. Sputum and throat swab specimens were collected from all patients on admission and tested by RT-PCR for SARS-CoV-2 RNA within 3 hours.

Clinical characteristics and laboratory data

Data of patients with COVID-19, including recent exposure history, clinical symptoms and signs, and laboratory findings, were obtained from electronic medical records. Laboratory assessments included complete blood count (CBC), biochemistry, and coagulation studies. The severity of disease was defined based on the international guidelines for community-acquired pneumonia. The result was cure and discharge, or mortality within 28 days.

This study was approved by the University of Health Sciences Izmir Bozyaka Training and Research Hospital Ethics Committee on Clinical Research (N°. 222/2019).

Statistical analysis

Statistical analyses were performed using SPSS version 17.0 software. The suitability of variables to normal distribution was examined using the analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test). Mean ± standard deviation was used for descriptive analyses. Deviation is given as frequency and percentage. Descriptive statistics were made by representing demographic characteristics as frequency and percentage values. In continuous data, the Mann–Whitney *U*-test or Student's *t*-test was used to compare binary variables in independent groups, such as mortality or ICU admission (Yes or No). Paired t-test or Wilcoxon signed rank test was used to compare biochemical parameters. The Pearson's χ^2 or Fisher's exact chi-square test was used in the analysis of categorical data. The sensitivity and specificity of biochemical parameters that may be the predictors of ICU admission

and survival (or death) were determined by receiver operating characteristic (ROC) analysis. The cases where the p-value was <0.05 were considered statistically significant.

RESULTS

The total number of patients hospitalized due to COVID-19 was 186. Their mean age was 56.0±18.5 years, where the youngest was 18 and the oldest was 96 years old. The mean age of the patients who were admitted to ICU (n=40) was 69.5±16.3 years, while it was 52.3±17.3 years for those who were not admitted (n=146). The difference between these groups was statistically significant (p<0.001, t=-5.622). The mean age of those who did not survive (n=30) was 71.8±14.6 years, while the mean age of those who survived (n=156) was found to be 53.0±17.6 years, with a statistically significant difference (p<0.001, t=5.482).

The biochemical parameters of patients who were and were not admitted to ICU were analyzed using the ROC analysis. The cutoff values and sensitivity–specificity ratios of the analyzed biochemical parameters, according to ICU admission, are shown in Table 1. The parameters with the most prognostic values were found to be ferritin, LDH, D-dimer, and CRP. In addition, the parameters other than ALT and aPTT may also predict ICU admission (Figure 1).

The biochemical parameters of COVID-19 patients were also analyzed for the risk of mortality using the ROC analysis. The cutoff values and sensitivity–specificity ratios of the analyzed biochemical parameters are shown in Table 2. The parameters with the most prognostic values were found to be RDW, D-dimer, LDH, urea, creatinine, PT, international normalized ratio (INR), CRP, and ferritin. However, the parameters other than ALT and CK may also predict mortality (Figure 2).

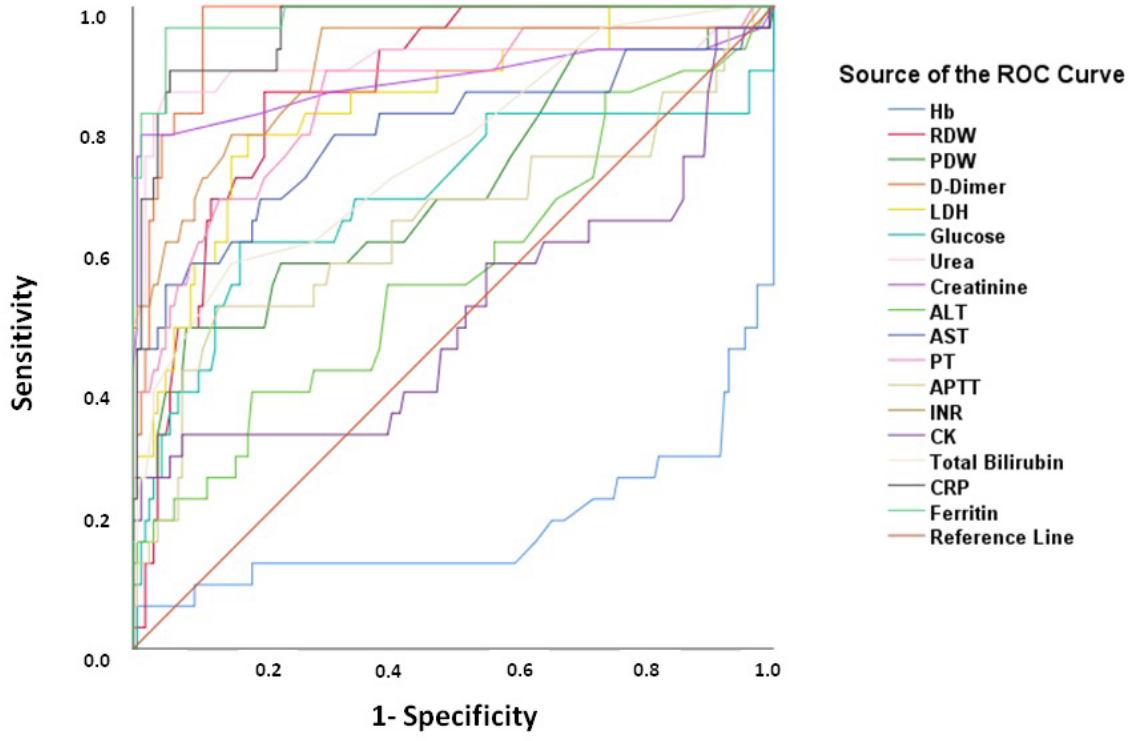
In our analyses, hemoglobin and RDW parameters exhibited the most distinct differences. However, the sensitivity and specificity of hemoglobin were remarkably low (for ICU admission, AUC: 0.290, sensitivity: 20.5%, and specificity: 59.3%). On the other hand, RDW values appeared to have higher significance on ICU admission and mortality as the sensitivity and specificity rates were much higher (AUC: 0.710, sensitivity: 71.8, and specificity: 75.9 for mortality; AUC: 0.869, sensitivity: 86.7%, and specificity 79.5% for ICU admission). A cutoff value of 15% and above for RDW appears significant in terms of mortality.

CRP, which is an inflammation marker, is found to be significant for mortality and ICU admission. For mortality, AUC

Table 1. Comparison of parameters at the time of ICU admission

Parameters	Cutoff Value	AUC	p-value	95%CI [min–max]		Sensitivity (%)	Specificity (%)
Hb	13.8	0.290	<0.001	0.185	0.396	20.5	59.3
RDW	13.8	0.710	<0.001	0.602	0.818	71.8	75.9
PDW	12.6	0.678	0.001	0.572	0.784	59.0	77.2
D-dimer*	326.0	0.867	<0.001	0.811	0.924	76.9	80.0
LDH*	316.0	0.870	<0.001	0.812	0.928	54.0	95.4
Glucose	122.5	0.754	<0.001	0.665	0.844	64.1	71.0
Urea	36.5	0.739	<0.001	0.633	0.846	69.2	78.6
Creatinine	1.25	0.304	<0.001	0.207	0.400	16.4	55.0
ALT	33.5	0.499	0.986	0.388	0.610	35.9	74.5
AST	31.5	0.723	<0.001	0.612	0.834	71.8	71.0
PT	12.8	0.692	<0.001	0.577	0.806	69.2	69.7
APTT	31.1	0.448	0.315	0.340	0.555	25.6	67.6
INR	11.4	0.784	<0.001	0.692	0.875	74.4	69.7
CK	159.0	0.389	0.034	0.276	0.503	20.5	80.0
Total Bilirubin	5.5	0.684	<0.001	0.584	0.785	56.4	71.0
CRP*	149.5	0.826	<0.001	0.759	0.893	79.5	76.6
Ferritin*	234.0	0.883	<0.001	0.821	0.945	87.2	84.1

AUC: area under the curve; CI: confidence interval (95%); Hb: hemoglobin; RDW: red cell distribution width; PDW: platelet distribution width; LDH: lactate dehydrogenase; ALT: alanine transaminase; AST: aspartate transaminase; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; CK: creatinine kinase; CRP: C-reactive protein. p<0.05 was considered significant. *Important predictors for intensive care unit admission.



ROC: Receiver Operating Characteristic.

Figure 1. ROC analysis of biochemical parameters related to intensive care unit admission.

Table 2. Comparison of parameters at mortality

Parameters	Cutoff value	AUC	p-value	95%CI [min–max]		Sensitivity (%)	Specificity (%)
Hb	13.8	0.189	<0.001	0.076	0.301	13.3	67.9
RDW*	15.0	0.869	<0.001	0.811	0.928	86.7	79.5
PDW	12.7	0.714	<0.001	0.601	0.827	60.0	76.9
D-dimer*	488.5	0.965	<0.001	0.941	0.989	96.7	89.1
LDH*	370.0	0.846	<0.001	0.766	0.926	50.0	93.6
Glucose	107.0	0.702	<0.001	0.574	0.829	70.0	65.4
Urea*	55.5	0.913	<0.001	0.829	0.998	86.7	94.9
Creatinine*	1.5	0.792	<0.001	0.702	0.881	43.3	96.2
ALT	48.5	0.586	0.137	0.464	0.708	40.0	81.4
AST	37.0	0.801	<0.001	0.693	0.909	70.0	80.1
PT*	13.6	0.854	<0.001	0.772	0.937	70.0	86.5
APTT	32.1	0.660	0.006	0.532	0.787	60.0	69.2
INR*	1.25	0.901	<0.001	0.831	0.972	70.0	90.4
CK	71.5	0.521	0.717	0.386	0.656	60.0	44.9
Total bilirubin	0.8	0.772	<0.001	0.674	0.871	60.0	84.6
CRP*	160.5	0.964	<0.001	0.936	0.992	70.0	98.7
Ferritin*	538.5	0.984	<0.001	0.967	1.000	96.7	94.9

AUC: area under the curve; CI, confidence interval (95%); Hb: hemoglobin; RDW: red cell distribution width; PDW: platelet distribution width; LDH: lactate dehydrogenase; ALT: alanine transaminase; AST: aspartate transaminase; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; CK: creatinine kinase; CRP: C-reactive protein. p<0.05 was considered significant. *Significant predictors for mortality.

was 0.964, sensitivity was 70.0%, and specificity was 98.7%, while the cutoff value was 160.5 mg/L. For ICU admission, AUC was 0.826, sensitivity was 79.5%, specificity was76.6%, and the cutoff value was 149.5 mg/L.

LDH, another significant parameter for both ICU admission and mortality, has an AUC of 0.870, sensitivity of 76.9%, and specificity of 82.1% with the cutoff value of 316.0 U/L for ICU admission, and an AUC of 0.846, sensitivity of 80.0%, and specificity of 82.1% with the cutoff value of 370.0 U/L for mortality.

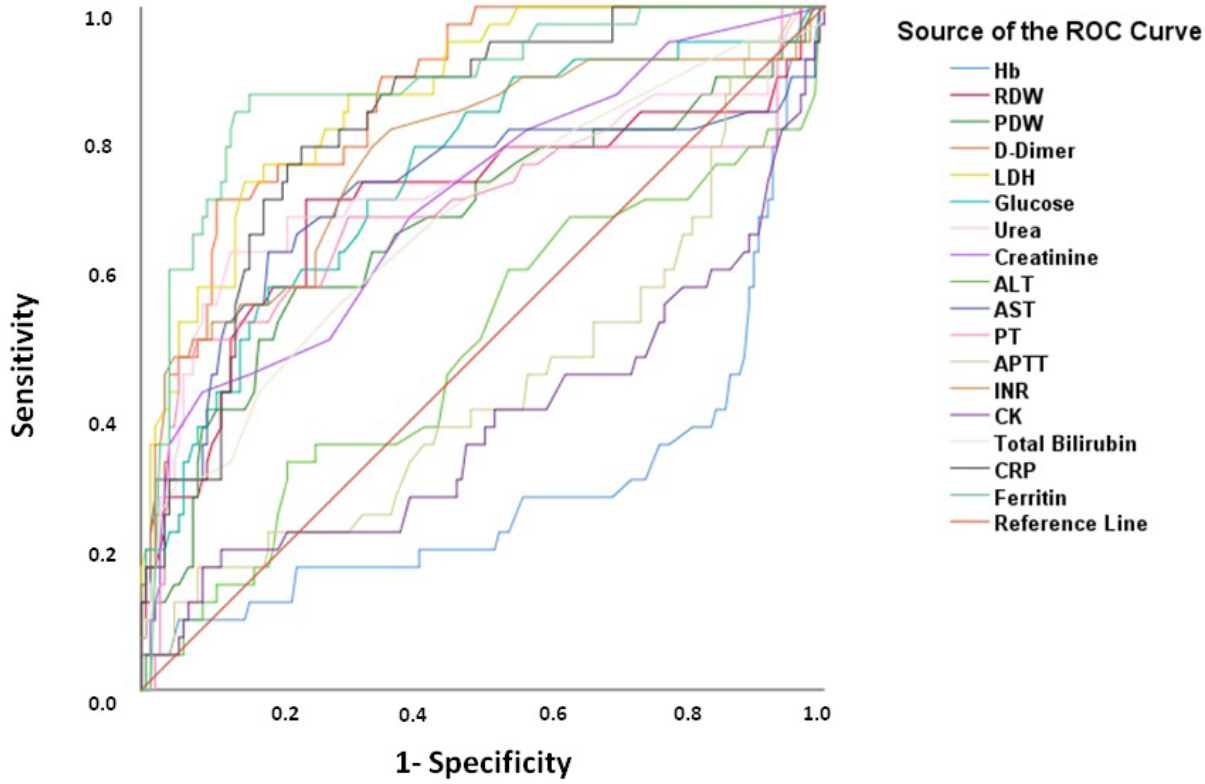
The elevated levels of ferritin were found to be an important risk factor for ICU admission and mortality. For ICU admission, AUC was 0.883, sensitivity was 87.2%, and cutoff value was 234, while for mortality AUC was 0.984, sensitivity was 96.7, specificity was 94.9%, and cutoff value was 538.5. As can be seen, ferritin is much more significant in terms of mortality.

It is observed that D-dimer, LDH, CRP, and ferritin levels predict the risk for both ICU admission and mortality. In terms of D-dimer, AUC was 0.867, sensitivity was 76.9%, specificity was 80.0%, and cutoff value was 326 for ICU admission, while the AUC was 0.965, specificity was 89.1%, sensitivity was 96.7%, and cutoff value was 488.5 for mortality. Considering the AUC values, it can be concluded that D-dimer level is especially more significant for mortality.

The elevated levels of urea, creatinine, PT, and INR had no statistically significant impact on ICU admission, yet they were significant for mortality. In terms of mortality, the cutoff value for urea was 55.5, AUC was 0.913, specificity was 94.9%, and sensitivity was 86.7. The cutoff value for creatinine was found to be 1.5, AUC 0.885, sensitivity 80.0%, and specificity 98.7%. Previous reports in the literature also found that creatinine values increased in severe COVID-19 patients[18]. The cutoff values for PT and INR were 13.6 and 1.25, AUC values were 0.854 and 0.901, specificity values were 86.5% and 90.4%, respectively, and sensitivity was 70.0% for both parameters.

DISCUSSION

COVID-19 is a viral infection that possesses a serious public health threat and results in high mortality at present. Worldwide, countries are experiencing serious challenges with the pandemic, both in terms of economy and burden on health systems.



ROC: Receiver Operating Characteristic.

Figure 2. ROC analysis of biochemical parameters related to mortality.

New disease-related findings are being revealed day by day and the treatment-related algorithms are continuously updated.

There are many studies in the literature which report that CBC abnormalities, especially low lymphocyte and platelet counts, and neutrophil/monocyte ratio affect prognosis. In this study, hemoglobin and RDW values were more distinctly different. However, the sensitivity and specificity of hemoglobin were remarkably low. On the other hand, the RDW values appeared to have higher significance on ICU admission and mortality as the sensitivity and specificity rates were much higher. A cutoff value of 15% and above for RDW appears significant in terms of mortality. In one study, it was shown that the RDW level with AUC value of 0.870 can be helpful in differentiating COVID-19 from community-acquired pneumonia[2].

In terms of biochemical parameters, D-dimer, LDH, CRP, and ferritin levels determined the risk of ICU admission while D-dimer, LDH, urea, creatinine, PT, INR, CRP, and ferritin predicted the risk of mortality.

In a study from Wuhan, China, Zhou et al.[15] reported that D-dimer is an independent risk factor for disease course and is significantly increased in severe pneumonia cases. In another study by different researchers in the same area, it was reported that the clinicians should be alert in the early period when D-dimer is >1 μg/mL[16]. Similarly, Li et al.[17] showed that the mean D-dimer level was 0.6 μg/mL (0.2–5.0) in severe cases.

A meta-analysis revealed that LDH levels were higher in severely ill patients than nonsevere patients as with the case in ICU than non-ICU patients[18]. Similarly, Wu et al[5]. evaluated 10 severe and 77 nonsevere patients with COVID-19 pneumonia and found that the mean LDH level was 442±17.47 U/L in nonsevere cases and 1040±158.3 U/L in severe cases. The researchers mentioned that the high LDH level was mostly due to the very wide normal range of the kit used[5]. In this study, the cutoff values were 316 and 370, while others report the levels of 401–435 U/L.

In a study that assessed the clinical parameters showing the severity of COVID-19, Shang et al.[19] reported that mean CRP level was 43.15 in severe cases and 10.05 in mild cases. In another study, the authors found that mean CRP level was 40 mg/L in COVID-19 survivors, while it was 125 mg/L in those who died[8]. In a study on CRP levels in the early disease period, the CRP was found to be 54.15±1.06 in the group with severe condition and 105±12.73 in the group with critical condition[10]. Although our findings on CRP values are consistent with the literature, it should be noted that the majority of those studies, excluding meta-analyses, had relatively lower sample size than that of our study.

In a study, Velavan et al.[8] claimed that ferritin is increased in COVID-19 patients with hemophagocytic lymphohistiocytosis and more cytokine storm. Consistently, Terpos et al.[11] stated that the ferritin level increases very high in ARDS development. There were also authors who claimed that there was a relationship between death and ferritin levels.

Velavan et al.[8] also noted that the PT was increased in patients admitted to ICU and aPTT was increased in nonsurvivors. Although the cutoff values of the parameters are close to normal values, the high AUC values indicate that they may still be significant despite their being relatively low for mortality.

Our findings indicated that the RDW levels of patients diagnosed with COVID-19 significantly predicted both ICU admission and mortality. We also showed that PT, INR, urea, and creatinine values were significant in terms of predicting mortality along with D-dimer, LDH, CRP, and ferritin. With the predictions of these values, fast and aggressive interventions can be made in the treatment plans.

The major limitation of this study was the relatively low sample size, considering the size of the pandemic and the total number of patients is growing beyond 150 million worldwide. With this study, we aimed to analyze the roles of certain hematological and biochemical parameters in predicting mortality and ICU admission in patients diagnosed with COVID-19, and revealed the cutoff values for these predictive parameters.

AUTHORS' CONTRIBUTIONS

FB: Investigation, Project Administration,Supervision, Methodology.
ŞÇ: Data Curation, Validation, Visualization, Formal Analysis.
ID: Resources, Software, Funding Acquisition, Conceptualization.
OB: Writing – Original Draft, Writing – Review& Editing

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Evaluation of coagulation parameters: Coronavirus disease 2019 (COVID-19) between survivors and nonsurvivors

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SUMMARY

OBJECTIVE: This study aims to investigate and compare the coagulation parameters of coronavirus disease 2019 (COVID-19) patients with mortal and nonmortal conditions.

METHODS: In this study, 511 patients diagnosed with COVID-19 were included. Information about 31 deceased and 480 recovered COVID-19 patients was obtained from the hospital information management system and analyzed retrospectively. Whether there was a correlation between coagulation parameters between the mortal and nonmortal patients was analyzed. Descriptive analyses on general characteristics of the study population were performed. Visual (probability plots and histograms) and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk test) were used to test the normal distribution. Analyses were performed using the SPSS statistical software package.

RESULTS: Out of 511 patients, 219 (42.9%) were females and 292 (57.1%) were males. There was no statistically significant difference between males and females in terms of mortality (p=0.521). In total, the median age was 67 (22). The median age was 74 (13) in the nonsurvivor group and 67 (22) in the survivor group, and the difference was statistically significant (p=0.007). The D-dimer, prothrombin time, international normalized ratio, neutrophil, and lymphocyte median age values with p-values, in the recovered and deceased patient groups were: 1070 (2129), 1990 (7513) µg FEU/L, p=0.005; 12.6 (2.10), 13.3 (2.1), p=0.014; 1.17 (0.21), 1.22 (0.19), p=0.028; 5.51 (6.15), 8.54 (7.05), p=0.001; and 0.99 (0.96), 0.64 (0.84), p=0.037, respectively, with statistically significant differences.

CONCLUSIONS: As a result of this study, D-dimer, prothrombin time, and international normalized ratio increase were found to be associated with mortality. These parameters need to be closely monitored during the patient follow-up.

KEYWORDS: Coronavirus infections. Blood coagulation. International normalized ratio. Prothrombin time. Fibrin fibrinogen degradation products.

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INTRODUCTION

The SARS-CoV-2 virus responsible for the COVID-19 pandemic first appeared in the city of Wuhan, China. Similar to SARS-CoV and MERS-CoV, it is also believed to be transmitted from animals to humans. On February 11, 2020, the World Health Organization (WHO) named this disease, caused by the novel coronavirus, as COVID-19 and recognized as a pandemic[1].

The incubation period of SARS-CoV-2 infection is between 2 and 10 days. Flu-like symptoms, such as fever, chills, cough, myalgia, and headache, are the main symptoms in this infection. High fever was not always present in the elderly patients. Respiratory symptoms appear approximately after 3 days of the onset of fever. Cough, shortness of breath, and oxygen deficiency are among the most significant symptoms[2].

Severe illness was reported in 16% of the cases hospitalized due to COVID-19. Venous thromboembolism (VTE) increased in patients with severe respiratory distress[3]. Coagulopathy and associated complications are common in patients with severe COVID-19[4]. The lifespan of platelets in circulation is about 7–10 days. Of them, one-third are found in the spleen and two-third are found in circulation. Thrombocytopenia, which occurs due to decreased production of platelets, may occur due to the involvement in the spleen or increased degradation. Infections can often cause thrombocytopenia since they suppress hematopoiesis[5].

The D-dimer is one of the important tests of the coagulation system and is formed by the activation of this system for any reason and degradation of the cruciate ligament by plasmin. In clinical studies, the D-dimer is mostly used in the diagnosis and follow-up of VTE and disseminated intravascular coagulation (DIC)[6]. In the literature, the D-dimer levels were also reported to be high in patients with severe COVID-19[7]. The D-dimer levels were found to be high in 59.6% of the COVID-19 patients[4]. It has also been stated that macrophage activation syndrome (MAS) may occur during the course of the infection in COVID-19 patients. The presence of persistent fever, elevated D-dimer levels in repeated measurements, lymphopenia, and thrombocytopenia in spite of treatment show that the disease is accompanied by the MAS[7]. The D-dimer levels were high in approximately half of the patients hospitalized with COVID-19 infection, and the reported levels were ≤0.5 µg/mL in 32% of the patients, 0.5–1 µg/mL in 26% of the patients, and >1 µg/mL in 42% of the patients[8].

The prothrombin time (PT) and international normalized ratio (INR) tests are primarily used to evaluate the extrinsic pathway of coagulation[9]. These tests were reported to be statistically significant and were at higher levels in COVID-19 patients compared to the healthy control group[10].

According to a review, the use of contraceptives and the women under menopause hormone therapy may have a greater risk of thromboembolism[11]. Hence, ensuring proper use of contraception is very important in COVID-19 period[12].

Since the COVID-19 pandemic is quite a recent phenomenon, studies on the characteristics and treatment of the virus and the disease are yet to be added in the literature. However, despite the numerous published scientific studies, there is not adequate and accurate information available about COVID-19 infection and its treatment. Considering the pathogenesis of the disease, manifestation, and test results in patients, it is observed that coagulation mechanisms/tests are impaired/affected in this infection.

There are a few studies in the literature, investigating the coagulation parameters, D-dimer, PT, platelet count in COVID-19 patients. The present study aims to investigate and compare the coagulation parameters of the deceased and survived COVID-19 patients.

METHODS

This study was approved by the Sakarya University Medical Faculty Ethics Committee (20.05.2020/No. 4637). A total of 511 patients who were diagnosed with COVID-19 were included in this study. Of these, information about 31 deceased patients and 480 recovered patients was obtained from the hospital information management system and analyzed retrospectively. COVID-19 was diagnosed by clinical findings such as computed tomography and SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR). The coagulation parameters such as platelet, D-dimer, and PT, and hematological parameters such as hemoglobin (HGB), hematocrit (HCT), neutrophil (NEU), lymphocyte (LYM), and neutrophil–lymphocyte ratio (NLR) were evaluated.

Sample collection, nucleic acid isolation, and RT-PCR

Combined nasopharynx and oropharynx swab samples were collected using Dacron swab, placed in viral transport medium immediately, and delivered to the laboratory by keeping them at 2–8°C in accordance with the rules of cold chain with the triple transport system, complying the infection prevention and control procedures.

After receiving the samples in microbiology laboratory, samples were taken to a negative pressure chamber with third-level biosafety. Bio-Speedy® Viral Nucleic Acid Isolation Kit (Bioeksen, Turkey) was used for total nucleic acid isolation from the specimens. The isolation procedure was carried out according to the recommendations of the manufacturer.

Bio-Speedy® COVID-19 RT-qPCR Detection Kit (Bioeksen, Turkey) was used for the RT-PCR assays. The PCR amplification and evaluation of the results were carried out according to the recommendations of the manufacturer.

Complete blood count and coagulation parameters

Hemogram tests were performed on CELLDYN 3700 (Abbott, USA) device, and D-dimer and PT tests were performed on DIAGON COAG XL (DIAGON, Hungary) device.

For the PT standardization, a model was defined based on the INR. The INR value can be calculated using the following equation: INR=(PT patient/PT Average Normal) ISI.

Statistical analysis

Descriptive analyses were performed to provide information on general characteristics of the study population. Visual (probability plots and histograms) and analytical (Kolmogorov–Smirnov and Shapiro–Wilk test) methods were used to test the normal distribution. Descriptive analyses were presented using medians and interquartile range (IR) for the non-normal distributed variables. The Mann–Whitney *U* test was used for nonparametric tests to compare these parameters. Pearson's χ^2 test was used to compare the categorical variables between two groups. The categorical variables were presented in frequencies (%). A p-value<0.05 was considered significant. Analyses were performed using the SPSS statistical software package (IBM SPSS Statistics, Version 22.0, IBM Corp., Armonk, NY). The result of post hoc power analysis of INR is 18%, and PT is 21%.

RESULTS

Out of the 511 patients included in this study, 219 (42.9%) were females and 292 (57.1%) were males. There was no statistically significant difference between males and females in terms of mortality (p=0.521). In total, the median age (IR) was 67 (22). The median age was 74 (13) in the nonsurvivor group and 67 (22) in the survivor group, and the difference was statistically significant (p=0.007). The D-dimer, PT, INR, NEU, LYM values (IR), with p values, in the recovered and deceased patient groups were: 1070 (2129), 1990 (7513) µg FEU/L, p=0.005; 12.6 (2.10), 13.3 (2.1), p=0.014; 1.17 (0.21), 1.22 (0.19), p=0.028; 5.51 (6.15), 8.54 (7.05), p=0.001; and 0.99 (0.96), 0.64 (0.84), p=0.037, respectively with statistically significant differences. NLR was 5.3 (9.59) in the survivor group and 11.18 (16.58) in the nonsurvivor group, and the difference between the two groups was statistically significant (p<0.001) (Figure 1). The HGM, HCT, and PLT values (IR), along with p values, in the recovered and deceased patient groups were: 11.9 (2.70), 11.5 (2.40), p=0.691; 37.3 (8.13), 36.2 (7.40), p=0.644; and 207 (129.75), 229 (138), p=0.758, respectively. There was no statistically significant difference (Table 1).

DISCUSSION

COVID-19 infection may have a variety of clinical outcomes ranging from viral pneumonia with severe respiratory failure to mortality[8]. During the infection, abnormalities are observable in some blood parameters in comparison to the pathogenesis of the disease. In this study, some coagulation and hemogram test parameters were investigated in the survived and deceased COVID-19 patients.

According to the previous studies, although individuals in the above-middle age group were affected by COVID-19, older individuals were more likely to develop a severe disease[13]. In this study, it was found that the COVID-19 patients were of old age (median 67 years, 22) and the deceased patients were of advanced age with an average age of 74 (13).

The thrombotic complications cause significant problems in the COVID-19 patients[14] Studies showed that thrombocytopenia was found in 36.2% COVID-19 patients[20]. In severe cases, it was found to be 57.7%[4]. A meta-analysis has shown significant thrombocytopenia in severe cases of COVID-19 patients, and this decreased platelet count was five times higher in some cases[15]. Similar to other viral infections, COVID-19 infection also activates clotting and causes excessive activation of platelets. In addition, it may cause systemic inflammatory response, affecting the procoagulant and anticoagulant mechanisms in hemostasis, thus

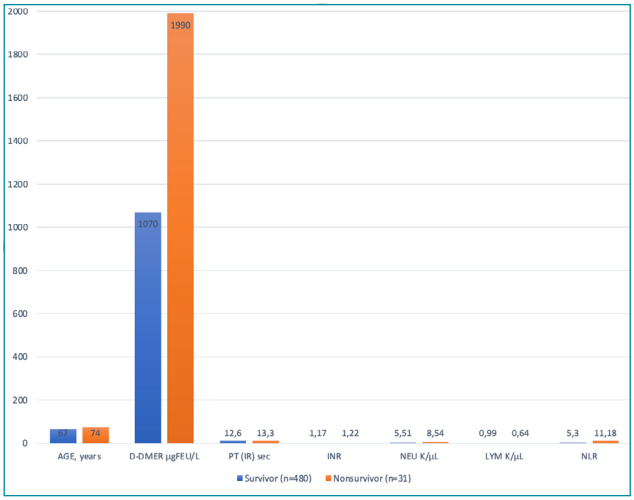

Figure 1. Parameters of the survivor and nonsurvivor patient groups.

distorting the balance between the two[16]. In the autopsies of deceased patients due to COVID-19 disease, there were thrombus in capillaries and small vessels, and numerous microthrombi in the liver venous portal system[17,18]. It may cause hypoxia due to the respiratory distress caused by COVID-19 in the lungs. As a result of this hypoxia, viscosity increases, and thrombus formation accelerates and increases[19]. Recent studies have reported that thrombosis and occlusion occur in small vessels in the lungs of severe cases of COVID-19[20]. The platelet level dropped below 100,000 in 20% of deceased patients, while this ratio was only 1% in survivors (p<0.001)[8]. In the comparison of thrombocytes of COVID-19 patients with that of healthy control group, no statistically significant difference was found[14]. Studies in COVID-19 patients found that the platelet values were low despite treatment[7]. In this study, there was no statistically significant difference between the COVID-19 survivors and nonsurvivors in terms of the platelet level (p<0.758).

The D-dimer levels were found to be higher in severe COVID-19 patients, indicating its association with mortality. In addition, these patients mostly have a coagulation disorder[4,21]. Fibrin degradation products and a significant increase in the D-dimer values result in the formation of large amounts of microthrombi in the body of patients with COVID-19. The formation of these thrombi and the combination of increased fibrinogen values with other data suggest a rapid increase in coagulation in these cases[22]. Studies have shown that there was an increase in D-dimer values by 46.4% in patients infected with COVID-19[21]. D-dimer prolongation is observed in the COVID-19 cases with poor prognosis[4]. In this study, a statistically significant difference was found in the D-dimer levels between recovered and deceased patients (p<0.005).

Some studies showed prolonged PT and INR[4]. In this study, the PT and INR levels were found increased in the nonsurvivors. In the comparison of the PT and INR values of the nonsurvivors with those of the survivors, a statistically significant difference was found (p<0.014 and p<0.028, respectively).

Studies have shown a higher NLR in COVID-19 patients, and NLR was found to be an independent prognostic biomarker for them[23]. NEUs, LYMs, and platelets play an important role in inflammation and used to identify many infections and types of cancer nowadays. In this study, the NLR values were 5.3 in the survivor group and 11.8 in the nonsurvivor group, with statistically significant difference (p<0.000).

Lymphopenia was detected in COVID-19 patients[23] In this study, lymphopenia was detected in the nonsurvivors group, showing statistically significant difference in LYM values between them and survivors (p<0.037).

There were no comparative studies on the HCB and HCT values in COVID-19 patients. We found that there was no statistically significant difference in the HCB and HCT values between nonsurvivors and survivors.

Owing to the small population size, we were unable to investigate more coagulation parameters (such as, fibrinogen and coagulation factors), which is a limitation of this study.

Table 1. Statistical data of the survivor and nonsurvivor patient groups.

Parameters	Total (n=511)	Survivors (n=480)	Nonsurvivors (n=31)	p
Age, years (IR)	67 (22)	67 (22)	74 (13)	0.007
Female, n (%)	219 (42.9)	204 (93.2)	14 (6.8)	0.521
Male, n (%)	292 (57.1)	276 (94.5)	16 (5.5)	
D-Dimer (IR), µg FEU/L	1090 (2270)	1070 (2129)	1990 (7513)	0.005
PT (IR), s	12.70 (2.15)	12.6 (2.10)	13.3 (2.1)	0.014
INR (IR)	1.17 (0.20)	1.17 (0.21)	1.22 (0.19)	0.028
NEU (IR), K/µL	5.73 (6.24)	5.51 (6.15)	8.54 (7.05)	0.001
LYM (IR), K/µL	0.99 (0.98)	0.99 (0.96)	0.64 (0.84)	0.037
NLR (IR)	5.99 (10.23)	5.3 (9.59)	11.18 (16.58)	0.000
HGB (IR), g/dL	11.9 (2.70)	11.9 (2.70)	11.5 (2.40)	0.691
HCT (IR), %	37.10 (8.10)	37.3 (8.13)	36.2 (7.40)	0.644
PLT (IR)	207 (130.5)	207 (129.75)	229 (138)	0.758

IR: interquartile range; FEU/L: fibrinogen equivalent units/Liter; PT: prothrombin time; INR: international normalized ratio; NEU: neutrophil; LYM: lymphocyte; NLR: neutrophil-lymphocyte ratio; HGB: hemoglobin; HCT: hematocrit; PLT: platelet.

CONCLUSION

We found that advanced age, increases in D-dimer, PT, INR, NEU and NLR values, and decrease in LYM levels were associated with mortality. These parameters need to be closely monitored during the patient follow-up. More comprehensive studies are needed on this subject.

AUTHORS' CONTRIBUTIONS

MO: Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **EC:** Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **SY:** Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **MK:** Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **ACG:** Conceptualization, Data Curation, Formal Analysis, Writing – Review & Editing. **DC:** Conceptualization, Data Curation, Formal Analysis, Writing – Review & Editing. **YA:** Conceptualization, Data Curation, Formal Analysis, Writing – Review & Editing. **AK:** Data Curation, Formal Analysis, Writing – Review & Editing. **AFE:** Data Curation, Formal Analysis, Writing – Review & Editing. **OK:** Data Curation, Formal Analysis, Writing – Review & Editing.

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Evaluation of cardiac parameters between survivors and nonsurvivors of COVID-19 patients

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SUMMARY

OBJECTIVE: The present study compares the cardiac parameters of the survivor and nonsurvivor patients with COVID-19 infection.

METHODS: This study was conducted in 379 patients diagnosed with COVID-19 disease. Information of 21 nonsurvivor and 358 survivor patients with COVID-19 was obtained from the hospital information management system and analyzed retrospectively. Relationship between cardiac parameters in patients categorized into the mortal and immortal groups was investigated.

RESULTS: Of the total 379 patients involved in this study, 155 (40.9%) were females and 224 (59.1%) were males. No statistically significant difference in mortality was found between females and males (p=0.249). The total median age was 70, the median age in the nonsurvivor group was 74 (35–89), and it was 69.5 (18–96) in the survivor group (p=0.249). The median values of high-sensitivity troponin (hs-Tn), creatine kinase MB form, and especially myoglobin in the survivor and nonsurvivor groups were 25/64.9 (p=0.028), 18/23 (p=0.02), and 105.5/322.4 (p<0.001), and the difference was statistically significant. Comparing mortality, while there was 1 (0.7%) nonsurvivor out of 134 patients in the service unit, there were 20 (8.2%) nonsurvivors out of 245 patients in the intensive care unit. This difference was statistically significant (p=0.003). The cutoff value of myoglobin, which may pose a risk of mortality, was found to be 191.4 µg/L, while it was 45.7 ng/l for hs-Tn and 60.1 U/L for creatine kinase MB.

CONCLUSIONS: Advanced age and increased levels of high-sensitivity troponin, creatine kinase MB, and myoglobin were found to be associated with mortality.

KEYWORDS: Troponin. Creatine kinase, MB form. Myoglobin. Mortality. Coronavirus infections.

INTRODUCTION

Coronaviruses cause severe acute respiratory syndrome (SARS) and were first appeared in 2002. The first zoonotic infection, which appeared in China in 2003, lead to SARS. The second coronavirus infection, Middle East Respiratory Syndrome (MERS), was found in Saudi Arabia in 2012. The coronavirus disease 2019 (COVID-19), which first appeared in city of Wuhan, the capital of China's Hubei Province, has caused infections that have resulted in a pandemic with a significant impact on health and lives of people. It has first spread

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in China, causing pneumonia-like disease. In January 2020, a novel SARS coronavirus (SARS-CoV-2, previously known as 2019-CoV), was reported by Chinese scientists linked to this disease[1-3].

As with SARS and MERS coronaviruses, the SARS-CoV-2 spike (S) protein uses the angiotensin-converting enzyme 2 (ACE2) receptor for host cell entry[4]. The main target cells of the virus are type II pneumocytes and enterocytes, where ACE2 expression is high[5]. The S protein binds to the catalytic domain of ACE2 with high affinity. Binding of the S protein to ACE2 causes a conformational change in the S protein of the coronavirus, allowing proteolytic digestion by host cell proteases, and thus viral RNA enters and infects the cell[4,5].

COVID-19 infection spreads especially through droplets and direct contact among people, and is quite contagious. Although the incubation period is 5.5 days on average, it is known to last up to 14 days[6]. Symptoms of COVID-19 are usually seen within the first 11–12 days of the disease. Fever, dry cough, fatigue, sore throat, and muscle pain are the most common symptoms in symptomatic cases. The additional, less-frequent symptoms include nausea/vomiting and diarrhea[7]. In _COVID-19 patients, pneumonia is the primary indication for hospitalization by 91%. Moreover, the causes of hospitalization include acute respiratory distress syndrome (ARDS) in 3.4% of cases and shock in 1.1% of cases[8]. Some patients with COVID-19 have signs of cardiac damage. For this reason, the effects of the disease on the cardiovascular system have also been taken into account[9]. It has been reported that the increased mortality due to cardiac damage observed in COVID-19 patients is also caused by the infection[10].

Myoglobin is a globular protein molecule consisting of 153 amino acids. It is a single-chain protein containing hem group at the center and has a molecular weight of 16,700 Da[11]. It is present in the heart and skeletal muscle. In addition to its oxygen storage task, myoglobin transfers oxygen to muscle cells[12,13]. It is not specific to the heart, but it is released earlier than creatine kinase MB form (CK-MB) in the necrotic myocardium and increases in circulation within 2 h. Its elevation in the serum lasts about 24 h[14].

Troponins (hs-Tn) are found in skeletal and cardiac muscle structures together with tropomyosin. Troponins are structural proteins involved in regulating skeletal and cardiac muscle contraction[15]. They are sensitive and specific markers for the damage in the heart muscle and were accepted as the standard marker in the year 2000 by the European Society of Cardiology/American College of Cardiology (ESC/ACC) in the diagnosis of acute myocardial infarction (MI), and by the ACC/American Heart Association (AHA) in the diagnosis and monitoring of unstable angina pectoris[16-18].

Creatine kinase (CK) is a dimeric enzyme consisting of two subunits of 40 kDa each. The CK measurements are mainly used in the diagnosis, follow-up, and in the treatment of MI. This enzyme is especially the most sensitive indicator of muscle damage. Although CK-MB has different levels in the heart muscle, its levels are very low in the skeletal muscle[19].

In their renewed criteria to classify acute coronary syndromes in 2000, the European Society of Cardiology and the American Society of Cardiology[20] proposed the cardiac troponin and CK-MB mass measurement as biochemical markers in the diagnosis of myocardial necrosis.

Since the COVID-19 pandemic is a quite recent phenomenon, studies on the characteristics and treatment of the virus and the disease are yet to be well established in the literature. Despite the numerous scientific studies published gradually in the literature, there is no adequate and accurate information about COVID-19 infection and its treatment. Considering the pathogenesis of the disease, manifestations, and test results in patients, the cardiac parameters/tests seem to be skewed/affected. There are only few studies investigating the cardiac parameters in patients with COVID-19 infection. Hence, this study aims to comparatively investigate the cardiac parameters of survivor and nonsurvivor COVID-19 patients.

METHODS

This study was approved by the Sakarya University Medical Faculty Ethics Committee (20.05.2020/N°: E.4618). A total of 379 patients diagnosed with COVID-19 disease and hospitalized in the service unit were included in this study. Information about these 21 nonsurvivor and 358 survivor patients was obtained from the hospital information management system and analyzed retrospectively. COVID-19 was diagnosed using clinical findings, computed tomography, and SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR).

The hs-Tn, CK-MB, and myoglobin parameters, which play an important role in cardiac assessment, were evaluated on the first day of hospitalization.

Cardiac parameters

Myoglobin and hs-Tn tests were studied using the Architect i2000 SR immunoassay analyzer (Abbott, USA), and CK-MB tests were studied using the Beckman Coulter AU5800 autoanalyzer (Beckman-Coulter, USA).

Statistical analysis

The descriptive analyses were performed to provide information on general characteristics of the study population. Visual (probability plots and histograms) and analytical

methods (Kolmogorov–Smirnov/Shapiro–Wilk test) were used to determine the normal distribution. The descriptive analyses were presented using medians and interquartile range (IR) for the non-normally distributed variables. The Mann–Whitney *U* test was used for nonparametric tests to compare these parameters. The Pearson's χ^2 test used to compare the categorical variables between two groups. The categorical variables were presented as the frequency (%). A p<0.05 was considered significant. Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 22.0, IBM Corp., Armonk, NY, USA).

RESULTS

Out of 379 patients, 155 (40.9%) were females and 224 (59.1%) were males with no statistically significant difference in mortality (p=0.249). The total median age range and IR was: 70 (18–96) [18]. The median age in the nonsurvivor group was 74 (35–89) [16] and was 69.5 (18–96) [19] in the survivor group (p=0.249). The median values of hs-Tn, CK-MB, and especially myoglobin in the survivor and nonsurvivor groups, range, IR with p values were: 25 (0.2–24,141.7) [79.85], 64.9 (8–30,515) [1889.85], p=0.028; 18 (5–218) [10.25], 23 (9–91) [16.85], p=0.02; and 105.5 (13.9–1188.4) [166.35], 322.4 (35.6–941) [344.9], p<0.001; and the difference was statistically significant. Comparing mortality, while there was 1 (0.7%) nonsurvivor out of 134 patients in the service unit, there were 20 (8.2%) nonsurvivor out of 245 patients in the intensive care unit. This difference was found to be statistically significant (p=0.003) (Table 1). The receiver operating characteristic (ROC) analysis was performed for the cutoff values of myoglobin, hs-Tn, and CK-MB in COVID-19 patients at our center. The area under the ROC curve (AUC), cutoff value, sensitivity, and specificity were calculated. The cutoff value of myoglobin, which may pose a risk of mortality, was found to be 191.4 µg/l (AUC 0.732; 95%CI 0.621–0.843; sensitivity 71.4; specificity 70.7; p<0.001). It was 45.7 ng/l for hs-Tn (AUC 0.643; 95%CI 0.529–0.756; sensitivity 57.1; specificity 65.6; p=0.028) and 60.1 U/L for CK-MB (AUC 0.651; 95%CI 0.53–0.772; sensitivity 61.9; specificity 60.1; p=0.02) (Figure 1 and Table 2).

DISCUSSION

COVID-19 infection can affect the respiratory tract, causing a wide range of clinical manifestations ranging from viral pneumonia, which leads to severe respiratory failure, to mortality[21]. According to the pathogenesis of the COVID-19 disease, it affects the respiratory tract and cardiovascular system, leading to noticeable abnormalities in some blood parameters related to the organs affected. In this study, hs-Tn, CK-MB, and myoglobin parameters were investigated in survivor and nonsurvivor COVID-19 patients.

According to the studies conducted so far, although individuals in the above-middle age group were found to be severely affected by COVID-19, the rate of severity of the disease is higher in individuals of advanced age[22]. The mortality risk is high when the elderly people with cardiovascular disease encounter the COVID-19 virus. The characteristics of the first 3200 patients who lost their lives in Italy, which initially

Table 1. Study parameters between survivor and nonsurvivors.

		Total (n=379)	Survivor (n=358)	Nonsurvivor (n=21)	p
Age (median, range, [IR])		70 (18–96) [18]	69.5 (18–96) [19]	74 (35–89) [16]	0.249[a]
Gender	Female, n (%)	155 (40.9)	147 (94.8)	8 (5.2)	0.788[b]
	Male, n (%)	224 (59.1)	211 (94.2)	13 (5.8)	
Hospitalization	Ward, n(%)	134 (35.4)	133 (99.3)	1 (0.7)	0.003[b]
	ICU, n (%)	245 (64.6)	225 (91.8)	20 (8.2)	
hs-Tn (median, range, [IR])		25.2 (0.2–30,515.4) [81.1]	25 (0.2–24,141.7) [79.85]	64.9 (8–30,515) [1889.85]	0.028[a]
CK-MB (median, range, [IR])		18 (5–218) [10.2]	18 (5–218) [10.25]	23 (9–91) [16.85]	0.02[a]
Myoglobin (median, range, [IR])		112.1 (13.9–1188.4) [175]	105.5 (13.9–1,188.4) [166.35]	322.4 (35.6–941) [344.9]	0.000[a]

[a]Mann–Whitney *U* test; [b]Pearson's chi-square test. Nonparametric values are expressed as median value, range values (min–max); interquartile range [IR]; hs-Tn, troponins; CK-MB, creatine kinase MB form. A p<0.05 was considered statistically significant.

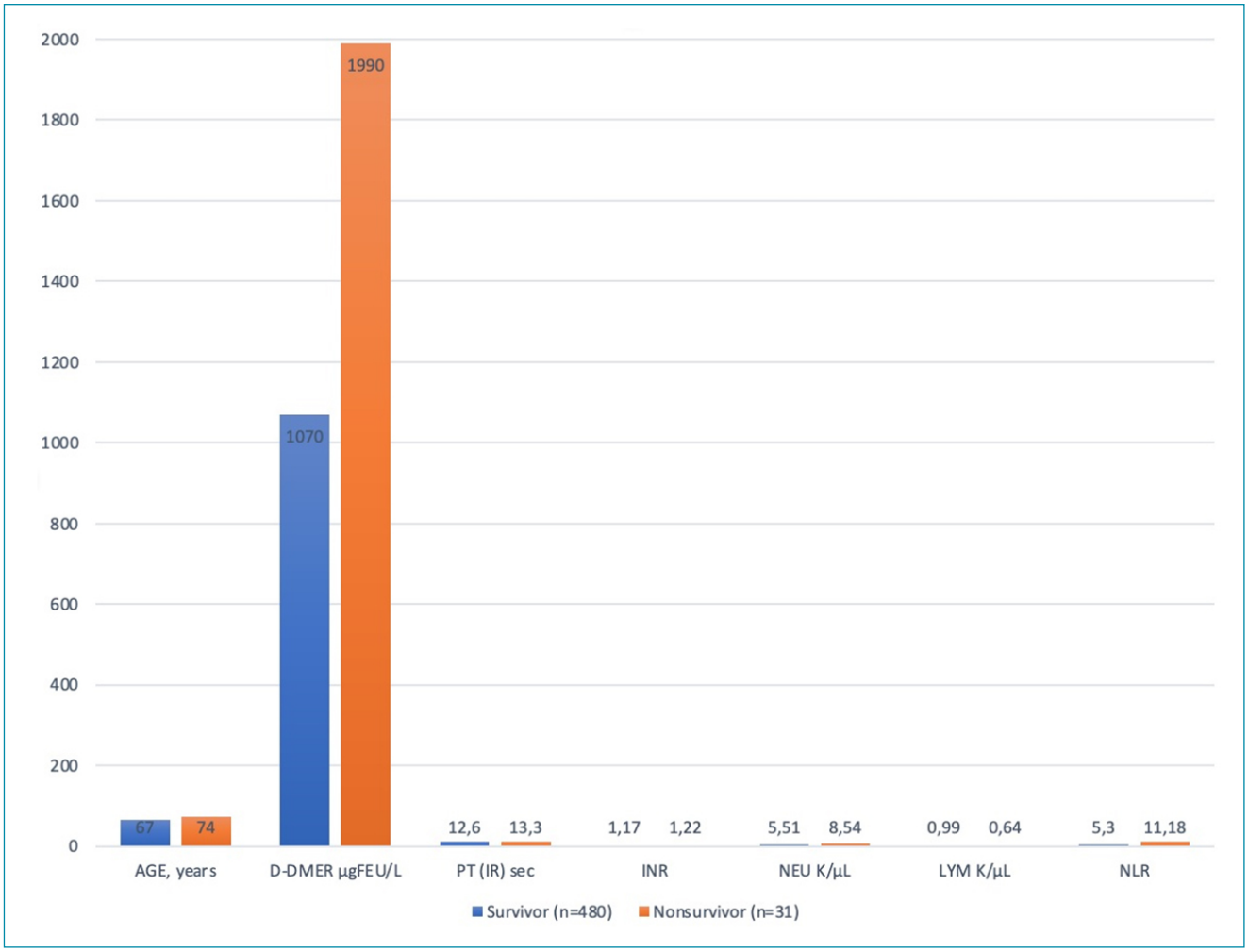

Figure 1. Receiver operating characteristic analysis chart for cutoff values of cardiac parameters to predict mortality risk in COVID-19 patients.

Table 2. Results of Receiver operating characteristic analysis to predict mortality in COVID-19 patients.

Risk factor	AUC (95%CI)	Cutoff	Sensitivity (%)	Specificity (%)	p
Myoglobin	0.732 (0.621–0.843)	191.4	71.4	70.7	0.00
hs-Tn	0.643 (0.529–0.756)	45.7	57.1	65.6	0.028
CK-MB	0.651 (0.53–0.772)	19.85	61.9	60.1	0.02

AUC: area under curve; 95%CI: confidence interval; hs-Tn, troponins; CK-MB: creatine kinase MB form.

had the highest rate of mortality worldwide due to COVID-19, were investigated in a study. As a result, the average age of nonsurvivor patients due to COVID-19 infection was found to be 78.5 (31–103, IR 73–85 years)[23].

In the present study, it was found that the COVID-19 patients were above the middle age and the nonsurvivor patients were of advanced age with an average age of 74.

The high-sensitivity cardiac hs-Tn levels are reported to be high in a significant proportion of COVID-19 patients. In a retrospective analysis study of 191 cases hospitalized due to COVID-19 infection, hs-cTnI levels were found to be >50% in nonsurvivor patients. Typically, the hs-Tn levels increase gradually within days in nonsurvivor patients. The troponin increase continues on the 16th day and after

until death. While the rate of cases was 46% among the nonsurvivor patients with hs-TnI >28 pg/mL, it was reported to be 1% in the survived patients (p<0.0001). In one-way analyses, a significant relationship was found between increased hs-Tn levels and mortality (p<0.0001). It is noted that a gradually increasing hs-Tn level day-by-day in COVID-19 patients is an important indicator of mortality[21]. A study of hs-Tn levels in severe COVID-19 patients found that the levels were significantly higher compared to cases with nonsevere infection[24]. Serum troponin-I levels that were high at the time of diagnosis or increased during follow-up were identified as poor prognostic factors associated with severity of the disease and mortality[21]. In a study of 273 COVID-19 patients with critical, severe, and mild cases, troponin levels of critical and severe cases were found to be statistically significantly different compared to mild cases (p<0.05)[25]. In this study, a statistically significant difference was found in the hs-Tn levels between survivor and nonsurvivor COVID-19 patients (p<0.028).

In a study of 273 COVID-19 patients categorized into critical, severe, and mild cases, statistically significant results were obtained in the myoglobin levels of critical and severe cases compared with mild cases (p<0.05)[25]. A study of COVID-19 patients found high levels of myoglobin in those patients[26]. In this study on COVID-19 patients, the difference in the myoglobin levels between survivor and nonsurvivor patients was found to be statistically significant (p<0.000).

In a study conducted in patients diagnosed with COVID-19, CK-MB levels, which are among the cardiac markers, were found to be high[3]. In a study of 273 COVID-19 patients categorized into critical, severe, and mild cases, statistically significant results were obtained comparing CK-MB levels of critical and severe cases with mild cases (p<0.05)[25]. In this study on COVID-19 patients, a statistically significant difference was found in the CK-MB levels between survivor and nonsurvivor patients (p<0.02).

In our study, the cutoff value of myoglobin, which may pose a risk of mortality, was found to be 191.4 µg/l, while it was 45.7 ng/l for hs-Tn and 60.1 U/L for CK-MB.

CONCLUSION

Advanced age and increased levels of hs-Tn, CK-MB, and myoglobin were found to be associated with mortality in COVID-19 patients.

AUTHORS' CONTRIBUTIONS

MO: Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **HY:** Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **SY:** Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **MK:** Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **ACG:** Conceptualization, Data Curation, Formal Analysis, Writing – Review & Editing. **IK:** Conceptualization, Data Curation, Formal Analysis, Writing – Review & Editing. **ABG:** Conceptualization, Data Curation, Formal Analysis, Writing – Review & Editing. **IY:** Data Curation, Formal Analysis, Writing – Review & Editing. **HK:** Data Curation, Formal Analysis, Writing – Review & Editing. **OK:** Data Curation, Formal Analysis, Writing – Review & Editing.

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Dealing with cancer screening in the COVID-19 era

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SUMMARY

OBJECTIVE: This article aims to alert health professionals for cancer screening in the face of the possibility of new waves of disease.

METHODS: A narrative review was conducted through a search in MEDLINE, Lilacs, Chinese Biomedical Literature Database, and international medical societies publications.

RESULTS: Breast cancer: in high-risk patients (confirmed familial cancer syndrome or with high-risk tools scores), clinicians should act according to usual recommendations; in average-risk individuals, consider screening with mammography with a longer time span (maximum of two years). Cervical cancer: women turning 25 years old who have already been immunized and with no previous Pap test can have the test postponed during the pandemic; if there is no previous dose of Human Papillomavirus vaccination, initiation of screening should be recommended following a more rigid approach for COVID prevention; in women over 30 years of age who have never participated in cervical screening, the first screening exam is also essential. Colorectal cancer: if the individual is at elevated risk for familial cancer, the screening with colonoscopy according to usual recommendations should be supported; if at average risk consider screening with Fecal Occult Blood Test. Prostate cancer: there is a trend to postpone routine prostate cancer screening until the pandemic subsides.

CONCLUSIONS: The decision to keep cancer screening must be discussed and individualized, considering the possibility of new waves of COVID-19.

KEYWORDS: Early detection of cancer. Neoplasms. Coronavirus infections. Pandemics.

INTRODUCTION

The COVID-19 pandemic has brought several challenges to healthcare systems, with a need to adopt interpersonal distancing, reduce activities to prevent new cases of coronavirus, make resources available to deal with the outbreak and, at the same time, face the dilemma of maintaining primary assistance. Regarding cancer patients, to minimize the risk of this vulnerable population, several medical societies worldwide have recommended canceling, postponing, or adapting non-urgent cancer-related procedures[1-3]. Even though COVID-19 effects on cancer are not limited to the care of patients already diagnosed, the pandemic has also impacted screening and delayed the diagnosis of cancers that benefit from screening tests, such as breast, cervix, prostate, and colorectal cancer.

The intensity and duration of measures against COVID-19 will depend on the dynamics of virus transmission, population immunity development, or the availability of an efficacious treatment or vaccine. A recent study suggested that social distancing strategies might be necessary until 2022 if a specific treatment or vaccine to combat the virus is not available before that[4].

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While recent publications from some medical societies have supported cancer treatment continuity, with adaptations to mitigate COVID-19 risk, they have defended postponement of cancer screening procedures during the peak of the pandemic[5]. However, after the peak incidence of cases in Brasil, around July 2020, there was a flexibilization of protective measures and a consequent return to the routine of these procedures. Massive demand for medical follow-up may represent a risk of exposure to those who have had their screenings delayed.

The risk of a new COVID-19 wave is associated with the premature relaxation of protective measures, which can lead to increased transmissibility of the virus[6]. With the reopening of services and reduction of social distancing, there is a greater risk for agglomerations due to the simultaneous search for solving the accumulated demands of the population during the critical period. For this reason, there must be a prior preparation of healthcare and government services to adjust resources to face the disease.

Therefore, this article aims to alert health professionals and decision-makers and gather recommendations from leading societies for screening neoplasms during the pandemic, in case there is a second wave of the disease.

METHODS

A search through MEDLINE, Lilacs, Chinese Biomedical Literature Database, and international medical societies publications was performed to gather recommendations about cancer screening in the COVID-19 pandemic.

Theory/calculation

The proposed postponement of tests for early cancer detection can cause several consequences depending on the rates of individuals that usually are up to date with the recommended guidelines. Data from Surveillance, Epidemiology, and End Results of North American Association of Central Cancer Registries showed that the United States performed screening tests for most of the population following recommendations. Neoplasms diagnosed in the initial stages represent more than half of the total cases of all cancer eligible for screening. Prevalence of screening for breast and cervical cancer was over 70% and early cases represent 81% and 57% of total diagnosis, respectively[7]. One concern is how testing policies loosening in the current pandemic state may further change this tendency. Initially, there might be a decrease in the number of cancer cases, which can be attributed to less testing and detection due to the postponement of non-essential assistance. Then, an increase in the number of more advanced stage cancer cases is expected, which has been described as one of the features of a new wave of infection within the COVID-19 pandemic. These consequences can be even more relevant in low-income countries, where the prevalence of screening is lower, and the incidence of advanced-stage cancer is higher[8].

Recent data has shown that the number of screening tests has already declined. In the United States a significant reduction in breast, colon, and cervical cancer screening of 94%, 86%, and 94%, respectively, have already been observed, relative to averages before January 2020[9]. PSA testing for prostate cancer has also decreased by 60%. Data also shows that gastrointestinal cancer screening has decreased in most countries – 47% of gastrointestinal divisions across Italy suspended their endoscopic screening program for colorectal cancer along with 97% of responding centers across North America[10]. In the first seven months of 2020, there was a 45% reduction among mammograms performed in Brasil, compared to 2019[11]. Particularly for colorectal cancer, it is known that delaying for more than 6 months the screening with colonoscopy, after a positive fecal occult blood test result, may result in higher mortality[12].

RESULTS AND DISCUSSION

Decision-making on screening appointments should be taken when evaluating patient-by-patient risks, health-care capacity, and local stage at the COVID-19 infection curve. It is necessary to weigh the risks and benefits of maintenance of cancer screening, regarding the magnitude of the impact that delays could lead to poorer outcomes. When considering the possibility of a second wave of infection, it is important to bring back the practices already established recommendations by reference societies, thus avoiding a new adaptation period as we had in the first semester of 2020.

Among women, breast cancer is the most diagnosed cancer and the leading cause of cancer death[12]. Recommendations about mammogram frequency differ among medical societies for women with average breast cancer risk, and, to mitigate the risk of infection, the interval for testing may follow guidelines already established in some countries that suggest a relatively longer time period when compared with annual recommendations starting before 50 years of age[13]. For example, the USPS-Task Force suggests breast cancer screening with mammograms every two years in women with average risk, starting at age 50[13]. However, in patients with confirmed familial cancer syndrome or with high scores through validated risk tools, clinicians should act according to previous recommendations specific for these patients in an attempt to avoid delaying a cancer diagnosis[14].

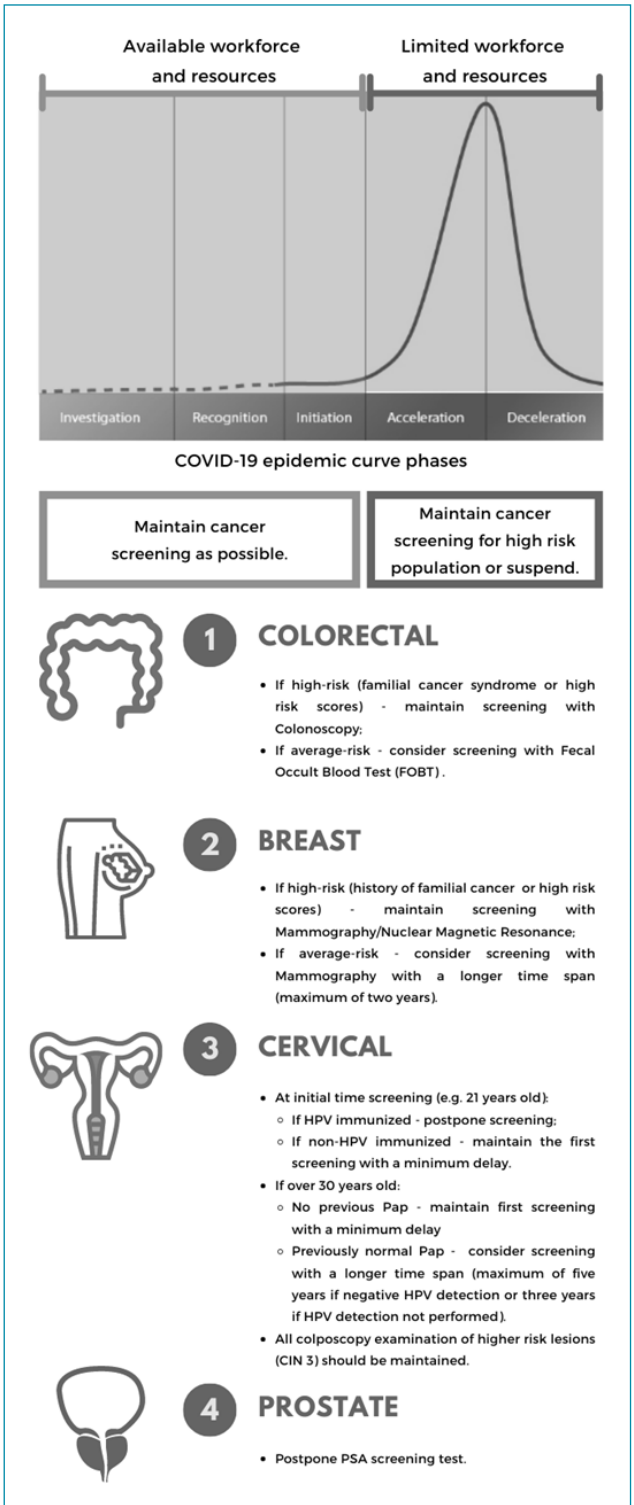
Regarding colorectal neoplasms screening, the individual risk for cancer should be evaluated. If there is a confirmed or

suspected familial cancer syndrome (e.g. Lynch Syndrome), or high scores through validated risk tools, it is suggested to maintain usual screening recommendations[14]. Colonoscopy should be restricted to those with elevated cancer risk while we face this pandemic. Annual Fecal Occult Blood Test should be considered for screening on the overall population, starting at age 45, as it does not require clinic visits[15].

Even though the incidence and mortality of cervical cancer have been declining in low-middle income countries after the discovery of the Pap test and HPV vaccination programs, it continues to be a leading cause of cancer morbidity and mortality in low and middle-income countries, which have been challenging the screening programs for decades[16]. The continuity of prevention strategies is essential to avoid worsening adverse outcomes of late cancer cases. Human Papillomavirus (HPV) vaccination program is recommended to be maintained during the pandemic. It is known that immunized individuals have significant protection for direct HPV cancers[17,18]. Regarding cancer screening, women turning 25 years old who have already been immunized and with no previous Pap test can have the test postponed during the pandemic. If there is no previous dose of HPV vaccination, initiation of screening should be recommended following a more rigid approach for COVID prevention. In women over 30 years of age who have never participated in cervical screening, the first screening exam is also essential, mainly because there is a higher chance of identifying suspect lesions after this age[19]. For women older than 30 years of age with previously normal cervical cancer screening, switching from a 3-yearly screening interval to a 5-yearly screening interval is a reasonable option if negative HPV detection screening has been previously made[20]. In those countries where the Pap test is the preferred screening method, consider increasing the time interval through more than 3 years after the last exam.

The decision to start or keep prostate screening is more complex. Prostate adenocarcinoma has a slow rate of progression[21]. An experimental study showed a reduction of only 3.1 diagnoses of advanced disease for every 1,000 men screened[22]. Is reasonable to postpone routine prostate cancer screening until the pandemic subsides[23].

Once a patient's cancer risk is established, the next step is to weigh the capacity of the healthcare system to conduct assistance needs. This requires knowledge about where the locality is in the COVID-19 epidemic curve phase[24]. During the pre-epidemic and initial phases, the healthcare workforce is intact and there is the availability of resources. Therefore, a continuation of screening for the whole population is a reasonable approach, following the suggestions described above. At a peak phase, the workforce has limited capacity. Through some strategic changes at this point, it is important to offer screening tests exclusively for the population under a higher risk to develop malignancies. In case of the massive



COVID-19 epidemic curve phases. In the figure, recommendations are tailored depending on the healthcare workforce and resource availability. FOBT: fecal occult blood test; HPV: human papillomavirus.

Figure 1. Epidemic curve phases and screening recommendations.

return of COVID-19 cases, cancer prevention programs should be re-started as soon as the post-pandemic phase is reached, considering the overload of health systems in the critical phase of the disease. Figure 1 illustrates this concept and summarizes recommendations for cancer screening that we have presented here.

Protective measures against COVID-19 specific for cancer centers have been endorsed by the American Society of Clinical Oncology (ASCO)[25]. Adaptive changes for screening sample gathering are also an alternative, as well as collecting feces for FOBT at home is a reasonable option. Health diagnostic centers should have a specific day and location to conduct prevention activities, such as mammography and colonoscopy. All those examination requests can be directly sent to the diagnostic center, avoiding the need for patient consultation. When adopted, these steps can make screening activities safer.

CONCLUSIONS

In summary, this report alerts that adaptation strategies for screening tests developed during the first semester of 2020 against COVID-19 can and should be used in the face of a second wave of infection in the future, balancing the risk of exposure to SARS-CoV-2 and late cancer diagnosis. The recommendations here described are alternatives to maintain cancer screening, as the duration of the pandemic is still uncertain. More specific measures should be tailored according to local COVID-19 status and considering the type of cancer and individual's risk factors.

AUTHORS 'CONTRIBUTION

TPF: Data Curation, Formal Analysis, Investigation, Methodology, Writing – Original Draft, Writing – Review & Editing. **RMA:** Data Curation, Visualization, Writing – Original Draft, Writing – Review & Editing. **DLPM:** Writing – Original Draft, Writing – Review & Editing. **LCCL:** Methodology, Supervision, Validation, Writing – Review & Editing. **GSFA:** Writing – Review & Editing. **CCC:** Writing – Original Draft, Writing – Review & Editing. **ANR:** Conceptualization, Methodology, Project Administration, Supervision, Validation, Writing – Review & Editing.

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ORIGINAL ARTICLE

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The role of serum inflammatory markers, albumin, and hemoglobin in predicting the diagnosis in patients admitted to the emergency department with a pre-diagnosis of COVID-19

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SUMMARY

OBJECTIVE: Serum inflammatory markers and albumin levels provide an assumption for the severity of COVID-19 infection. Our objective was to investigate the determinant role of serum inflammatory markers, albumin, and hemoglobin (Hb) in predicting the diagnosis in patients with a pre-diagnosis of COVID-19.

METHODS: Demographic findings, complete blood count and serum biochemical values of the patients analyzed.

RESULTS: Of the patients included in the study, 48 were COVID (+) and 253 were COVID (-). Statistically significant difference was found in terms of hemoglobin, mean platelet volume, and monocyte/eosinophil ratio.

CONCLUSIONS: The levels of serum albumin, hemoglobin, monocyte/eosinophil ratio, and mean platelet volume can be predictive factors for diagnosis in patients with COVID-19.

KEYWORDS: Hypoalbuminemia. Hemoglobins. Mean platelet volume. Monocytes. Eosinophils. Coronavirus infections. Emergency service, hospital.

INTRODUCTION

The COVID-19 infection (2019-nCoV), which first occurred in China and spread all over the world in December 2019, was accepted as a pandemic by the World Health Organization[1]. COVID-19 infection causes high morbidity and mortality in patients due to the risks of severe pneumonia, ARDS (Adult Respiratory Distress Syndrome), acute kidney injury, and acute heart failure[2]. It has been observed that there is a relationship between hypoalbuminemia and severe COVID-19 infection[3,4]. The rate of hypoalbuminemia in the patients who died due to COVID-19 infection is higher than those who recovered from the disease[5]. Albumin down-regulates the expression of ACE-2 (Angiotensin Converting Enzyme) which is the main receptor of COVID-19 infection[6]. Among the COVID-19 patients, hypoalbuminemia was observed in 38.2% of patients who developed non-critical patients, 71.2% in critically ill patients, and 82.4% in the patients who developed mortality during hospitalization[7]. Anemia is an independent risk factor for severe COVID-19 infection[8]. The inflammatory response within the first 24 hours after admission to hospital in COVID-19 patients may be related to the severity of the disease[9]. This study aims to investigate the determinant role of serum inflammatory markers, albumin, and hemoglobin in predicting the diagnosis in patients with a pre-diagnosis of COVID-19 who are admitted to the emergency department.

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METHODS

Study Design

Our study was planned retrospectively. The demographic findings, complete blood count, and serum biochemical values of the patients (pre-diagnosed with COVID-19) who were admitted to the emergency department of the Health, Practice and Research Hospital between March 31, 2020 and June 10, 2020 were analyzed. Our study started after the approval of the Local Ethics Committee (Date of Approval: 01.07.2020, N°: 2020-09).

Patients

The information in the automation system was obtained retrospectively in the patients between the ages of 18 and 80 who were admitted to the emergency department with a pre-diagnosis of COVID-19 infection. Patients under the age of 18, patients with trauma, patients for whom sufficient information could not be obtained in the automation system were not included in the study. COVID-19 and non-COVID-19 patient groups were determined based on their nucleic acid test (PCR) results. All of the COVID (+) patients had pneumonia.

Laboratory Analysis

Serum creatinine, urea, and albumin analyses of the patients were examined with the colorimetric method on the Roche Cobas 6000 device 501 module. CRP (C-reactive protein) analyses were performed on the Cobas 6000 e501 module using a turbidimetric method, and complete blood count analyses were performed in the biochemistry laboratory using the electrical impedance method on the Beckman Coulter DXH 800 device.

In complete blood count, hemoglobin (Hb), leukocyte, mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), monocyte to eosinophil (MER), neutrophil to monocyte ratio (NMR), red cell distribution width (RDW) and platelet parameters were analyzed.

Statistics

In data analysis, COVID (+) 48 (15.9%) and COVID (-) 253 (84.1%) patients were studied. The distribution of patients with and without the diagnosis of COVID (+) by gender was compared using chi-square analysis and the average age with the Mann-Whitney U Test (since age data did not show a normal distribution). MPV, NLR, PLR, leukocyte, Hb, platelet, RDW, LMR, NMR, MER, serum CRP, urea, creatinine, and albumin values of patients with and without COVID (+) diagnosis were compared using Mann-Whitney U Test (since the data did not show normal distribution). Serum albumin value was divided into two categories: 2.49-lower and 2.50-above. Then, the low and high albumin patient groups with and without COVID diagnosis were compared using the chi-square test. Does having a low or high serum albumin level an impact on whether being diagnosed with COVID or not? Analysis of this question was tested using Binary Logistic Regression in SPSS 19.0.

RESULTS

Three hundred and one patients (125 female and 176 male), 48 of whom were COVID (+) and 253 COVID (-), were included in the study. The average age of the patients was 54.76±20.8. The comparison of the patients with COVID (+) and COVID (-) according to gender and age were given in table 1.

According to the results in table 1, there was no significant relationship between whether or not diagnosed with COVID-19 and gender distribution (p>0.05). While 20% of the females

Table 1. The comparison of the patients with COVID (+) and COVID (-) according to gender and age.

Groups		Gender		Total	χ^2	SD	P*
		Female	Male				
COVID (-)	f	99	154	253	2.794	1	0.095
	for COVID diagnosis%	39.1	60.9	100			
	for Gender %	79.8	87.0	84.1			
COVID (+)	f	25	23	48			
	for COVID diagnosis %	52.1	47.9	100			
	for Gender %	20.2	13.0	15.9%			

		n	Mean (Standard Deviation)	Median (Min–Max)	P**
Age	COVID (-)	253	54.58 (21.54)	57 (19–92)	0.878
	COVID (+)	48	55.69 (16.81)	54 (22–93)	

P*: Chi-Square Test; P**: Mann Whitney U Test; SD: Standard deviation.

were diagnosed with COVID-19, 80% did not. While 13% of the males were diagnosed with COVID-19, 87% did not. On the other hand, 61% of 253 people with a diagnosis of COVID-19(-) were men and 39% were women. Of the 48 people with a diagnosis of COVID-19(+), 52% were female and 48% were male. There was no statistically significant difference between the groups in terms of age and gender (p>0.05).

Serum biochemistry and complete blood count values of the patients with COVID (+) and COVID (-) are shown in table 2. There was no statistically significant difference between the groups in terms of average serum albumin values (p=0.194). There was a statistically significant difference between the groups in terms of average hemoglobin, MPV, and MER (p values 0.029, 0.009, 0.008, respectively). There was no statistically significant difference between the groups in terms of serum CRP, leukocyte, and NLR (p values 0.281, 0.153, 0.886, respectively).

When the serum albumin cut-off value was determined as 2.5g/dL, two subgroups were formed in the patients to be below and above this value. The comparison of patient subgroups

Table 2. The comparison of serum biochemistry and complete blood count values of the patients with COVID (+) and COVID (-).

		N	Mean (SD)	Median (Min–Max)	P
MPV	COVID (-)	253	8.59 (1.016)	8.5 (6.7–12)	0.009
	COVID (+)	48	8.25 (1.26)	8.1 (6.3–13.6)	
NLR	COVID (-)	253	8.24 (13.05)	3.9 (0.03–133.0)	0.886
	COVID (+)	48	6.95 (7.89)	4.4 (0.70–39.5)	
PLR	COVID (-)	253	24.19 (40.53)	12.9 (2.30–470.0)	0.524
	COVID (+)	48	21.1 (23.7)	15.10 (2.70–158.0)	
Leukocyte (mm^3)	COVID (-)	253	10196.4 (4883.1)	9200 (2700–44300)	0.153
	COVID (+)	48	9481.2 (4738.4)	7750 (2600–20400)	
Hb (g/dL)	COVID (-)	253	13.21 (2.21)	13.4 (3.30–17.80)	0.029
	COVID (+)	48	12.48 (2.33)	12.6 (8.10–17.00)	
Platelet (mm^3)	COVID (-)	253	243.27 (89.72)	232 (29–688)	0.683
	COVID (+)	48	254.7 (106.4)	232 (47–523)	
CRP (mg/dL)	COVID (-)	253	4.51 (6.65)	1.30 (0.02–33.0)	0.281
	COVID (+)	48	6.37 (8.93)	1.55 (0.07–31.40)	
RDW	COVID (-)	253	14.66 (2.10)	14.10 (12.10–24.90)	0.176
	COVID (+)	48	15.3 (2.85)	14.35 (11.9–24.1)	
LMR	COVID (-)	253	2.72 (2.03)	2.10 (0.10–13.90)	0.503
	COVID (+)	48	2.32 (1.32)	1.90 (0.30–5.80)	
NMR	COVID (-)	253	13.25 (17.55)	8.90 (0.90–190.20)	0.608
	COVID (+)	48	11.6 (10.5)	8.95 (2.10–65.90)	
MER	COVID (-)	253	17.77 (29.49)	7 (0.10–173.0)	0.008
	COVID (+)	48	24.57 (26.45)	13.0 (1.30–94.0)	
Urea (mg/dL)	COVID (-)	253	38.84 (38.64)	29.50 (8.60–528.0)	0.136
	COVID (+)	48	48.56 (44.10)	34.40 (11.40–277.0)	
Creatinine (mg/dL)	COVID (-)	253	1.04 (0.79)	0.88 (0.29–7.70)	0.815
	COVID (+)	48	1.14 (0.88)	0.86 (0.45–5.89)	
Albumin (g/dL)	COVID (-)	253	4.07 (0.610)	4.23 (1.82–5.02)	0.194
	COVID (+)	48	3.88 (0.77)	4.18 (2.17–5.05)	

SD: Standard deviation; P: Mann-Whitney U Test; MPV: mean platelet volume; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; RDW: red cell distribution width; LMR: lymphocyte to monocyte ratio; NMR: neutrophil to monocyte ratio; MER: monocyte to eosinophil.

with low and high serum albumin values was shown in Table 3. It was found that the patients with low serum albumin level (<2.5 g/dL) were diagnosed 75%with COVID (-), and 25% with COVID (+). It was found that the patients with high serum albumin level (>2.5 g/dL) were diagnosed 86.1% with COVID (-) and 13.9% with COVID (+). The effect of low or high serum albumin on COVID (+) diagnosis is shown in table 3. Serum albumin level was found to be a statistically significant determinant in the diagnosis of COVID (+) ($p < 0.05$). It was found that a high serum albumin level (>2.5 g/dL) increased the diagnosis of COVID (-) approximately twice compared to being low (<2.5 g/dL) (Exp [B]=2.069).

DISCUSSION

It is known that there is a relationship between hypoalbuminemia and severe COVID-19 infection[3,4]. Hypoalbuminemia has a negative impact on the morbidity and mortality caused by COVID-19 infection[7]. In acute infections, there is a rapid increase in albumin degradation at the cell level within hours[10]. Hypoalbuminemia is frequently encountered during COVID-19 infection[7]. Serum albumin levels of severe COVID-19 cases were found to be lower than those with mild cases[11]. In our study, the average serum albumin level of COVID (+) patients was found to be lower than in the patient group with COVID (-), but this is not a statistically significant difference. Serum albumin cut-off value was determined as 2.5g/dL, and subgroups below (low) and above (high) were formed and analyzed again. Serum albumin level was found to be a determinant factor in the diagnosis of COVID (+). It was found that the group with high serum albumin level increased the diagnosis of COVID (-) approximately twice than the group with low levels. The constant term was found to be significant in the regression analysis. We can conclude from this finding that there may be another variable that affects the diagnosis of COVID-19 other than the serum albumin level taken into the regression equation.

In severe COVID-19 cases, Hb level was found to be lower than in patients with milder cases[11,12] Anemia is an independent risk factor to severe COVID-19 infection[8]. Among the COVID-19 patients, Hb level was found to be lower in the patient group with comorbidity compared to the group without[13]. In our study, Hb levels in the COVID (+) patient group were found to be statistically significantly lower than the COVID (-) group.

There are several studies in the literature comparing COVID (+) and COVID (-) patients in terms of complete blood count. It has been shown that in the patients diagnosed with COVID-19, the number of leukocytes and lymphocytes is lower than those with non-COVID-19[14]. In another study, it was found that COVID-19 patients had lower leukocyte, lymphocyte, and eosinophil counts in complete blood count[15]. In a meta-analysis study, it was found that the platelet count is important for the diagnosis and prognosis of COVID-19 and the leukocyte and neutrophil count is a determinant factor, but high values reflect disease progression. In the same study, it was found that serum CRP levels in the patients with severe COVID-19 were not diagnostic[16]. In a study by Paliogiannis et al.[17], COVID-19 patients had lower leukocyte, monocyte, and neutrophil counts and serum CRP levels compared to those with non-COVID-19 pneumonia. On the other hand, platelet count and MPV level were found to be

Table 3. Comparison of the patient groups with low (<2.5 g/dL) and high (>2.5 g/dL) serum albumin levels and the effect of low or high serum albumin on the diagnosis of COVID (+) (Binary Logistic Regression).

Groups		Albumin		Total	χ^2	SD	P*	Effect Size (ϕ)
		Low	High					
COVID (-)	f	42	211	253	4.207	1	0.040	0.118
	for COVID %	16.6%	83.4%	100.0%				
	for albumin %	75.0%	86.1%	84.1%				
COVID (+)	f	14	34	48				
	for COVID %	29.2%	70.8%	100.0%				
	for albumin %	25.0%	13.9%	15.9%				

	B	S.E.	Wald	df	Sig.	Exp(B)
Serum albumin >2.5 g/dL	727	360	4.084	1	043	2.069
Invariant	-1.825	185	97.579	1	000	161

P*: Chi-Square Test, Reference Group: COVID (+). SD: standard deviation; B:beta; SE:standard error; df:degree of freedom; Sig.:significant; Exp (B): expected beta.

high. Differently, in the study conducted by Djakpo et al.[13], no difference was found between COVID-19 patients and non-COVID-19 patients in terms of leukocyte, lymphocyte, and platelet values in complete blood count. In the same study, serum CRP levels were found to be statistically significantly higher in COVID-19 patients. In our study, a difference was observed between the COVID (+) and COVID (-) groups in terms of MPV and MER.MPV is lower in the COVID (+) group compared to COVID (-) group, and the MER was found to be high. There was no difference between the groups in terms of leukocyte, platelet, and serum CRP levels.

MER, NLR, and PLR are some of the inflammation parameters that play a key role in inflammatory oncological and cardiovascular diseases[18,19]. In our study, no difference was found between COVID (+) and COVID (-) groups in terms of NLR and PLR, but MER was found to be higher in the COVID (+) group, and the difference was statistically significant. In a meta-analysis study, NLR was found to be higher in severe COVID-19 patients compared to non-COVID patients[20]. In a study by Qu et al.[21], while the PLR level of severe COVID-19 patients during admission to the hospital was similar to those of COVID patients who did not have severe disease, this situation changed during the period of the platelet peak and the PLR rate increased in severe cases. Our study is observational and cross-sectional and based on the laboratory data of COVID-19 patients at the time of their admission to the emergency department. Therefore, biochemical data of the patients' follow-up in the service or intensive care unit were not used in the study.

There were several limitations of our study. Since it was a single-center study, the number of COVID-19 (+) patients was low. Complete blood count and serum biochemistry values of the patients at the time of admission to the emergency department were studied. The values of the hospitalized patients in the service and intensive care unit were not included in the study.

In conclusion, high serum albumin level (>2.5 g/dL) increases COVID (-) diagnosis approximately twice as compared to low (<2.5 g/dL). In COVID (+) patients, Hb level is lower than in COVID (-) patients. MER and MPV could be a new indicator that predicts COVID-19 infection.

Main points

- Serum albumin level is a statistically significant determinant in the diagnosis COVID (+).
- High serum albumin level (>2.5 g/dL) increases COVID (-) diagnosis approximately twice as compared to low (<2.5 g/dL).
- MER and MPV could be a new indicator that predicts COVID-19 infection.
- In COVID (+) patients, Hb level is lower than in COVID (-) patients.

AUTHORS' CONTRIBUTIONS

CA: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. SB: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

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ORIGINAL ARTICLE
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Clinician's perspective regarding medication adherence in patients with obstructive lung diseases and the impact of COVID-19

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SUMMARY

OBJECTIVE: Failure to achieve high levels of medication adherence in obstructive lung diseases is a major cause of uncontrolled disease. The purpose of this study is to reveal clinicians' opinions on the level of patient adherence and the change in adherence during the COVID-19 pandemic.

METHODS: A questionnaire containing multiple-choice questions about treatment adherence in patients with obstructive lung diseases was voluntarily applied to doctors working in a tertiary hospital for chest diseases.

RESULTS: Eighty-one doctors (mean age, 37.2 years [standard deviation, 9.7 years]; 57 (70.4%) women) answered the questionnaires. Almost all clinicians participating in the study reported that they always or frequently asked patients if they adhered to treatment. Most clinicians think that in 20–50% of patients with asthma and less than 20% of patients with chronic obstructive pulmonary disease, a decrease in medication adherence appears in the first year of treatment. Most clinicians think the main reason for patients with obstructive lung diseases not adhering is patients' reluctance to be treated regularly. Regarding the impact of the COVID-19 pandemic on patients' drug adherence, 43.2% of clinicians observed that adherence increased after the start of the pandemic.

CONCLUSION: Adherence to medication is not at the desired levels in patients with obstructive lung diseases. However, when faced with a serious health threat, such as the COVID-19 pandemic, patients realize the severity of their illness and begin using their treatments more regularly.

KEYWORDS: Asthma. Pulmonary disease, chronic obstructive. Coronavirus infections. Medication adherence.

INTRODUCTION

Despite significant advances in the treatment of asthma and chronic obstructive pulmonary disease (COPD), the control of patients cannot be raised to desired levels. One of the leading causes of uncontrolled disease in patients with asthma and COPD is poor medication adherence[1,2]. Proper medication adherence is a key factor in determining uncontrolled asthma instead of diagnosing severe asthma in asthmatics. It is also important to determine medication adherence in calculating the risk of exacerbation in asthmatics. Therefore, asthma guidelines strongly recommend that all asthmatics be evaluated by clinicians at each visit. If asthmatics are not provided to use their treatment with high adherence, uncontrolled asthma rates, asthma exacerbation frequency, and the risks of fixed airway

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obstruction in the future will increase. In addition, in patients with uncontrolled asthma with poor adherence to treatment, the disease cannot be adequately managed, and the unnecessary use of biological agents puts an additional burden on the country's economy[1].

The guidelines for patients with COPD, as well as for patients with asthma, highlight the importance of medication adherence. Poor medication adherence in patients with COPD has implications for disease management. It is a main risk factor for exacerbation and hospitalization in patients with COPD. Therefore, assessing and improving medication adherence in COPD patients is a necessity in COPD care[2].

Close follow-up of patients with asthma and COPD is a key factor in improving treatment adherence. In addition, patients' treatment concerns such as perceived need for treatment and side effects and economic factors may also be important in medication adherence. An example of this is the reported improvement in treatment adherence of patients with asthma and COPD during the first weeks of the COVID-19 pandemic, likely due to the patients' perception of the disease[3].

The aim of this study was to determine the opinion of clinicians on medication adherence and factors affecting it in patients with obstructive lung diseases and to determine how clinicians manage poor inhaler treatment adherence. In addition, the objective was to evaluate clinicians' views on the impact of the COVID-19 outbreak on patient compliance with inhaler therapy.

METHODS

Recruitment and data collection

A questionnaire consisted of multiple-choice questions was applied to allergy and chest diseases physicians working in a training and research hospital in Ankara, Turkey, on a voluntary basis. The questionnaire used in the study was prepared based on the questions found in the questionnaire that Kardas et al[4]. used in their study in 2015. Clinicians participating in the survey were questioned about their age and gender and their opinions about the treatment adherence of the patients with asthma and COPD they followed.

Statistical Analysis

Descriptive statistics were used in the survey findings. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as numbers (percentages). Analyses were performed using the Statistical Package for the Social Sciences®, version 22.

Standard Protocol Approvals and Patient Consents

This study was approved by the Ethics Committee of the University of Health Sciences, Keçiören Training and Research Hospital on October 14th, 2020, under decision number 2174. Informed consent was obtained from all participants.

RESULTS

Within the scope of this study, 81 clinicians working in a tertiary hospital for thoracic diseases were administered a questionnaire containing questions about the adherence of patients with asthma and COPD they followed. All 81 clinicians agreed to participate in the study and answered the questionnaires. Seven of the clinicians who completed the questionnaire were allergists and 74 were pulmonologists. Clinicians' mean age was 37.2 years (SD 9.7 years), and the gender distribution was 57 females (70.4%) and 24 males (29.6%).

Almost all clinicians participating in the study reported that they always or often asked patients whether they adhere to treatment. Almost all participant clinicians reported that they always or often could correctly determine the treatment adherence in patients. The rate of clinicians who think that more than 50% of asthmatic patients discontinue treatment within 1 year after diagnosis is 24.7% and that of clinicians who think that patients with COPD stop treatment within 1 year after diagnosis is 4.9%. The majority of clinicians think that 20–50% of patients with asthma and less than 20% of patients with COPD experience a decrease in medication adherence in the first year of treatment (Table 1). Most clinicians think that the main reason for non-adherence of patients with asthma and COPD is the reluctance of patients to be treated regularly. Most clinicians prescribe combined inhaled medications containing multiple active ingredients in a single dose to improve adherence in patients with asthma and COPD (Table 2). Regarding the impact of the COVID-19 outbreak on treatment adherence of patients with asthma or COPD, 43.2% of clinicians thought that patients' adherence to treatment increased after the onset of the COVID-19 outbreak, while 18.5% of clinicians thought that it decreased during the COVID-19 outbreak (Table 3).

DISCUSSION

The major finding of our study is the incomplete adherence to treatment in patients with asthma and COPD, in the opinion of the clinicians. According to the study findings, 24.7% of clinicians think that more than 50% of patients with asthma discontinue treatment within 1 year after diagnosis. It appears that medication adherence is slightly higher in patients with

Table 1. Clinicians' views on treatment adherence of patients with obstructive lung diseases (n=81).

At what rate do clinicians ask patients' adherence to treatment	
Rarely	3 (3.7)
Frequently	39 (48.1)
Always	39 (48.1)
To what extent do clinicians think they can understand patients' adherence to treatment	
Rarely	7 (8.6)
Frequently	62 (76.5)
Always	12 (14.8)
To what extent do clinicians think that patients with asthma stop treatment within 1 year after diagnosis	
Less than 20%	17 (21.0)
20–50%	31 (38.3)
50–80%	15 (18.5)
More than 80%	5 (6.2)
No opinion	13 (16.0)
To what extent do clinicians think that patients with COPD stop treatment within 1 year after diagnosis	
Less than 20%	42 (51.9)
20–50%	15 (18.5)
50–80%	3 (3.7)
More than 80%	1 (1.2)
No opinion	20 (24.7)

Data indicated in n (%). COPD: chronic obstructive pulmonary disease.

COPD than in patients with asthma. The rate of clinicians who think that more than 50% of patients with COPD discontinue treatment within 1 year after diagnosis is 4.9%. The majority of clinicians think that less than 20% of patients with COPD discontinue medication adherence in the first year of treatment. The most important reason for poor adherence in patients is the reluctance of patients to use regular treatment. Another important finding of the study is that clinicians realized that after the onset of the COVID-19 pandemic, treatment adherence increased in patients with obstructive lung diseases. Although patients with obstructive lung diseases do not use their treatments regularly enough, increased medication adherence when they face a serious health threat such as the COVID-19 pandemic shows that patients do not understand the severity of their illness and this hinders the regular use of their treatment.

Table 2. According to the participants, the main causes of treatment non-adherence in patients with obstructive lung diseases and the interventions performed by the respondents in case of treatment non-adherence (n=81).

The main reason for medication non-adherence	
Side effects of medications	17 (21.0)
Price of drugs	9 (11.1)
Frequency of dosing	18 (22.2)
The effects of the treatment are not noticed by the patient	43 (53.1)
Unwillingness of patients to be treated with a regular treatment regimen	56 (69.1)
Patients' lack of information about their diseases	46 (56.8)
Interventions performed by the respondents to improve medication adherence	
To prescribe drugs named short and easy to remember	5 (6.2)
To prescribe cheap drugs	14 (17.3)
To prescribe combination inhaled drugs containing multiple active ingredients in a single dose	77 (95.1)
To prescribe inhaled drugs not including glucose	1 (1.2)
To prescribe drugs that are used once a day	48 (59.3)

Data indicated in n (%).

Table 3. Impact of the COVID-19 outbreak on medication adherence in patients with obstructive lung diseases, according to respondents (n=81).

Increase in medication adherence	35 (43.2)
Decrease in medication adherence	15 (18.5)
No change in medication adherence	18 (22.2)
No opinion	13 (16.0)

Data indicated in n (%).

Adherence to inhaler therapy in patients with obstructive lung diseases has become a clinical problem with the age of this therapy[5]. Poor adherence in patients with asthma and COPD is associated with failure to control the disease, frequent exacerbations, and increased mortality[6-12]. Almost all of the clinicians participating in the present study stated that they questioned patients about their drug adherence. There are some objective methods in the follow-up of adherence. Biochemical measurements in blood can precisely determine the treatment

adherence of patients. However, such a method is costly, invasive, and provides an estimate of adherence over a point period. Smart electronic inhalers can also aid in the objective tracking of adherence, but are not currently used worldwide. Pharmacy refills or prescription renewals in the clinic can be used to identify nonadherent patients, and can help target interventions to those who would most benefit from the intervention. Regular face-to-face interviews that provide effective patient-clinician communication are effective in building real insight into adherence[13]. Each method to track adherence has its own strengths and weaknesses, and none are specifically designed for a particular type of adherence.

Medication adherence issues can differ on a patient basis and between countries. Each country should search its own adherence problems and develop appropriate strategies. For example, in our country, as drugs are within the scope of reimbursement, the price of drugs is not specified among the prominent factors for treatment non-adherence in patients. However, in different countries, this factor may be an important determinant of adherence. Unfortunately, there is no magic statement in medicine to increase adherence. In the present study, clinicians stated that they tried to prescribe inhalation drug combinations containing more than one active ingredient at a time, and to prescribe drugs used once a day, in line with the causes of inhaler treatment non-adherence in patients.

While some patients show poor adherence with to the treatment from the beginning, others start to disrupt their treatment regimen in the long term[14]. In the present study, it was revealed that the compliance of asthmatic patients to their treatment decreased at a higher rate in the first year after diagnosis compared to patients with COPD. The reasons for this situation may be that asthmatic patients do not feel the need to continue their treatment after clinical improvement and fear the prospective side effects of inhaled steroids. According to the clinicians involved in this study, the main reason for non-adherence to treatment with inhalers in patients is that they do not want to use a regular treatment regimen. Other factors underlying non-adherence to inhaler treatment are the patients' inability to feel the effect of the treatment, the necessity of frequent administration of the drugs, and the hesitation toward drug side effects. In the past, the poor adherence of patients to inhaler therapy has been attributed to similar factors. It was stated fourteen years ago that patients' perception about their medications as unnecessary and their worrying about possible side effects were prominent factors for poor medication adherence[15]. This shows that we, as clinicians, have not been able to go a long way toward improving adherence in the past ten years. It is clear that more effective ways to address patients' concerns about disease perceptions and treatments are necessary.

The results of our study coincide with the results of the Recognise Asthma and Link to Symptoms and Experience (REALISE) Asia study published in 2016. In that study, the most important reason of treatment non-adherence reported by clinicians is that patients do not want to use their treatment regularly[16]. Similarly, in another study conducted in Poland, clinicians reported that the main reasons why asthma and COPD patients stopped treatment were primarily discouragement and insufficient knowledge of the disease[4]. These findings tell us that clinicians should clearly explain patients why treatment is necessary. They should also address patients' concerns about possible side effects. In this way, important causes of medication non-adherence will be solved to a larger extent. Similar to a previous report, the finding that inhaler treatment adherence increased during the COVID-19 epidemic in our study indicates that patients should be warned about the absolute need for treatment[3].

The major limitation of the present study is the small number of participants. However, its strength is that it includes specialist physicians who are experts in this field and regularly follow-up patients with asthma and COPD in a tertiary thoracic diseases hospital.

As a conclusion, it has been demonstrated by the experts of this subject that the adherence to inhaler treatments in patients with asthma and COPD is poor. Thus, it is clear that attempts should be made to improve adherence in patients with obstructive lung diseases. The observations of the clinicians participating in our study are also consistent with the increase in treatment compliance in patients with asthma and COPD after the previously reported COVID-19 pandemic.

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AVAILABILITY OF DATA AND MATERIAL

The dataset used and/or analyzed during the present study is available on reasonable request.

AUTHORS' CONTRIBUITION

MY: Conceptualization, Data Curation, Methodology, Writing – Original Draft. **FA:** Conceptualization, Methodology, Formal Analysis, Writing – Original Draft. **NY:** Conceptualization, Methodology, Writing – Original Draft. **KA:** Conceptualization, Methodology, Formal Analysis, Writing – Original Draft.

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REVIEW ARTICLE
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Physical Exercise and Immune System: Perspectives on the COVID-19 pandemic

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ABSTRACT

Physical exercise training (PET) has been considered an excellent non-pharmacological strategy to prevent and treat several diseases. There are various benefits offered by PET, especially on the immune system, promoting changes in the morphology and function of cells, inducing changes in the expression pattern of pro and anti-inflammatory cytokines. However, these changes depend on the type, volume and intensity of PET and whether it is being evaluated acutely or chronically. In this context, PET can be a tool to improve the immune system and fight various infections. However, the current COVID-19 pandemic, caused by SARS-CoV-2, which produces cytokine storm, inducing inflammation in several organs, with high infection rates in both sedentary and physically active individuals, the role of PET on immune cells has not yet been elucidated. Thus, this review focused on the role of PET on immune system cells and the possible effects of PET-induced adaptive responses on SARS-CoV-2 infection and COVID-19.

KEYWORDS: Exercise. Immune system. Coronavirus infections. Pandemics.

INTRODUCTION

The beneficial effects of physical exercise training (PET) for individuals with type 2 diabetes and obesity[1], inflammatory illneses[2], arterial hypertension[3], heart failure[4], Alzheimer´s disease[5], among other diseases, are well established. Improved immune function is demonstrated with all types of PET, such as walking, running, swimming, and cycle ergometer. The beneficial effects on the immune system include cell regulation and modulation of gene expression and signaling pathways associated with the inflammatory process[6].

The effects of PET on the immunomodulatory response are related to the type of stimulus applied, taking into account exercise duration, intensity and frequency, both in physiological and pathological situations[7,8]. Notably, the acute response (during or shortly after exercise) of high-intensity exercise results in transient suppression of the immune system, making individuals more susceptible to infections by viruses and bacteria[9], as well as viral reactivation, whereas continued training (long training period) generates a chronic adaptation of this organism, increasing the defense of the immune system against microorganisms and pathogens[10].

The ongoing COVID-19, caused by the novel coronavirus (SARS-CoV-2) rose questions about the appropriateness of PET during quarantine time, given the fact

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that infection also affects the immune system[11]. Seen that, PET being used as a non-pharmacological tool during the COVID-19 pandemic is thus questionable. We aimed to briefly debate in two topics the enigmatic role of PET in favoring or not a positive adaptation of the immune system to prevent COVID-19: 1 – how PET acutely and chronically induces adaptation of the innate immune system cells in response to aerobic and resistance training, and 2 – the possible effects of PET-induced adaptive responses on SARS-CoV-2 infection.

INNATE AND ADAPTIVE IMMUNOLOGIC RESPONSE

The immune response is highly dynamic and involves cell components that can be simplistically described as belonging to the Innate (II) and Adaptive Immune System (AI). The Natural Killers, Macrophages, Eosinophils, Neutrophils, and Dendritic Cells are the II cells, and they act on the primary defense against infectious agents, by quickly recognizing atypical molecules of pathogens, toxic products or damaged tissue, and triggering the "danger" signal, that directs AI cells to a specific response against the invader[12-15]. The II cells are formed in the germ line; they do not divide, do not form clones, and do not produce memory cells. In contrast, AI cells bear specific antigen receptors (T lymphocytes and B lymphocytes), they are formed in the somatic lineage and may undergo hypermutations, thereby increasing their affinity to the antigen. B and T cells possess genetically rearranged and highly diverse antigen receptors, imparting specificity in recognition to these cells.

In contrast with the II response, the AI response becomes more efficient with each successive encounter with the same pathogen, a phenomenon called immune memory[16,17]. AI response is induced by successive memory formation by B an T cells and is influenced by the II response. PET induces changes in these lymphocytes because of the high shear stress on artery walls, of the stimulation of the sympathetic nervous system and of the increased adrenaline secretion. It induces lymphocytosis of both B and T lymphocytes[18,19], and these changes are proportional to PET duration and intensity[20]. However, negative effects on AI function were also reported, such as T lymphocyte apoptosis after physical testing to exhaustion (Figure 1)[21].

As SARS-CoV-2 is a new virus, human immunity is being developed during the pandemic outbreak in the general population. Thus, this review's focus is mainly on PET-induced chronic and acute adaptation in the II cells, as described in the topics below.

PHYSICAL EXERCISE AND NEUTROPHILS

PET induces changes in the phagocytic activity of neutrophils. This activity may be reduced as an acute response to different high-intensity exercise modalities[22] or increased after moderate-intensity training as a chronic adaptation[23]. However, this response is still controversial, since there are different protocols for the same PET modality, besides the inherent peculiarities of the studied populations. PET induces the production of reactive oxygen species (ROS) through the acute response or chronic adaptation of the immune system, according to its modality and protocol[24]. For example, increased ROS production mediated by neutrophils and apoptosis were related to PET[25]; however, other studies have shown an opposite effect, with reduced ROS production by neutrophils after moderate intensity PET[24,26]. Still regarding the impact of PET on neutrophils, several studies have shown reduction of chemotaxis after high-intensity aerobic exercise[9,27].

PHYSICAL EXERCISE AND MACROPHAGES

Acute and chronic adaptation of macrophage functions were shown as a result of PET. Unlike neutrophils, studies unanimously report increased phagocytic activity of macrophages after PET, regardless if moderate or of high intensity until exhaustion[6,28]. Other PET-modulated biological processes in macrophages include augmented ROS production after intense exercise to exhaustion; improved antitumor activity upon moderate and high intensity exercise, due to increased cytotoxic activity against neoplastic cells[29], higher nitric oxide production after moderate-intensity PET[6], reduced expression of class II antigen presenting molecules in high and moderate-intensity PET and increased macrophage chemotaxis after intense PET until exhaustion[30]. As observed in neutrophils, there are controversies regarding the beneficial effects of exercise on macrophage function due to the variety of types, modality, and protocols of PET, as well as the diversity of biological process evaluated.

PHYSICAL EXERCISE AND NATURAL KILLER CELLS

High-intensity PET reduced the cytotoxic activity of Natural Killer (NK) cells[31]. Increased NK cell apoptosis has also been reported after treadmill running[32] and after a marathon competition[33]. However, other studies have shown that both acute exercise and chronic PET increase NK cell number[34], NK cytotoxicity, and the production of cytokines, such as IFN-γ,

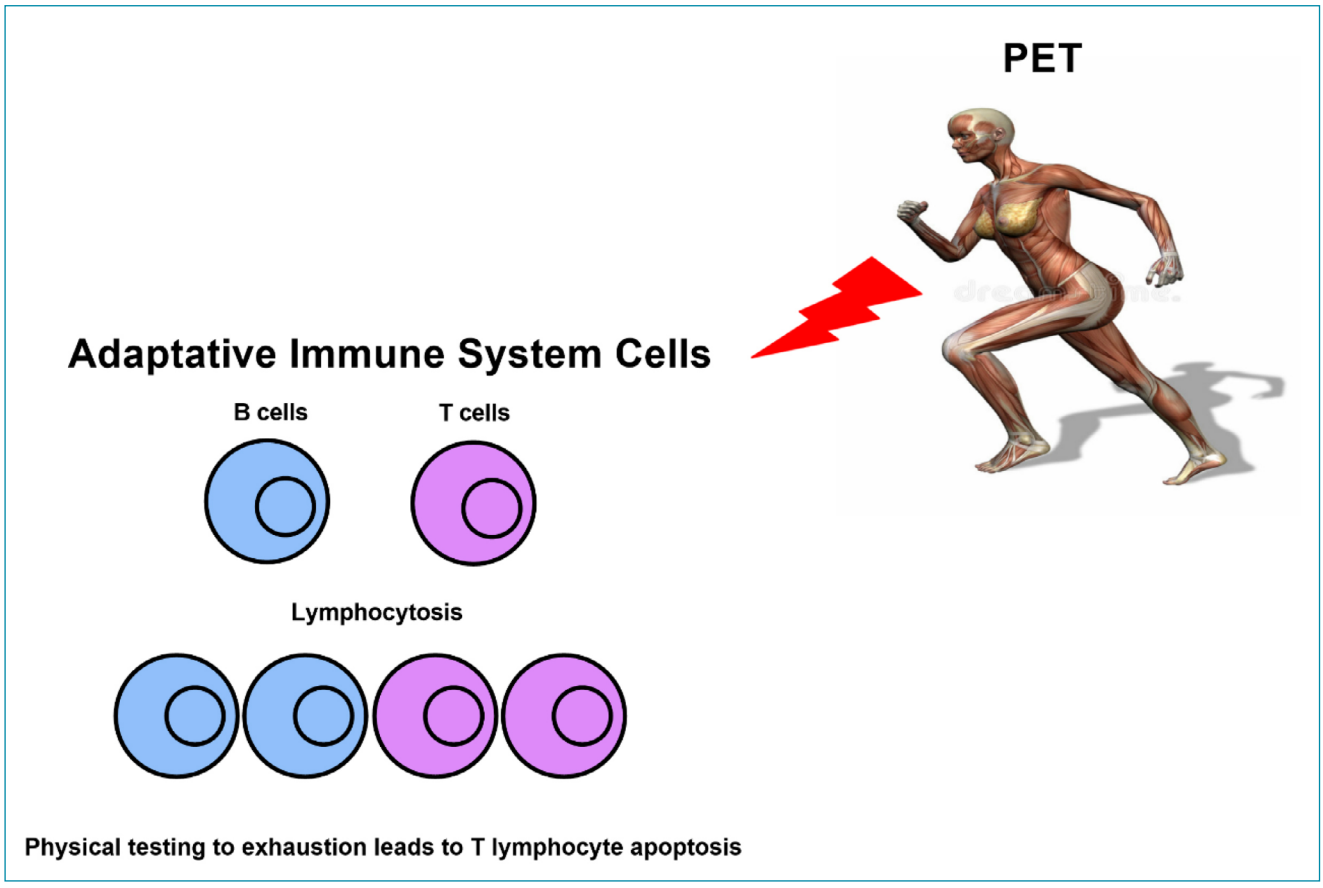

Figure 1. Impact of physical exercise training (PET) on cells of the adaptative immune system

TGF-β, and interleukin 10 (IL-10), after both moderate and high-intensity exercise[35,36]. The responses obtained may vary due to the different protocols analyzed, as well as different types of PET used (Figure 2).

PHYSICAL EXERCISE AND EXTRACELLULAR SUPEROXIDE DISMUTASE (ECSOD) ENZYMES

Moderate-intensity PET increased the expression of EcSOD enzymes and reduced ROS production, attenuating cytotoxic activity of immune cells[37,38]. Furthermore, EcSOD, a molecular transducer of health benefits of exercise, has been associated with lower endothelial tissues damages[39].

PHYSICAL EXERCISE, IMMUNE SYSTEM AND COVID-19: WHAT IS THE EVIDENCE?

There is no available data about the effects of PET on the immune response against coronaviruses. The only original study considering possible effects of PET in the context of the COVID-19 pandemic focused on the need to consider the health condition of people who were not infected by SARS-CoV-2, especially regarding individuals that ceased labor activities due to restrictive measures enforced during the outbreak. This condition may predispose subjects to the development of mood disorders, such as depression[36], and possibly modulate the responses of their immune system. Since there is no consistent biological basis of a beneficial biological effect of exercise during the COVID-19 pandemic, the main focus to prescribe a PET program at this time should be light- to moderate-intensity aerobic exercises, recreation, wellness and resilience-related to a new routine, and not to the development of sports performance (Figure 3).

FINAL CONSIDERATIONS

PET produces controversial effects on the immune system, depending on the protocols adopted. Although many beneficial effects of PET were demonstrated in the prevention or treatment of a wide range of diseases, whether prescribing

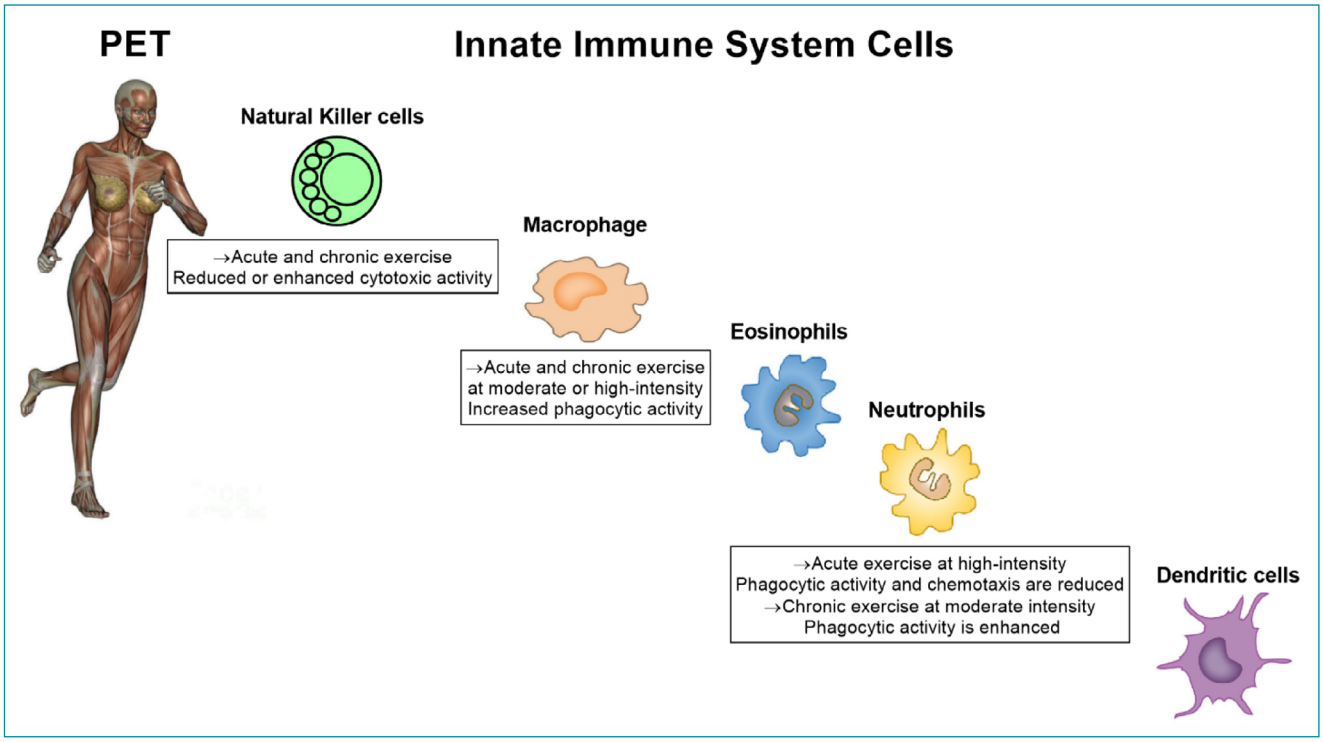

Figure 2. Effects of physical exercise training (PET) on innate immune system cells.

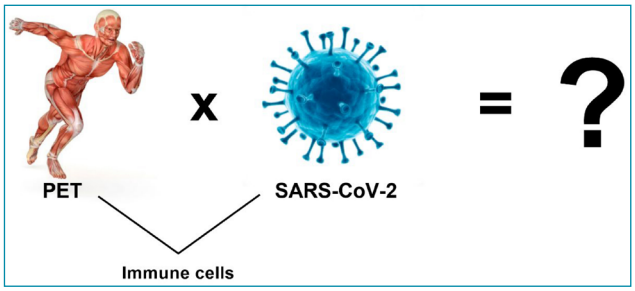

Figure 3. Elucidation of the mechanisms of physical exercise training (PET) on immune system cells in individuals with COVID-19: the great challenge

PET during COVID-19 leads to improved defense against the virus, when employed as a prophylactic measure, or induces changes in immune system, which would increase susceptibility to virus infection, or stimulate inflammatory processes and virus-induced damage, in the context of treatment, remains unknown. Considering that high-intensity PET sessions might result in transient immune depression and predispose individuals to viral infections as well as viral reactivation, we suggest that exercise prescription during quarantine should be done with caution. We advise for intensified monitoring rather than what is usually performed in gymnasiums, focusing mainly on the control of exercise intensity, duration, and frequency.

Further caution should be taken for PET practice given the fact that some individuals infected with SARS-CoV-2 CAN BE asymptomatic, but may still develop symptoms as a result of PET-driven transient immune depression, which can be more harmful than beneficial for these individuals. On the other hand, uninfected individuals who perform PET may undergo adaptation of their immune defense system that may improve innate immune cell functionality, leading to a reinforced adaptive sensibilization and production of antibodies, compared to uninfected individuals who are not training, which can help in infection prophylaxis and symptoms attenuation in case of infection.

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AUTHORS 'CONTRIBUTION

ACIC: Conceptualization; Data Curation; Formal Analysis; Investigation; Supervision; Writing – Original Draft; Writing – Review & Editing. **UPRS:** Data Curation; Formal Analysis; Investigation; Writing – Original Draft. **CSP:** Investigation; Writing – Original Draft. RAJ: Supervision. **RALS:** Investigation; Writing – Original Draft; Validation. **TCBB:** Formal Analysis; Supervision; Validation.

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REVIEW ARTICLE
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Ototoxic effects of hydroxychloroquine

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SUMMARY

OBJECTIVE: To present scientific evidence based on a systematic review of the literature (PRISMA), aiming to systematize evidence of the ototoxic effects of hydroxychloroquine (HCQ).

METHODS: The studies were selected using a combination based on the Medical Subject Headings (MeSH). The databases searched were MEDLINE (PubMed), LILACS, SciELO, and BIREME, encompassing articles from January 2010 to May 2020, with no restrictions of language and place of publication.

RESULTS: A total of 148 articles with the potential to be included were retrieved. Of these, two answered the research question, which consisted of seeking evidence of the ototoxic effects of hydroxychloroquine. These studies scored 11 in their quality assessment with the modified protocol by Pithon et al.[13].

CONCLUSIONS: The studies reported possible ototoxicity of HCQ. Audiovestibular changes, such as hearing loss, peripheral vestibular syndrome, and tinnitus were evidenced in patients submitted to HCQ. The improvement in the audiological examinations and the regression in the vestibular syndrome after stopping the treatment with HCQ are strong arguments in favor of the ototoxicity caused by this medication. However, there are still divergences about the relationship between ototoxic effects and the use of HCQ.

KEYWORDS: Hydroxychloroquine. Hearing. Ototoxicity. Medication errors.

INTRODUCTION

Hydroxychloroquine sulfate (HCQ) is analogous to chloroquine, which can inhibit plasma levels. It is an antimalarial agent used to treat diabetes mellitus, dyslipidemias, coagulopathies, infectious and certain autoimmune diseases, e.g., Sjogren's syndrome, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE)[1].

HCQ is currently being investigated – without scientific evidence at this point—to be a possible treatment of choice for the new coronavirus (SARS-CoV-2) or COVID-19, which is responsible for the ongoing pandemic.

HCQ has side effects, the most common being nausea, diarrhea, pruritus, rash, and hyperpigmentation. However, the most serious side effect is ocular toxicity, which must be routinely monitored[2]. Various publications point out the ototoxic effects of HCQ, which may be associated with varying degrees of destruction to the cochlear sensory hair cells. HCQ decreases the neuronal population, changes the supporting structures, and results in atrophy and vacuolization of the stria vascularis, a possible consequence of ischemia[3]. The main symptoms are tinnitus, sensorineural hearing loss, and vertigo[4].

Medication-related ototoxicity is defined as either a temporary or permanent auditory and/or vestibular function disorder, induced by therapeutic substances[10]. This impairs functional activities and quality of life, and can appear after a relatively short period, in small dosages[7,9,11]. It is important to highlight the ototoxic effects of HCQ due to its indiscriminate use without clarity about pathological effectiveness.

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Therefore, this study presents scientific evidence for HCQ use and, based on a systematic review of the literature using preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, aims to find answer to the following question: Does the use of hydroxychloroquine have ototoxic effects on patients?

METHODS

Research design and search strategies

For a systematic review, we followed the –PRISMA recommendations[12]. The search was conducted by two independent researchers, using MEDLINE (PubMed) (https://www.ncbi.nlm.nih.gov/pubmed/), LILACS (http://lilacs.bvsalud.org/), SciELO (http://www.scielo.br/), and BIREME (https://bvsalud.org/) databases, for scientific articles without restriction on language or geography from January 2010 to May 2020. In addition to this, manual searches were conducted using Google Scholar for the above criteria that include the gray literature. The result was structured using the population, intervention, control/comparison, outcomes and study type (PICOS) framework (Table 1).

Descriptors selected based on the dictionary of Health Sciences Descriptors and Medical Subject Headings (DeCS/MeSH) were hydroxychloroquine and chloroquine and malaria and COVID-19 or diabetes mellitus or systemic lupus erythematosus or rheumatoid arthritis or dyslipidemia or Sjogren's syndrome or ototoxicity and audiology.

Selection criteria

Inclusion criteria

The selected literature includes descriptive cross-sectional studies, cohort studies, and case studies published from January 2010 to May 2020, without restrictions on language or geography.

Table 1. Description of the PICOS framework research model.

Acronyms	Definitions
P	Patients
I	Hydroxychloroquine
C	Ototoxicity
O	Medication
S	Descriptive study Cross-sectional study Observational study

Source: developed by the authors.

They were evaluated for quality, with a score higher than 6, as per the modified protocol given by Pithon et al.[13]

Exclusion criteria

Studies published as letters to the editor, guidelines, literature reviews, systematic reviews, meta-analyses, and abstracts were excluded.

Data analysis

For a systematic review, data were extracted from the selected studies in a spreadsheet developed by researchers using Excel®. The extracted data were selected by one researcher and validated by another. The data from eligible studies were transferred to the spreadsheet and organized as described in Figure 1.

Out of 148 articles selected, 145 unique studies were retained. After analysis, 138 papers were excluded as they failed to meet the inclusion criteria, and 7 articles remained. Out of these, 3 articles were excluded based on the information given in their abstracts. Among the rest, 2 more studies were excluded, leaving the last 2 articles for full review (Figure 1).

Data extracted from the studies were descriptively analyzed. Due to the small number of selected studies and the lack of homogeneity between extracted variables, the meta-analysis was not performed. The quality of the studies was carefully analyzed.

RESULTS

After careful evaluation, the two eligible articles[2,14] met all the pre-established criteria and answered the research question: Does the use of hydroxychloroquine have ototoxic effects?

The studies[2,14] in this review were case reports. In the final analysis, they were categorized according to the theme, focusing on the use of HCQ and its ototoxic effects when treating patients. With respect to the quality of evaluation, these studies achieved a score of 11, representing the rationale for their inclusion and in-depth analysis. Their main characteristics can be found in Table 2.

The first study was conducted by a French pharmacovigilance group[14]. It reports the case of a female, diagnosed with SLE, initially treated with HCQ. The exact dates of treatment were unknown, but when she was 33 years-old and many years after being on a dosage of 400 mg/day of HCQ, the patient had a sudden bilateral hearing loss associated with vestibular syndrome. Magnetic resonance imaging (MRI) did not find lesions in the brainstem. After administering three 1000 mg doses of methylprednisolone, the patient had a partial hearing recovery, assessed for improvement using control audiometry.

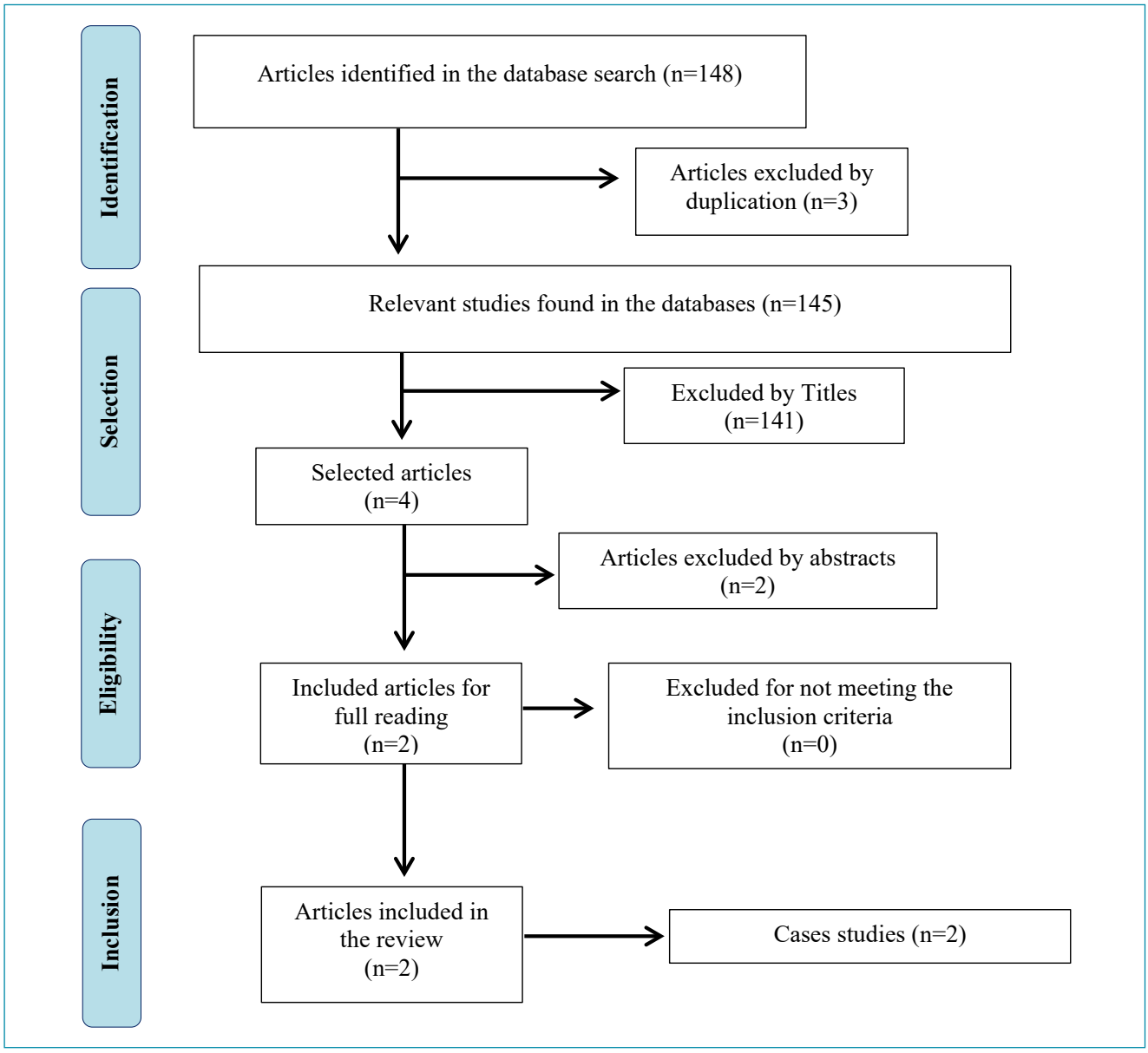

Figure 1. Flowchart of the research method and analysis. Source: Research model developed by the authors.

The researchers[14] hypothesized that the hearing loss was an effect of HCQ administration. Treatment was stopped and replaced with methotrexate (15 mg/week). In a clinical examination after 6 months of initial diagnosis, a regression was observed with sudden hearing loss, including hearing impairment, which was not perceived by the patient. For join pain, methotrexate, in combination with glucocorticoids, was prescribed to the patient for approximately 15 years. In this context, HCQ treatment was resumed at 400 mg/day, 5 days/week. Three months later, the patient presented with peripheral vestibular syndrome, and diagnosed by an otorhinolaryngologist as neuritis. Brain MRI focused on the inner ear, and pontocerebellar angles did not present any notable issues. HCQ administration was stopped in the following month (i.e., four months after the beginning of the treatment).

The otorhinolaryngologist confirmed a mild bilateral hearing loss (30 dB) at frequencies of 1000 Hz. In the next month, a dosage of 800 mg of methylprednisolone was given. For the next five months, no subjective improvement in auditory thresholds could be discerned. However, there was no recurrence of vestibular syndrome, and the patient's hearing loss did not become worse[14].

The second selected study was published in the year 2020, conducted by the Department of Rheumatology and Clinical

Table 2. Summary of the selected research articles.

Author(s)/ Year/Place of publication	Objective(s)	Examinations	History of medications	Results	Conclusion(s)
Chatelet et al.[14], 2017 France	To report the case of a patient treated with HCQ. She presented hearing loss, which improved when the medication was discontinued.	Auditory assessment with pure--tone threshold audiometry (PTA); diagnosed with sudden bilateral hearing loss. Brain MRI revealed the absence of lesions in the brainstem. A new visit to the otorhinolaryngologist, 4 months after discontinuation of HCQ for the second time, when the stabilization of the hearing loss was evidenced.	Use of 400 mg/ day of HCQ. Ototoxicity was treated with three 1000-mg doses of methylprednisolone. Use of methotrexate (15 mg/ week) in combination with glucocorticoids, for 15 years. Reintroduction of HCQ, 400 mg/ day, 5 days a week, posteriorly removed	After using methylprednisolone, the hearing loss was partially solved, with an improvement in the audiometry. The hypothesis of hearing loss related to HCQ was considered, and the treatment was stopped. After 15 years of treating with methotrexate in combination with glucocorticoids, it was necessary to reintroduce HCQ. The patient presented peripheral vestibular syndrome 3 months after resuming the drug and was shortly after diagnosed with a mild bilateral hearing loss. After final discontinuation, there was neither recurrence of the vestibular syndrome nor worsening of the hearing loss.	Possible ototoxicity related to the use of HCQ.
Patil et al.[2], 2020 India	To report the case of a middle-aged woman who developed auditory toxicity in relation to the use of HCQ	Audiological follow-up with PTA, in which the patient was diagnosed with a mild idiopathic sensorineural hearing loss. The thresholds worsened 6 months after beginning the treatment with HCQ. However, these symptoms improved after intervention.	Treated with HCQ (400 mg/day) and steroids (40 mg/ day of prednisolone gradually reduced to 5 mg/day and maintained) for 1 year. After intervention, the patient was treated with mycophenolate mofetil and with increased the dosage of prednisolone to 10 mg/ day	During therapy, the patient complained of tinnitus and gradual worsening of hearing. There was no history of vertigo, vomit, or other characteristics of involvement of the vestibular system. Diagnosed with mild idiopathic sensorineural hearing loss. The patient did not use any medication with the potential for auditory toxicity other than HCQ. A new audiogram obtained after stopping the use of HCQ showed auditory stabilization, with an improvement in the auditory thresholds, bilaterally.	Ototoxicity related to the use of HCQ was demonstrated.

HCQ, hydroxychloroquine; PTA, pure-tone threshold audiometry. Source: data from Chatelet et al., 2017[14] and Patil et al., 2020[2].

Immunology of India[2]. This work examined the case of a 51-year-old female patient, diagnosed with mixed connective tissue disease (MCTD), and treated with HCQ (400 mg/day) and steroids (40 mg/day of prednisolone, gradually reduced to 5 mg/day, maintained for one year). After six months of therapy, the patient complained of tinnitus and a gradual loss of hearing. She had no history of vertigo, vomiting, or involvement of the vestibular system. The otorhinolaryngologist diagnosed a mild idiopathic sensorineural hearing loss.

Pure-tone threshold audiometry (PTA), performed 6 months after starting HCQ administration, showed progression of the loss, with a decrease of approximately 20 dB in both the ears. The otorhinolaryngological assessment did not reveal any anatomic cause. Blood sugar levels and thyroid function were found normal. Her medication history was analyzed, which indicated that she had not taken any other medication with potential auditory toxicity, except HCQ. Treatment with HCQ was stopped and continued with mycophenolate mofetil and with an increased dosage of prednisolone (10 mg/day). PTA was repeated 3 months after the suspension of HCQ administration, which confirmed stabilized hearing and improved thresholds.

DISCUSSION

This study presents the evidence of ototoxic effects of HCQ. Antimalarial medications have been prescribed for years, given their low cost and good results[15], especially HCQ[16]. Nevertheless, some cases of audiovestibular toxicity along with the use of HCQ were reported in the literature[6,7,9,11,17].

Studies selected for this research[2,14] confirmed ototoxic effects of HCQ. In one of the studies[2], this was understood as the patient had no history of ototoxic medications, other than HCQ. Moreover, the patient had no anatomic, blood sugar level, or thyroid function changes. Her hearing stabilized, as some auditory thresholds improved. In the other study[14], ototoxicity was attributed to HCQ, with auditory and vestibular effects (sudden hearing loss associated with vestibular syndrome); this regressed soon after the medication was stopped. The patient developed peripheral vestibular syndrome with hearing loss 3 months after reintroducing the medication.

Ototoxicity of HCQ may be related to differing degrees of deterioration of cochlear sensory hair cells, atrophy, and vacuolization of the stria vascularis[18]. Tinnitus, sensorineural hearing loss, and vertigo are the leading symptoms[4].

In the French pharmacovigilance databank (since December 2015), there were 23 registered cases of hearing loss with HCQ treatment—none in which a positive reintroduction was observed[14]. In 17 of the registered cases, HCQ was the only questionable medication. Hearing loss was frequently sudden, either unilateral (eight cases) or bilateral (seven cases). In almost half of the cases, this was associated with cochleovestibular symptoms, such as dizziness and/or tinnitus; the disorders occurred within days to years of treatment. Most often, the damage was irreversible. However, in seven cases a total or partial improvement of hearing was observed; in two cases, however, this was not reported[14].

A study at the Medical University of Lodz (Poland) found that 28.6% (n=10) of the subjects developed sensorineural hearing loss with 80% treated with chloroquine diphosphate. This research revealed that dizziness and tinnitus were the most frequently reported vestibulocochlear symptoms, with at least 1% population on this drug[17]. These complaints were described in other studies[18,19], with tinnitus reported in one study, which was selected for our systematic review.

On the other hand, a recently published study reported that auditory changes occurred in patients on HCQ, as a consequence of the pathology being treated. Most changes were found in patients not using antimalarials[20].

The studies in this review diverged from the use of HCQ administration and the identification of the onset of auditory and vestibular effects. In one study, the patient used the drug for many years before the symptoms appeared[14]; in the other, symptoms occurred a few months after the treatment began[2]. Auditory changes after prolonged therapy with HCQ[5-7], or its ototoxic effects in the short time use[8,9,11], were already reported in the literature.

In the research with a total of 28 people, audiovestibular symptoms occurred in four patients within 24 hours of HCQ administration. However, 53% of the complications were reported a month after starting the medication. Two subjects had serious adverse effects, with significant irreversible functional sequelae (hearing loss in one patient, and hearing loss and vertigo in another)[21].

Some authors suggest that most HCQ-related ototoxicity takes place after its prolonged use[11]. Previous reports suggested that HCQ ototoxicity was related to higher HCQ dosages along with its prolonged use[5].

Another aspect is the reversibility of auditory and vestibular effects, which vary within and between studies. In the first episode, change was observed in the first study[14], with reversibility of effects after the discontinuation of HCQ and switching to methylprednisolone. Effects that appeared after reintroducing HCQ were not completely resolved, without any subjective improvement in auditory thresholds. In the second study[2], PTA was repeated 3 months after interrupting HCQ administration, showing the hearing stabilized and the thresholds improved. There is no consensus in the literature on the reversibility of

auditory and vestibular changes, with some studies found to be reversible[8,9] and with some others, irreversible[5,7].

Some studies suggest that HCQ-related ototoxicity is reversible when it is detected early. However, the first manifestations of a cochlear lesion can only be detected with auditory-evoked potentials[10].

CONCLUSIONS

The studies[2,14] reported possible ototoxicity of HCQ. Audiovestibular changes such as hearing loss, peripheral vestibular syndrome, and tinnitus were found in patients administered with HCQ. The improvement in the audiological examinations and the regression in the vestibular syndrome after discontinuing HCQ are strong indications of ototoxic effects of HCQ. However, there are still more studies required to establish the relationship between ototoxic effects and the use of HCQ.

AUTHORS' CONTRIBUTIONS

LFG: Conceptualization, Investigation, Methodology, Writing – Original Draft. **PH:** Conceptualization, Data Curation, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – Original Draft. **FSAP:** Data Curation, Formal Analysis, Supervision, Validation, Visualization, Writing – Review & Editing. **KMP:** Data Curation, Formal Analysis, Supervision, Validation, Visualization, Writing – Review & Editing.

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REVIEW ARTICLE
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Pediatric multisystem inflammatory syndrome associated with COVID-19: urgent attention required

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SUMMARY

OBJECTIVE: To identify epidemiological and clinical characteristics of multisystemic inflammatory syndrome associated with coronavirus infection as one of the severe forms of COVID-19 involvement in children and adolescents.

METHODS: review was based on articles published in 2020 in the PubMed, Medline, Scopus, SciELO and Cochrane databases.

SUMMARY: Multisystemic inflammatory syndrome is a serious clinical disorder that affects children and adolescents and is associated with the detection of previous exposure to SARS-CoV-2. It is characterized by the installation of a shock picture, with a significant increase in inflammatory markers such as presentations of Kawasaki Disease or shock syndrome related to Kawasaki Disease, or even toxic shock syndrome, with the clinical picture being characterized by fever of difficult control, rash, conjunctivitis, peripheral edema, generalized pain in the extremities and gastrointestinal symptoms.

CONCLUSIONS: Although the vast majority of children with COVID-19 have mild symptoms, it is necessary to consider that some have a hyperinflammatory response. It is essential that health professionals receive information that can assist in the recognition of this clinical condition, differentiating it from other diagnoses, so that early and appropriate treatment is instituted.

KEYWORDS: Betacoronavirus. Coronavirus infections. Child. Systemic inflammatory response syndrome. Mucocutaneous lymph node syndrome.

INTRODUCTION

The first case of a disease with significant pulmonary impairment caused by a new species of coronavirus (SARS-CoV-2) was reported In China, in December 2019. Due to its high transmissibility, it was quickly declared a pandemic, responsible for more than 19 million confirmed cases and over 728,000 deaths worldwide by August 10th, 2020[1]. Its incidence among children and adolescents can reach 5% of all cases[2] and mortality is probably low[3], but children under one year of age are more likely to have complications of the disease[4]. Obese children are also at risk for serious manifestations[5], including higher risk of multisystem inflammatory syndrome[6].

On the other hand, adults with comorbidities and older adults represent the main risk groups; the majority of affected children and adolescents are asymptomatic or have mild airway infection or gastrointestinal symptoms, abdominal pain, vomiting, and diarrhea[7]. However, in view of clinical peculiarities manifested during the evolution of some cases, a group of children who had severe forms of a systemic inflammatory disease could be identified, similar to Kawasaki Disease (KD), which was called multisystemic inflammatory syndrome in children (MIS-C) due to coronavirus infection[8]. KD is a febrile and acute vasculitis that affects young children, primarily not belonging to any specific risk group[9]. Given this syndrome does not yet have adequately defined etiological factors, it

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becomes even more challenging to understand its overlapping with MIS-C[10-12] and its relation with COVID-19, as well as its causes and prognosis, which are still being better studied. Due to its severity, different scientific societies have sought to create criteria for defining cases and treatment, and alert health professionals about the disease[13-16].

This article seeks to review current knowledge about MIS-C, with the main objective of providing health professionals with the necessary knowledge so that they can make the diagnosis and implement the treatment of this condition in face of the COVID-19 pandemic.

MULTISYSTEMIC INFLAMMATORY SYNDROME IN CHILDREN ASSOCIATED WITH SARS-COV-2 (MIS-C)

Case series

MIS-C refers to a new and serious clinical disorder, first described in April 2020 by Riphagen et al.[17], affecting previously healthy children. They studied eight cases in England, and all patients evolved with circulatory shock refractory to volumetric expansion, requiring use of vasoactive drugs for hemodynamic support; pleural, pericardial effusions and ascites were common findings; ventricular dysfunctions were observed in most patients, and an eight-year-old child developed significant coronary dilation. Most children did not have significant respiratory involvement, although ventilatory support was required in seven (87.5%) of the eight patients. An obese 14-year-old patient died, secondary to extensive cerebral infarction. During hospitalization, everyone tested negative for SARS-CoV-2 in bronchoalveolar lavage or nasopharyngeal aspirates. However, four children had previously known family exposure to COVID-19[17].

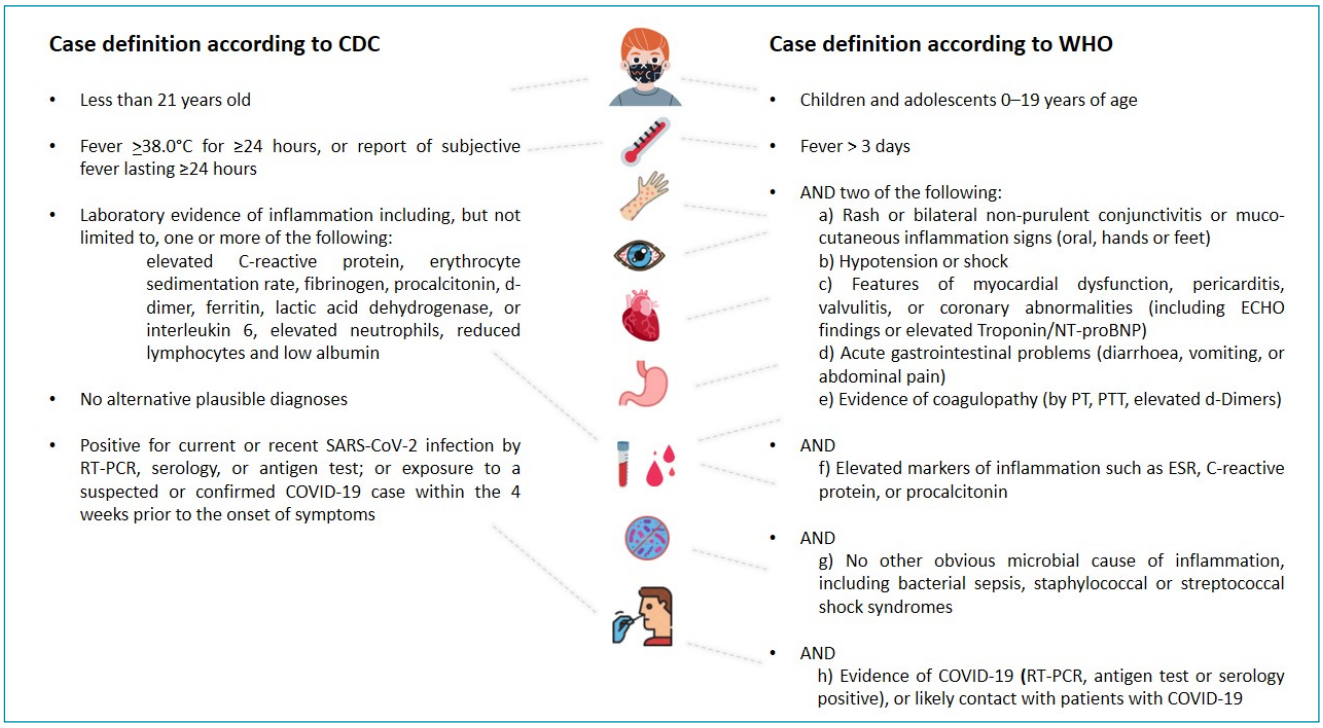
After this initial report, others were published. In an American series with 186 children and adolescents under 21 years of age (mean 8.3 years) with MIS-C, 70% of the individuals were positive for SARS-CoV-2 (RT-PCR or antibodies); 40% had symptoms that met the criteria for KD, and 15%, coronary aneurysms. A total of 92% had a significant increase in at least four inflammation markers, and four patients died[8]. In another series, 90% of 21 patients under 18 years of age (mean 7.9 years) with MIS-C treated at a hospital in Paris, presented evidence of infection by SARS-CoV-2; 57% manifested signs and symptoms of shock syndrome associated with KD, and 76%, myocarditis. No patient died, but 24% had coronary dilation and significant increase in inflammation markers[18]. Among individuals in whom the presence of previous symptoms related to COVID-19 could be identified, the time interval between the onset of those symptoms and the onset of MIS-C was 25 days in American and 45 days in French series.

As to the features of the case series already described, some conclusions can be drawn: the syndrome has been manifested in children and adolescents about four weeks after contact with SARS-CoV-2. It appears to affect patients aged between four and 14 years old and is associated with detection of previous exposure to SARS-CoV-2. Children present with shock and increase in inflammatory markers, as seen in KD[17], however, the age range in the MIS-C seems to be more advanced (average age of 10 years compared to two years for KD) and respiratory, gastrointestinal and neurological symptoms are more frequent[19]. The clinical condition of MIS-C can be characterized by difficulty to control fever, rash, conjunctivitis, peripheral edema, generalized pain in the extremities, and gastrointestinal symptoms[17]. Affected children show marked lymphopenia and thrombocytopenia, coagulopathy, increased cardiac enzymes (troponin and cerebral natriuretic peptide, brain natriuretic peptide), hyponatremia, hypoalbuminemia, and increased serum lactate dehydrogenase and ferritin[20].

Diagnostic criteria and classification

Recently, the American Centers for Disease Control and Prevention (CDC) proposed a criteria for screening MIS-C, which has been adopted in the United States to notify new cases (Figure 1). They also suggested a classification into three classes (Figure 2), aiming to better identify the most common presentations of the disease[6]. Both definitions were based on a series of 570 patients diagnosed with MIS-C in 40 states in the U.S., between March 2 and July 18, 2020. These patients had median age of eight years, 55.4% were male, and 40% were Hispanic/Latino. Two thirds were previous healthy, and 25.6% were obese. Regarding organ system, 86% had four or more involved. The majority were admitted at intensive care units (63.9%) and had severe complications: cardiac dysfunction (40.6%), shock (35.4%), myocarditis (22.8%), coronary artery dilatation or aneurysm (18.6%), and acute kidney injury (18.4%)[6]. The World Health Organization (WHO)[21] also proposed a diagnostic criteria for preliminary case definition of MIS-C (Figure 1).

These CDC data also show that 99% (n=565) of confirmed MIS-C cases in the United States tested positive for SARS-CoV-2[22]. Although available data suggest that MIS-C is an uncommon complication of SARS-CoV-2 infection in children and adolescents[8], current evidence does not support the conclusion that SARS-CoV-2 infection is the cause of MIS-C, with only a temporal relation being established. It should be noted that some cases may have a different underlying cause, such as toxic shock associated with other viruses[23,24]. In addition,



MIS-C: multisystemic inflammatory syndrome in children; CDC: centers for disease control; WHO: World Health Organization.

Figure 1. Case definition for multisystemic inflammatory syndrome in children, according to the centers for disease control and the World Health Organization.

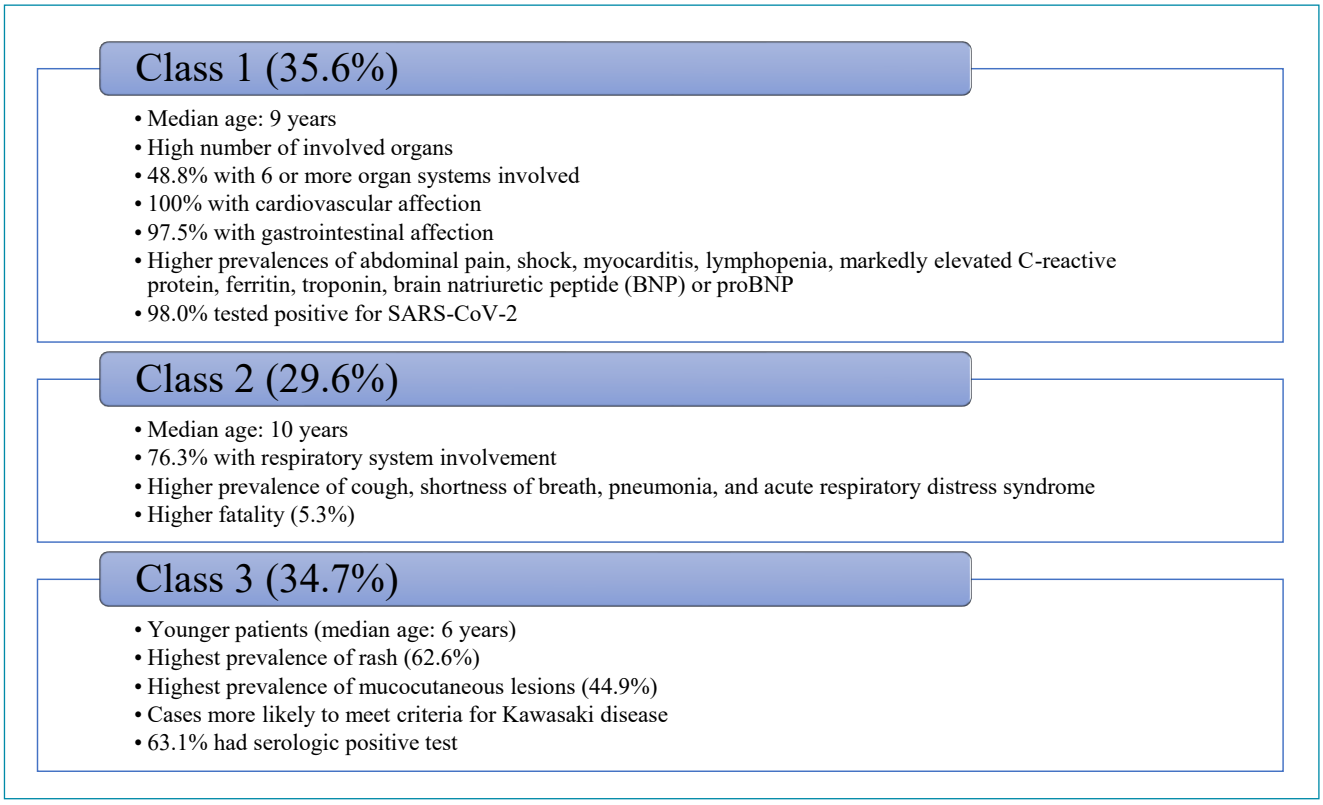


Figure 2. Classification in accordance with the centers for disease control, of 570 patients affected by multisystemic inflammatory syndrome.

several cases of MIS-C have been identified at hospitals units, so the results are not generalizable beyond the surveillance population. Seen that, in the absence of a comparison group, caution is warranted when interpreting data to infer risk factors for MIS-C.

Treatment

In the screening of patients with clinical and epidemiological symptoms of COVID-19, initial ambulatory evaluation may be considered. A preliminary laboratory workup is necessary, including complete blood count with differential, liver function tests, urinalysis, electrolytes, erythrocyte sedimentation rate, C-reactive protein, and tests for SARS-CoV-2. Patients who are in good general condition, with stable vital signs, can be followed up on an outpatient basis. Hospital admissions are indicated for patients under investigation for MIS-C with the following symptoms or conditions[13,25]:

- Abnormal vital signs (tachycardia, tachypnea);
- Respiratory distress of any severity;
- Neurologic deficits or change in mental status (including subtle manifestations);
- Even mild renal or hepatic injury;
- Severe abdominal pain, uncontrollable vomiting, inability to eat;
- Dehydration;
- KD disease-like features (partial or complete);
- Markedly elevated inflammatory markers;
- Abnormal EKG, BNP, or troponin T;
- Shock;
- Comorbidities (lung diseases, chronic heart diseases, immunodeficiencies, neoplasms, and autoimmune diseases);
- Impossibility of outpatient follow-up.

The need for admission to the intensive care unit will depend on the severity of the signs and symptoms of each patient[25]. As MIS-C is a post-infectious and immune-mediated disease, the need for isolation must be based on positive RT-PCR or serological tests for SARS-CoV-2[25]. During hospitalization, patients under investigation for MIS-C must be followed by a multidisciplinary team, which includes pediatric rheumatologist, cardiologist, immunologist, infectious disease specialist, hematologist, and intensive care pediatrician[13,26].

In addition to supportive care, treatment consists primarily of addressing the underlying systemic inflammatory state of the syndrome and its consequent complications. Figure 3 shows the basis of current proposed treatment[13,25,26].

FINAL CONSIDERATIONS

Since the beginning of the COVID-19 pandemic, much has been discussed and reported in the scientific community. Unlike adults, the vast majority of children with COVID-19 have mild symptoms. However, there are reported cases of children who present conditions related to a hyperinflammatory

- Intravenous immunoglobulin (IVIG) has been used in moderate and severe cases and in patients who present with Kawasaki disease-like features (partial or complete) or even with macrophage activation syndrome. IVIG is also indicated in patients who present with toxic shock syndrome refractory to conventional treatment. The dose is 1–2 g/kg; a repeated dose of IVIG can be used in refractory cases.
- Methylprednisolone has been used along with IVIG for severe and refractory cases. The initial dose is 10 to 30 mg/kg/day (from one to three days), followed by 2 mg/kg/day for another five days, and being tapered in two or three weeks.
- Immunomodulators, such as anakinra, canakinumab, and tocilizumab should be considered in cases with poor response to IVIG and corticosteroids.
- Acetyl salicylic acid (ASA) is recommended for the treatment of embolic phenomena, especially in patients with Kawasaki disease-like features and/or thrombocytosis (≥450,000/μl). The dose is 30–50 mg /kg/day and it is started during the active phase of the disease. As soon as the patient remains afebrile for 48 hours, the dose should be reduced (3–5 mg/k/day). This dose is maintained until the platelet count is within the normal range and if no coronary abnormalities are observed. Enoxaparin, associated with low doses of ASA, should be used in cases of major coronary artery aneurisms; the use of enoxaparin alone is indicated in cases of ventricular dysfunction (ejection fraction <35%) or documented thrombosis.
- Inotropic support, with vasoactive drugs (dobutamine, milrinone, and epinephrine), may be required in more than 50% of patients with MIS-C.
- Antibiotics are indicated when secondary bacterial infection is suspected or in cases with shock and sepsis. Ceftriaxone associated with clindamycin has been the most used regimen. In principle, the use of antivirals is not indicated because MIS-C is considered a post-infectious syndrome.

Figure 3. Basis of current proposed treatment for multisystemic inflammatory syndrome in children.

response, similar to that observed in adults. The full spectrum of MIS-C is not yet clear, as well as it is not clear yet if geographic distribution in North America and Europe reflects a true pattern or if the condition has simply not been recognized elsewhere. Therefore, there is an urgent need to collect standardized data describing clinical presentations, severity, outcomes, and epidemiology[21]. Until further robust data on the etiology of MIS-C is available, pediatricians should be alert to the rapid recognition of these cases, enabling appropriate management in emergency services, hospital wards, and intensive care units (ICUs).

Health professionals must receive information that can assist in the recognition of the MIS-C diagnosis. Common clinical features of MIS-C include fever and other clinical signs, such as findings of rash, conjunctivitis, hands and feet edema, red and / or chapped lips, "strawberry" tongue, myocardial dysfunction, cardiac conduction abnormalities, shock, gastrointestinal symptoms, and lymphadenopathy, as well as neurological changes. However, these findings can occur both in other infectious and in non-infectious diseases. Thus, the diagnostic evaluation must include other differential diagnoses more common in pediatric population and relate clinical presentation to the high prevalence of COVID-19 cases with patient's geographic region. Distinguishing patients with MIS-C from those with acute COVID-19 and other hyperinflammatory conditions is essential for early diagnosis and appropriate treatment.

AUTHORS'CONTRIBUTION

CANA: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft, Writing – Review &Editing. LADC: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration Resources, Supervision, Validation, Visualization, Writing – Original Draft, Writing – Review &Editing. ISF: Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing. IRLC: Validation, Visualization, Writing – Original Draft, Writing – Review & Editing. AAC: Formal Analysis, Methodology, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing. FVU: Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing.

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REVIEW ARTICLE
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Cardiovascular damage due to COVID-19: what do we need to know?

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SUMMARY

Severe Acute Respiratory Syndrome Coronavirus 2 is part of the *Cononaviridae* family and is the causative agent of the 2019 (Covid-19) Coronavirus pandemic declared by the World Health Organization in March, 2020. This virus has a high rate of transmission, affecting several individuals, and has caused thousands of deaths. The clinical manifestations of Severe Acute Respiratory Syndrome Coronavirus 2 infection are not restricted only to the respiratory tract, and there is an express involvement of the cardiovascular system with a higher risk of death in this group. In such patients there is an overactivation of renin-angiotensin-aldosterone system, which promotes an increase in the expression of angiotensin-converting enzyme – 2 that acts as a receptor for the SPIKE protein expressed by the virus and enables the interaction between the host cell and Severe Acute Respiratory Syndrome Coronavirus 2. This process of infection causes a hyperinflammatory state that increases the inflammatory markers of cardiac injury. Hence, an adequate understanding and clinical guidance regarding the monitoring, and controlling the damage in these patients is essential to avoid worsening of their clinical condition and to prevent death.

Keywords: SARS-CoV-2. Inflammation mediators. Shock, cardiogenic. Heart failure. Heart decompensation.

INTRODUCTION

At the end of December, 2019, a series of cases of pneumonia caused by a new virus was reported in the Chinese city of Wuhan[1,2]. The coronavirus 2 acute severe respiratory syndrome virus (SARS-CoV-2) has been identified as the etiological agent of coronavirus disease, officially named Covid-19 by the World Health Organization (WHO)[1]. This virus is part of the *Coronaviridae* family, and SARS-CoV-2 was the seventh identified member of this family.

The new coronavirus has a high dissemination potential, since it is transmitted from person to person through saliva and through the nasopharyngeal route by direct transmission. It can also infect people indirectly due to its ability to survive on different types of surfaces, which increases the infectious potential of the virus[3,4].

In the beginning, Covid-19 was known only for its high potential to infect the respiratory system. However, as it spread throughout Asia and Europe, turning into a pandemic, it was observed that the disease goes beyond the manifestations of the respiratory tract. Reports emerged about its effects of variable severity on the cardiovascular system including cardiac dysfunction, acute cardiac injury, tachycardia, arrhythmias, and heart failure, which were further aggravated in individuals with a previous history of heart disease[5].

Hence, we conducted a literature review to understand how the cardiovascular system is affected by the SARS-CoV-2 infection, and to identify the main phenomena and biochemical markers associated with the inflammatory response and cardiovascular damage. We also focused on the interaction between the angiotensin-converting enzymes with ACE inhibitors (ACE ACE) and angiotensin II receptor blockers (ARB) in the individuals infected by SARS-CoV-2.

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METHODS

Literature search for studies published between 2019 and 2020 involving patients affected by SARS-CoV-2 treated for cardiovascular complications.

In all, six studies were selected, two of which were case reports, three were retrospective cohort studies, and one was a case series. The data extraction was determined after analyzing the information available in the selected studies to understand the pathophysiological, clinical, and laboratory aspects of SARS-CoV-2. Additionally, we have grouped a series of clinical findings in Table 1, to provide information about the possible cardiovascular damage resulting from the clinical repercussions caused by Covid-19,

DISCUSSION

Relationship between Sars-Cov-2 and angiotensin 2 converting enzyme (ACE2)

The angiotensin-2 converting enzyme (ACE2) is mainly expressed in the lungs, more precisely in the alveolar epithelial cells of type II6. In patients with cardiovascular comorbidities such as hypertension, atherosclerosis, and congestive heart failure (CHF) that hyperactivate the renin-angiotensin system (RAS), overexpression of ACE2 occurs in the cardiac muscles[7].

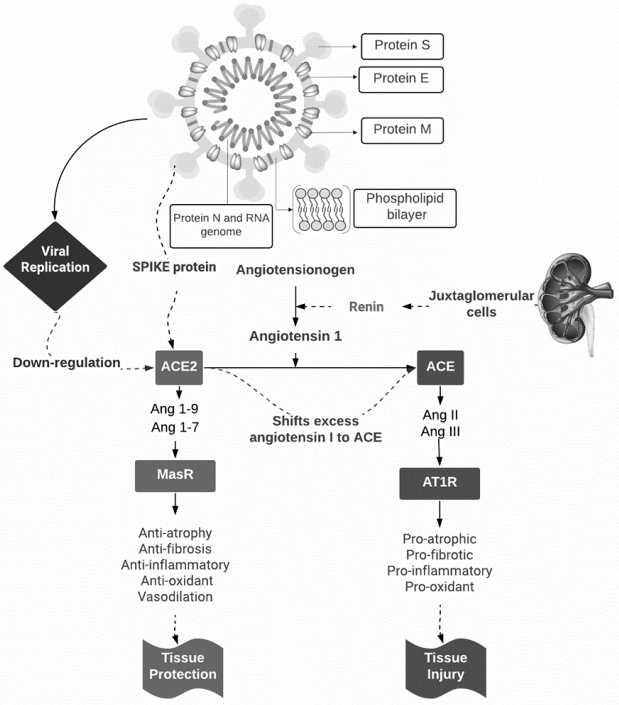
This is crucial because SARS-CoV-2 has surface proteins with high affinity for ACE2 receptors, which are expressed in

Table 1. Main cardiovascular repercussions in patients infected by covid-19.

Authors	Type of Study	Number of participants	Purpose of the study	Main clinical implications
Wang et al.[14], 2020	Case series	138	Describe the clinical and epidemiological characteristics of patients with the new coronavirus pneumonia.	Shock Acute Heart Injury Arrhythmia
Rente et al.[15], 2020	Case Report	01	Case report of a patient with diabetes mellitus who contracted the new coronavirus through community transmission, developed cardiac complications and died.	Thickening of the myocardial wall with slight increase in the cardiac area
Ruan et al.[18], 2020	Retrospective cohort	150	Investigating the cause of death of patients with SARS-CoV-2.	Myocarditis, Fulminant Heart Failure
Inciardi et al.[19], 2020	Case Report	01	Acute myocardial inflammation in a patient with Covid-19 who recovered from influenza-like syndrome and developed fatigue, and signs and symptoms of heart failure one week after recovering from upper respiratory tract symptoms.	Myopericarditis with ventricular dysfunction
Gho et al.[25], 2020	Retrospective cohort	187	To evaluate the association between previous cardiovascular disease and myocardial injury in patients who died of Covid-19.	Malignant arrhythmia – ventricular tachycardia with degeneration to ventricular fibrillation or hemodynamic instability
Zhou et al.[21], 2020	Retrospective cohort	191	To explore the risk factors of hospital death in patients with Covid-19 and describe the course of symptoms and changes in laboratory data during hospitalization.	Septic shock Coagulopathies Acute heart damage

high rate in the cardiac muscle and lung tissue, making these organs more susceptible to infection. This phenomenon is exacerbated in individuals with a pre-existing cardiac disease because they have a higher concentration of ACE2 compared to that in healthy individuals[7], as shown in Figure 1. Thus, it is assumed that the cardiac and lung injury is more severe due to the high concentration of ACE2 in these organs[7-9].

Some studies indicate that SARS-CoV-2 binds to ACE2 through one of its four structural proteins: *spike protein* (S), nucleocapsid protein (N), membrane protein (M), and the protein envelope[7], as shown in Figure 1. The viral protein that promotes interaction with the receptor of ACE2 is the S protein, and through this interaction it is able to infect the cells, and inactivate ACE2 causing lung injury, since the protective function provided by ACE2 is inhibited by the viral action. Thus, there is a displacement of angiotensin I to ACE type 1, causing an increase in the levels of angiotensin II and III. These have a harmful effect on the tissues, especially the cardiac tissue, because they have pro-apoptotic, pro-fibrotic, pro-inflammatory, and pro-oxidant activity, resulting in severe impairment of the cardiovascular function.



Ang: angiotensin; SARS-CoV-2: severe acute respiratory syndrome 2; ACE: angiotensin converting enzyme 1; ACE2: angiotensin converting enzyme 2; MasR: angiotensin receptor 1-7; At1R: angiotensin I receptor.

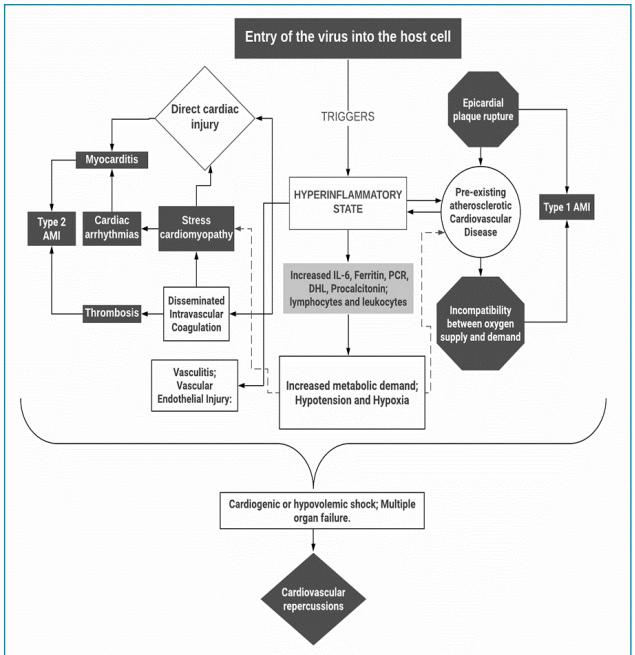
Figure 1. Molecular mechanism of the interaction between SARS-COV-2 and ACE2. The virus causes inactivation of ACE2, which results in the loss of its tissue protection function, displacing the angiotensin I to ACE1, leading to tissue injury.

Cardiovascular diseases and SARS-CoV-2 infection

Individuals with cardiovascular diseases (CVD) are more susceptible to infection due to the presence of proteins that act as viral receptors; in addition, CVD itself makes the individual more likely to develop clinical upsetting due to the hyperinflammatory state[10-13] as shown in Table 1. In individuals with hypertension with long-term intake of antihypertensives of the angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARB) class, the susceptibility to infection can increase and it can develop into a more aggressive form that leads to death[4].

Several clinical presentations resulting from cardiovascular damage in patients with Covid-19 have been observed. In a study that evaluated 138 individuals admitted for Covid-19, 16.7% presented arrhythmia and 7.2% presented acute cardiac injury[12]. The study could not identify a single cause for these changes, and the clinical and laboratory phenomena were interpreted as multifactorial causes resulting from the hyperinflammatory state caused by SARS-CoV-2, as shown in Figure 2.

In the case report by Rente et al. (2020)[15], a diabetic patient with Covid-19 presented with a severe cardiovascular involvement secondary to the inflammatory process. Computed Tomography (CT) revealed thickening of the myocardial wall with a slight increase in the cardiac area.



IL-6: interleukin-6; PCR: C-reactive protein; LDH: lactate dehydrogenase; AMI: acute myocardial infarction.

Figure 2. Main cardiovascular complications in patients infected with SARS-COV-2.

The study by Puntmann et al., (2020)[16], assessed the presence of myocardial injury in patients who had recently recovered from Covid-19, with a mean interval of 71 (64 - 92) days between diagnosis and cardiac magnetic resonance imaging (CMRI). Compared to individuals from a healthy control group, with patients presenting compatible risk factors with recently recovered patients from COVID-19, this last one had low left ventricular ejection fraction, high left ventricular volume, and left ventricular mass on native T1 and T2 MRI images. Of the 100 individuals in the study, 78 presented abnormal findings on CMRI, including 73 patients with myocardial elevation on native T1 and 60 on T2, in addition to delayed myocardial enhancement on gadolinium imaging in 32 and pericardial enhancement in 22 patients.

Increased native T1 values indicate the presence of diffuse myocardial fibrosis and/or edema, while native T2-weighted images are specific for edema. Thus, individuals with increased T1 and native T2-weighted sequences correspond to those with an active inflammatory process, while those with increased native T1 and normal native T2-weighted sequences no longer present with a hyperinflammatory state, but only diffuse residual damage to the myocardium[16]. However, native T1-weighted images might be increased in a variety of diseases involving different pathways leading to diffuse fibrosis, such as SAH or genetic cardiomyopathies[16].

In a study conducted and published by the Chinese Center for Disease Prevention and Control, involving data from 44,672 individuals who were positive for SARS-CoV-2, the mortality rate was 2.3%. The majority of deaths was seen among individuals above 70 years of age or those who had some comorbidity that compromised the cardiac function, such as CVD, SAH, and diabetes mellitus (DM)[17].

Other authors[4,10-11] reported venous thromboembolism in individuals infected by SARS-CoV-2, which is related to vascular inflammation, hypercoagulability, and endothelial dysfunction. In addition, cases of fulminant myocarditis and heart failure (HF) associated with SARS-CoV-2 infection were found[18].

However, in a study conducted in Germany involving the autopsy of 39 individuals infected with SARS-CoV-2, it was demonstrated that the virus does not necessarily infect the cardiomyocytes, but the interstitial cells or macrophages that end up invading the myocardium. The inflammatory response with increased cytokines was seen in cases with a viral load greater than 1,000 copies[20].

This indicates that the clinical manifestations of Covid-19 are not restricted to the lower and upper respiratory tract, and might have repercussions on other systems, such as the cardiovascular system. In some cases, it might not affect the respiratory system and compromise only the cardiac function, in which the patient with SARS-CoV-2 presents with myopericarditis with significant ventricular dysfunction, and absence of pulmonary manifestations[19].

Severe cases of rapid evolution can still occur in patients infected by SARS-CoV-2 in which 20% evolved to severe cases with shock[13,21].

Main biochemical markers of the impairment of cardiovascular function in patients infected with SARS-CoV-2

Direct injury to the heart occurs due to a systemic inflammatory response resulting from SARS-CoV-2 infection, in which high levels of cytokines involved with injury to the cardiovascular system are observed. Thus, there is an elevation of troponin I concomitant with the increase in other inflammatory markers such as D dimer, ferritin, IL-6, lactate dehydrogenase (LDH), C-reactive protein, procalcitonin, and lymphocyte count[22-24].

The increase in troponin I was indicated as a marker of severe Covid-19 infection compared to the non-serious form, in a meta-analysis of four studies including 341 patients. Malignant arrhythmias (ventricular tachycardia with degeneration to ventricular fibrillation or hemodynamic instability) were most frequent in individuals with high troponin I at 11.5% versus 5.2% in individuals in which it was not elevated[25].

In a study by SHI et al., (2020) which involved 416 patients admitted with Covid-19, the presence of myocardial injury was verified by increasing troponin I levels higher than the 99th percentile. This was associated with increased mortality and adult respiratory distress syndrome (ARDS), wherein the group of patients without cardiac injury had an average troponin I level of <0.006 μg/L (<0.006–0.009), while the group with cardiac injury had an average level of 0.19 μg/L (0.08–1.12)[25].

The mortality rate for individuals who developed Covid-19 without CVD involvement and with normal troponin levels was 7.6%[25]. However, the mortality rate for patients affected by Covid-19 with CVD and troponin normal levels was 13.3%, and in those infected by SARS-CoV-2 without prior CVD and with high troponin levels, the mortality rate was 37%[25]. In those who had prior CVD and were infected with SARS-CoV-2 with high troponin levels, the mortality rate was 69.4%[26]. Furthermore, patients who presented with increased troponin needed more mechanical ventilation and had a higher incidence of ventricular arrhythmias[25].

In a study by Puntmann et al. (2020)[16], high-sensitivity troponin T was correlated with native T1 ($r=0.35$; $p<0.001$) and native T2 mapping ($r=0.22$; $p=0.03$), showing significant results, which illustrates that during the active inflammatory process, troponin T levels are higher, being concordant with the findings of CMRI that reveals the presence of myocardial fibrosis and edema.

In another study, it was reported that patients who presented with D-dimer values higher than 1 µg/mL at admission had a higher risk of death, regardless of other laboratory parameters, as well as advanced age and high q-SOFA score[19].

In addition to the inflammatory markers, there is a concomitant increase in the levels of BNP (cerebral natriuretic peptide) or NT-proBNP (cerebral N-terminal natriuretic propeptide). These proteins have biological effects such as diuresis, decreased peripheral vascular resistance, inhibition of SARS, and sympathetic activity. However, when there is an impairment of the cardiac function, the values of these markers of myocardial dysfunction are quite high in patients of Covid-19 with previous cardiac dysfunction, which makes them more likely to develop a severe impairment.

Do patients who use ACE inhibitors have a greater risk of death than those who do not?

It should be noted that although ACE2 and ACE have homologous structures, the activation sites are different; hence, inhibition of ACE would theoretically have no effect on the activity of ACE2. The function of ACE2 is to promote recovery of the ventricular activity in patients with harmful damage to the cardiomyocytes, through the inhibition of angiotensin II activity[26]. However, some researchers cite that cardiac damage during infection by SARS-CoV-2 is due to angiotensin II, and one way to reduce this damage would be to administer recombinant ACE2 to stabilize the angiotensin II levels[26].

Given the fact there are few published studies, and numerous studies that are currently ongoing, the current recommendation of the Brazilian Society of Cardiology (2020)[27], the European Society of Cardiology, and the *American College of Cardiology* (2020)[28] is that ACE inhibitors and ARB should not be discontinued in patients who are stable and have been taking these medications regularly, given the proven efficacy of these drugs for the treatment of SAH and HF. However, in specific cases in which the patient presents with Covid-19 in its severe form, it is necessary to evaluate the hemodynamic stability and renal function, to make a decision about continuation or discontinuation of antihypertensive therapy.

CONCLUSION

The SARS-CoV-2 virus has a potential to cause several clinical repercussions in the body of an infected individual. Patients with pre-existing cardiac diseases need special attention, since they are at a high risk of complications and death. A possible increase in the chronic repercussions due to the cardiac lesions caused by an hyperinflammatory process triggered by the infection that alters the cardiovascular homeostasis should be considered. It is still recommended that users of ACE inhibitor or ARB should not discontinue their antihypertensive treatment, unless they develop hemodynamic or renal instability, and the decision to change the antihypertensive drugs should be taken by the specialist. In view of these findings, it is essential to maintain measures of social distancing, hands hygiene, protecting the mouth and nose when coughing or sneezing, and continued use of masks.

AUTHORS' CONTRIBUTIONS

CRN: Conceptualization, Methodology, Writing – Review & Editing. **SCL:** Methodology, Writing – Review & Editing. **RHAB:** Methodology, Writing – Review & Editing. **PPT:** Conceptualization, Supervision, Methodology, Writing – Review & Editing.

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REVIEW ARTICLE
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Potential impact of the COVID-19 in HIV-infected individuals: a systematic review

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SUMMARY

BACKGROUND: Although much has been studied about the SARS-Cov-2 virus, its effects, and the effectiveness of possible treatments, little is known about its interaction with other infectious diseases.

OBJECTIVE: The aim is to study its clinical features and morbidity, and mortality outcomes of COVID-19 patients with HIV/AIDS coinfection.

DATA SOURCES: MEDLINE, Web of Science, Embase, CINAHL, LILACS, Scopus, ClinicalTrials.gov, and Cochrane.

STUDY ELIGIBILITY CRITERIA: Atudies in any language, published after 2019, were describing COVID-19 patients with HIV/AIDS.

STUDY APPRAISAL: JBI Levels of Evidence, Joanna Briggs Institute.

SYNTHESIS METHODS: As shown in the PRISMA flow diagram, two authors separately screened the search results from the obtained titles and abstracts.

RESULTS: Chest CT was observed in patients with pneumonia by SARS-CoV-2 with findings of multiple ground-glass opacities (GGO) in the lungs, there is a need for supplemental oxygenation. One patient developed encephalopathy and complicated tonic-clonic seizures; four patients were transplanted (two, liver; two, kidneys), one patient developed severe SARS-CoV-2 pneumonia and 30 patients died (mortality rate, 11%).

CONCLUSION: HIV did not show any relevance directly with the occurrence of COVID-19. Some studies suggest that HIV-1 infection through induction levels of IFN-I, may to some extent, stop the apparent SARS-CoV-2 infection, thus leading to undetectable RNA. Moreover, some authors suggest retroviral therapy routinely used to control HIV infection could be used to prevent COVID-19 infection.

KEYWORDS: COVID-19. SARS-CoV-2. HIV. Acquired Immunodeficiency Syndrome. Antiretroviral therapy, highly active.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19) pandemic is unprecedented in scale and speed reaching several countries, affecting countless individuals and causing thousands of deaths around the world. Since HIV infection is a common disease, the concurrence between HIV infection and SARS-CoV-2 can become an important and frequent concern. Therefore, nowadays, it seems essential to clarify whether the HIV infection could alter the clinical course of SARS-CoV-2 infection[1-3].

As the outbreak grew to a pandemic, many centers worldwide raised the concern that immunocompromised patients

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may be at high risk of developing severe respiratory disease (COVID-19)[4-6]. Patients immunosuppressed for various reasons have effects on humoral and cell-mediated immunity and neutrophil function, increasing the risk of severe infections caused by viral agents, such as adenovirus, rhinovirus, norovirus, influenza virus, and respiratory syncytial virus[4,6]. Many of these latter viruses, including coronaviruses, implicate the host response as an important contributor to the disease process; in this respect, dysregulated and excessive innate immune responses appear particularly important drivers of tissue damage during infection[7,8]. These aspects may be relevant when it comes to infection of an immunocompromised host, potentially protected by a weaker immune response against the infection.

However, curiously reviewing the mortality and morbidity reports published on severe acute respiratory syndrome (SARS), middle-east respiratory syndrome (MERS), and more recently on COVID-19, immunosuppression is not mentioned as a risk factor for more severe disease or mortality coronaviruses when compared with the general population, both children and adults[1,3,9]. Mascolo et al.[9] proposed a hypothesis that could explain the interaction between HIV infection and the clinical course of SARS-CoV-2 infection. The latter suggests that patients with conditions that impair the state of the immune system, as immunosuppression for solid organ transplantation or HIV infection, could be protected against severe clinical manifestations, despite the susceptibility to SARS-CoV-2 infection[9,10].

This fact could be explained by the activation of the immune system, especially T cells, which represent a landmark of the histological picture of lung injury related to COVID-19[9]. Additionally, the antiretroviral treatment started (lopinavir/ritonavir, LPV/r) as management of SARS-CoV-2 infections, and it could play a double effect: inhibition of SARS-CoV-2 replication, facilitating the viral clearance and inhibition of HIV replication that could allow a slight activation of the immune response, just enough to contrast the SARS-CoV-2 infections without the beginning of the hyperinflammatory state[9,10]. Furthermore, the antiretroviral (LPV/r) administration could be useful for a potential and not yet confirmed direct anti-SARS-CoV-2 antiviral effect[9-11].

There is much to be clarified about the existing immunological interactions between HIV and SARS-CoV-2, and further studies are urgently required to face this lack of data. For this reason, this study aims to clarify the clinical features and morbidity and mortality outcomes of patients with coinfection COVID-19 and HIV/AIDS.

METHODS

This study adhered to PRISMA guidelines[12]. The review was not registered in PROSPERO, and corresponding authors were not contacted due to time constraints. Ethical approval was not required for this type of study.

Literature Search Strategy

Eligible studies were identified by searching the following databases: MEDLINE, Web of Science, Embase, CINAHL, LILACS, Scopus, ClinicalTrials.gov, Cochrane, and Google Scholar. The studies were identified by a literature search of databases following medical subject heading (MESH) terms: (COVID-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS-CoV-2) AND (Human Immunodeficiency Virus OR HIV OR Acquired Immune Deficiency Syndrome Virus OR Acquired Immunodeficiency Syndrome Virus OR AIDS Viruses OR AIDS Virus).

Reference lists of the identified publications for additional pertinent studies were reviewed. Three researchers (KSM, ACS, and LASS) searched for articles published between December 2019 and July 2020, considering the first case of COVID-19 was registered in the city of Wuhan, China, in December 2019[13].

Inclusion Criteria

Studies meeting the following criteria were included: (a) all the studies that were describing patients affected by the SARS-CoV-2/COVID-19 and with HIV/AIDS, for example, primary case reports, case series, observational studies, randomized controlled trials, and others, (b) there were no language restrictions while selecting the studies, and (c) studies published after 2019.

Selection of Studies

The authors KSM and LASS separately screened the search results using the titles and abstracts. Duplicate studies and reviews were excluded. The author ACS contributed along with the first two went through the full text articles to determine whether the studies meet the inclusion criteria. Discrepancies were resolute for author AKG. The selection of the studies was summarized in a PRISMA flow diagram (Figure 1).

Data Collection and Analysis

Various characteristics of the eligible studies were extracted, including the first authors' last names, year of publication, location of the study (country), study design, primary objective, level of evidence, patients (population), signals and symptoms, mean patients age, patient outcome, laboratory tests, and treatment. Standardized data extraction forms were specifically being created for this review, and

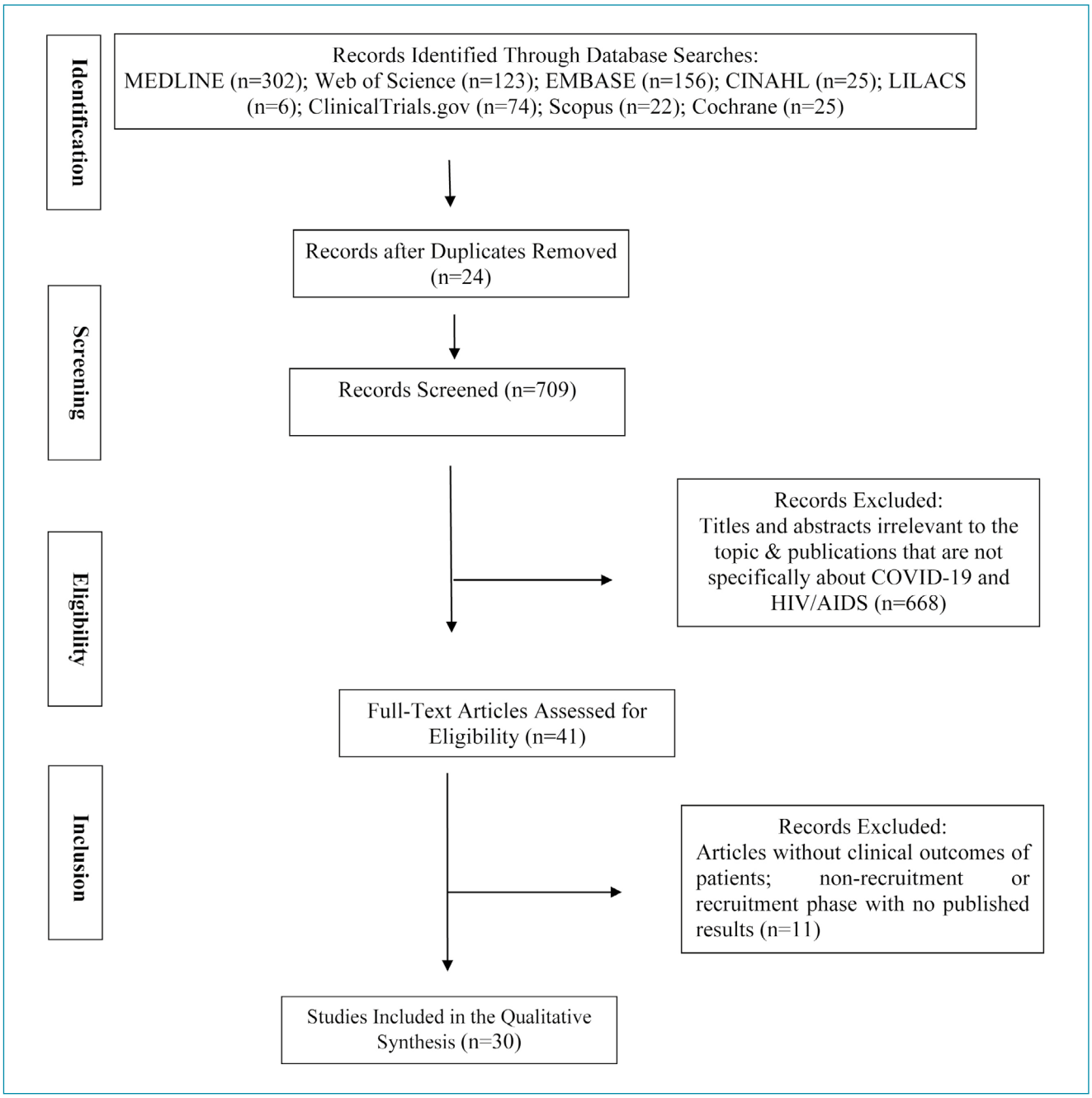

Figure 1. Flow diagram of the search for eligible studies of COVID-19 and HIV/AIDS. CENTRAL=Cochrane Central Register of Controlled Trials.

the results were entered into a database. All data entered were double-checked.

Quality of Evidence

The quality of included studies was assessed using New Joanna Briggs Institute (JBI) Levels of Evidence, developed by the JBI Levels of Evidence and Grades of Recommendation Working Party (October 2013)[14].

RESULTS

Selection of Relevant Studies

The virtual searches retrieved a total of 733 studies (302 from PubMed, 123 from Web of Science, 156 from Embase, 25 from CINAHL, 06 from LILACS, 74 from ClinicalTrials.gov, 22 from Scopus, and 25 from Cochrane). Excluding duplicates (24), 709 articles were selected. After evaluating the title

and abstract, 668 additional articles were excluded. For the 41 studies that had full-text analysis, 30 met the eligibility criteria for this study and were later included in the review. The PRISMA flow diagram for selecting available studies is given in Figure 1.

The characteristics of the included studies are shown in Table 1. The number of participants in each study ranged from 1 to 51. The articles were published in China[15-17,21,31,37,43], Spain[18,23], Uganda[19], Turkey[20], Germany[22], New York[33,34], Austria[25], the United States[24,25,32,40,41], Italy[27,29,44], Japan[28], Cyprus[30], Chicago[35,38], the United Kingdom[36,39], and Singapore[42] in 2020, although COVID-19 was described in 2019[13]. All the articles were in English.

Study Designs

A total of 28 articles were case reports or case series (level of evidence 4.d)[15,16,18-22,24-44] and two were cohort studies (level of evidence 4.b)[17,23]. Thus, the studies included in this review have low levels of evidence according to our classification.

Study Characteristics

In total, 266 patients coinfected with HIV and COVID-19 were included, of whom 209 were men and 57 were women. In the case studies, male patients were 24 and 75 years old[15,16]. Before the observational study, the median age of patients (n=8) was 57.0 years (47.5–61.5)[17].

Clinical Manifestations

The principal clinical manifestations were fever, coughing, shortness of breath, diarrhea or gastrointestinal symptoms, and pneumonia, as shown in Figure 2. The study by Guo et al.[17] showed that till March 3, 2020, 6 of the COVID-19/HIV patients were considered mild cases, 1 was severe, and 1 was a critical case who died. In the study with 33 patients presented by Härter et al.[22], mild clinical cases were 25/33 (76%), severe in 2/33 cases (6%), and critical in 6/33 cases (18%), with 3/33 both patients with known comorbidities. Two other cases of similar deaths were reported by Gervasoni et al.[29] The first was a 47-year-old overweight patient, but without known comorbidities, needed mechanical ventilation, and the second had cardiovascular disease plus a recent diagnosis of lung cancer during hospitalization.

There have also been reports of deaths in other studies. Aydin et al.[20] related the patient, who had potential comorbidities such as obesity, diabetes, hypertension, and chronic obstructive pulmonary disease (COPD), refused to undergo regular treatment for the comorbidities. In the series of cases presented by Suwanwongse and Shabarek[33], all 9 patients mentioned had comorbidities and 7 died – 4 due to hypoxemic respiratory failure and 3 due to septic shock and multiple organ failures. In the study by Shalev et al.[34], of the studied 31 patients, 8 died, of these 4 were above 65 years old, and the other 4 were between 50 and 65 years old. At the time of death, four of them were not ordered to perform cardiopulmonary resuscitation maneuvers. One patient required intubation and mechanical ventilation in the ICU and died of multiple organ failure caused by COVID-19 pneumonitis[36]. Childs et al.[39] mentioned 18 patients in their study, of these 5 died with a mean hospital stay until 8 days, with an interval of 3 and 28 days until death. Okoh et al.[40] reported 27 patients observed in their study and 2 died, who were elderly and had multiple coexisting conditions complicated by septic shock and multi-organ dysfunction syndrome.

Diagnosis

Clinical and epidemiological information are the important factors in the investigative process. Thus, as a travel history for COVID-19 epicenters, direct or indirect contact with persons suspected or confirmed of SARS-CoV-2 infection was decisive on the front line against COVID-19 in the control, treatment, and care as in diagnosis[16,17,19,21,22,24,26,29,35,41-43].

Even though the patients had some main distinctive manifestations of COVID-19, the SARS-CoV-2 tests using reverse transcriptase polymerase chain reaction (RT-PCR) were persistently negative in different samples at various times during the hospitalization period[16,21,24,25,30,37,38,44]. The principles of the diagnostic methods were nasopharyngeal swabs for RT-PCR[15,16,18-35,37,44], nucleic acid test (NAT) of SARS-CoV[17], laboratory test[19,20,22,24,31,37,39,40,42-44], chest radiography[24,27,29-31,34,38,39], computed tomography (CT) of the chest[15-18,20,21,24,28,29,37,41,43,44], brain magnetic resonance imaging (MRI) with and without contrast[41], electrocardiogram (ECG)[41], sputum, aspiration of the lower respiratory tract[23], or bronchoalveolar lavage[22].

Patients' Outcomes

The principal patients' outcomes were as follows:

- Mild lymphopenia with a lymphocyte count of 1.1 × 10^9/L[15,18,20,21,28,31,33,34,36,37,39,41,44];
- Low CD4+ T-lymphocyte percentage[15-17,21-23,28,29,33,34,36,38,39];
- The chest CT indicated the SARS-CoV-2 pneumonia with findings of multiple ground-glass opacities (GGO) in lungs[15,16,20,21,23,25,27-31,33,34,37-39,41,43,44];
- On supplemental oxygen, arterial blood gas analysis revealed: pH 7.41, PCO_2 37.4 mmHg, PO_2 63.9 mmHg, and HCO_3^- 23.4 mmol/L[15,21,25,34,38,44];
- Thirty patients died, so the mortality rate was 11%[17,20,22,29,33,34,36,39,40];

Table 1. Characteristics of the included studies.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
Zhu et al.[15] (2020)	We reported on an identified unique severe case involving coinfection of SARS-CoV-2 and HIV.	01 man	61	On admission, physical examination revealed a body temperature of 39°C, respiratory rate of 30 breaths per minute and oxygen saturation of 80%, which reached 91% while the patient was given mask flow oxygen at a rate of 5 L/min. On supplemental oxygen, arterial blood gas analysis revealed: pH 7.41, PCO2 37.4 mmHg, PO2 63.9 mmHg, and $HCO_3^{\boxtimes}$ 23.4 mmol/L. Lymphopenia also got worse, with a lymphocyte count of 0.56 × 10^9/L and a low CD4+ T-lymphocyte of 4.75%.	The chest CT indicated the SARS-CoV-2 pneumonia with findings of multiple ground-glass opacities (GGO) in bilateral lungs. The follow-up chest CT displayed progressive GGO and consolidation in lungs.	Isolation at home; anti-HIV drug, lopinavir/ritonavir 400/100 mg per dose, twice daily for 12 days; moxifloxacin 400 mg once daily for 7 days, γ-globulin 400 mg/kg once daily for 3 days; and methylprednisolone 0.8 mg/kg once daily for 3 days.	RT-PCR and chest CT.
Zhao et al.[16] (2020)	We reported a unique case of COVID-19 with preexisting immune dysfunction from previous coinfection of HIV and HCV.	01 man	38	Nasal congestion, runny nose, cough, expectoration, chest tightness, palpitation, and abdominal distension. Low fever of 37.2°C and normal pulse, breath and blood pressure.	A chest CT showed right lower pneumonia.	Oseltamivir and IFN-α inhalation and taking lamivudine, tenofovir, and efavirenz.	RT-PCR and chest CT.
Guo et al.[17] (2020)	We investigated 1178 HIV/AIDS patients in Wuhan and surveyed their health status and whether they were directly contacted with confirmed COVID-19 patients.	07 men and 01 women	The median age of patients was 57.0 years old (47.5–61.5).	Fever, non-productive cough, dyspnea, myalgia, and diarrhea. Till March 3, 2020, 6 of the COVID-19/HIV patients were with mild cases, 1 was with severe case, and 1 was with critical case who died. Six of them had CD4 counts >350/μL, and 2 with CD4 counts between 101 and 350/μL. All patients have a low HIV-VL as less than 20 copies/mL.	NA	All 8 COVID-19 patients' ARV regimens are nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). None of those COVID-19/HIV patients took LPV/r-based ART regimen, which seemed to support the use of LPV/r in PrEP and cope with COVID-19.	CT scan and virus nucleic acid test (NAT).

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
Blanco et al.[18] (2020)	We described the first single-center experience of COVID-19 in patients infected with HIV-1, including clinical characteristics, antiviral and antiretroviral treatment, and outcomes.	05 men	The median age of patients was 39.8 years old (29–49).	Two patients had comorbid conditions. Four were virologically suppressed: two with protease-inhibitor (darunavir-boosted cobicistat) and two with integrase inhibitor (dolutegravir)-based ART. CD4 counts were above 400 cells/μL in all patients apart from Patient 5, who was ART naive and a very advanced late presenter. Two patients had upper respiratory tract infections, and three had viral pneumonia, including two requiring admission to the intensive care unit (ICU) with invasive (Patient 2) and non-invasive (Patient 5) mechanical ventilation.	NA	We started all five patients on anti-SARS-CoV-2 treatment on the day of diagnosis. Patient 1 and 5 with darunavir-boosted cobicistat, and patients 2–4 were adapted to lopinavir-boosted ritonavir. We left Patient 1, who had mild infection, on his normal ART. We gave the other patients hydroxychloroquine (patients 2–5) with azithromycin (patients 3–5), and interferon β-1b (patients 2 and 5). We administered concomitant antibacterials in all three patients who had pneumonia (patients 2, 4, and 5), and corticosteroids in two patients (patients 4 and 5) and tocilizumab in one (Patient 2).	RT-PCR and chest CT.
Baluku et al.[19] (2020)	We described a case of HIV/SARS-CoV-2 coinfection.	01 woman	34	On admission (Day 1), she was in a good general condition with no symptoms. There was no wasting, lymphadenopathy, or pallor and her temperature was 36.4°C) (normal). She had a blood pressure of 110/80 mm of mercury (mmHg) and a pulse rate of 84 beats per minute (b/min), both of which were normal. The	NA	Azithromycin (500 mg daily for 5 days), hydroxychloroquine (400 mg twice on day 3 and 200 mg twice daily for the subsequent 5 days), and paracetamol (1 g three times a day for 5 days). Oral	RT-PCR and laboratory test.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				respiratory exam was significant for tachypnea (a respiratory rate of 26 breaths/min) with normal oxygen saturation (SpO_2) of 96% on ambient air. There was no respiratory distress, and auscultation of the chest was normal. On Day 3, she reported headache, chest pain, anorexia, and muscle aches but no cough or shortness of breath. Her vitals were normal, except for a respiratory rate of 24 breaths/min and a pulse rate of 97 b/m. On Day 6, she developed watery nonbloody diarrhea without vomiting, abdominal pain or fevers. Clinically, she had dry mucus membranes and the blood pressure was 96/60 mmHg. All symptoms had resolved by Day 12. The respiratory rate was 16 b/min, the pulse rate was 80 b/min, and she had a blood pressure of 126/88 mmHg.		ciprofloxacin (500 mg twice daily for 5 days) and oral rehydration.	
Aydin et al.[20] (2020)	These cases are presented to show the course of coinfection with COVID-19 in HIV-infected cases.	P1 – man	34	With 10 years of known HIV/HBV coinfection but without treatment compliance due to bipolar disorder was admitted with the complaints of dyspnea, dry cough, and fever. On physical examination, there was no pathology other than cachectic appearance, low-grade fever (38°C), and bilateral coarseness in the lungs on auscultation.	Chest CT showed multiple GGO in the bilateral lower lung	Trimethoprim-sulfamethoxazole (TMP-SMX) and oseltamivir	RT-PCR, chest CT, and laboratory test.
		P2 – man	44	Due to HIV infection, it has been using TDF/FTC+dolutegravir for the past 2 years. Although obese patient (body mass index: 35.5 kg/m^2)	X-ray and chest CT showed bilateral patch-like paving stone view, large	Hydroxychloroquine, azithromycin, and oseltamivir.	

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				had diabetes, chronic obstructive pulmonary disease (COPD), and hypertension, he refused to get regular treatment for these comorbidities. On March 25, 2020, he applied with a complaint of fever, dry cough, and shortness of breath. In the ICU, he suffered a sudden cardiac arrest, despite cardiopulmonary resuscitation, the patient has died.	glass-ground lesions, and was interpreted as mid-advanced viral pneumonia positive		
		P3 – man	35	Has been using TAF/FTC+elvitegravir/cobicistat (EVG/c) for 2 years with the diagnosis of HIV infection and followed up regularly for HIV RNA negative according to the EACS guidelines. On March 29, 2020, he applied with severe weakness, dry cough, and non-bloody diarrhea (5–6 times per day) that had been going on for 11 days. Although there was no pathological finding in the physical examination of the patient and normal oxygen saturation SpO2 95% in room air.	Chest CT showed bilateral peripherally located incomplete ground-glass density infiltrations.	Hydroxychloroquine and oseltamivir.	
		P4 – man	36	Viral suppression continued for 4 years under TAF/FTC/EVG/c treatment, admitted with a dry cough and persistent fever for 6 days.	Chest CT revealed bilateral extended GGO.	Hydroxychloroquine, azithromycin, and oseltamivir	
Wang et al.[21] (2020)	We described a case of HIV/SARS-CoV-2 coinfection.	01 man	37	He denied any other diseases before this onset. The initial physical examination revealed a body temperature of 38.8°C, oxygen saturation (SpO2) 85–90% under ambient air, respiratory rate of 40 breaths/min, blood pressure	The chest CT of this patient showed multiple infiltrations in both lungs, consistent with viral infection. On the second chest	High-flow oxygen and arbidol; methylprednisone, moxifloxacin, and sulbactam/cefoperazone (sulperazone); human	RT-PCR and chest CT.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				of 145/93 mmHg, and pulse of 119 bpm. His vital signs remained stable for the first 3 days, apart from dyspnea and chest pain. On 14 February, he developed a high fever of 39.4°C accompanied with dyspnea and palpitations. His body temperature returned to normal, but he still had dyspnea, palpitations, and chest pain and he still needed high-flow oxygen (10 L/min) through a mask.	CT, it showed inflammation absorption compared with the previous one.	serum albumin, thymosin, and ulinastatin; tocilizumab.	
Härter et. al.[22] (2020)	We described our early experiences with COVID-19 and clinical characteristics in patients with documented HIV infection.	30 men and 03 women	The median age of patients (n = 33) was 48 years old (26–82).	Two patients with detectable (HIV)-1 viremia needed hospital admission including intensive care treatment and mechanical ventilation, and one of these patients died. Comorbidities other than HIV infection were documented in 20/33 patients, including arterial hypertension (P10), chronic obstructive pulmonary disease (P6), diabetes mellitus (P4), cardiovascular disease (P3), and renal insufficiency (P2). Coinfection with hepatitis B has been documented in five patients: a resolved hepatitis B in four patients, and in one patient a chronic hepatitis B. In one patient, a cured hepatitis C. Common symptoms were cough in 25/32, fever in 22/32, arthralgia/myalgia 7/32, headache 7/32, and sore throat in 7/32. Sinusitis and anosmia occurred in 6/32 for each. At the last available follow-up, 29/32 of patients with documented outcome had recovered from COVID-19. Altogether, 14/33	NA	Antiretroviral regimens included NRTIs in 31, integrase strand transfer inhibitors (INSTI) in 20, protease inhibitors (PI) in 4 and Non-NRTIs in 9 cases. NRTIs were mainly tenofovir alafenamide (16 cases), tenofovir disoproxilfumarate (6 cases) and a cytidine analog, either emtricitabine (P22) or lamivudine (P9).	RT-PCR, laboratory test, bronchoalveolar lavage or sputum.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				patients were admitted to hospitals. Treatment on intensive care units (ICU) was necessary in 6 of 14 hospitalized patients. Of the 14 patients, requiring treatment in hospitals, 10 have been discharged in the meanwhile. One patient is still in hospital but discharged from ICU. In one patient, a spontaneous pneumothorax could be seen as a complication of persisting cough. Three out of 32 patients with documented outcome had died (P9, P20, and P24).			
Vizcarra et al.[23] (2020)	We compared the characteristics of HIV-infected individuals with COVID-19 with a sample of HIV-infected individuals assessed before the COVID-19 pandemic, and described the outcomes of individuals with COVID-19.	43 men and 08 women.	The median age of patients was 53.3 years old.	Fever was defined as an axillary temperature of 37.3°C or higher. Severe disease was defined as fever or suspected respiratory infection plus respiratory rate greater than 30 breaths per min, oxygen saturation of 93% or less on room air, or acute severe respiratory distress (acute lung infiltrate in chest imaging and ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air [PaO2/FiO2] of ≤300). Critically ill individuals were those with rapid disease progression and respiratory failure with need for mechanical ventilation or organ failure that needs monitoring in an intensive care unit (ICU). Lymphocytopenia occurred in 15 (43%) of 35 individuals, thrombocytopenia in four (11%), increased alanine aminotransferase in eight (23%), and median PaO2/FiO2 was 462 (IQR 404–474; with	Radiological information was available for 38 (75%) individuals, of whom 17 (45%) had consolidation, 11 (29%) had an interstitial lung pattern, and 21 (55%) had bilateral pulmonary infiltrates.	Regarding ART, a significantly higher proportion of individuals with COVID-19 were receiving tenofovir, either as tenofovir alafenamide (n = 36) or tenofovir disoproxil fumarate (n = 1), before COVID-19 diagnosis (37 [73%]) than those without COVID-19 (487 [38%], p = 0.0036), whereas the use of protease inhibitors or integrase strand transfer inhibitors (INSTIs) was similar in both groups.	RT-PCR, sputum or lower respiratory tract aspirates.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				five [10%] patients with a ratio <300) at hospital consultation. Notably, 15 (43%) individuals had increased D-dimer concentrations, and the serum cytokine profile showed high interleukin-6 concentrations in 7 (70%) of 10 analyzed cases.			
Benkovic et al.[24] (2020)	We described patients with covid-19 and HIV.	P1 – man	The median age of patients was 59.7 years old (56–65).	Was diagnosed with HIV in 1995. His only other comorbid condition is hyperlipidemia. He began to feel tired and noticed a decrease in his sense of taste and smell. Although he had no fever or respiratory symptoms, he was concerned when his symptoms did not resolve after 9 days and went to an emergency clinic. Two days after his positive test his symptoms of anosmia and ageusia resolved.	NA	Emtricitabine, tenofovir alafenamide, dolutegravir, and maraviroc.	RT-PCR
		P2 – man		Started to developed subjective fevers and fatigue. A total of 19 days after the initial onset of fatigue he developed a temperature of 102°F (38.9°C) when he went to urgent care. He had no shortness of breath or cough.	Chest X-ray was suggestive of pneumonia.	Emtricitabine, tenofovir alafenamide, etravirine, and abacavir; Lisinopril 10 mg daily.	RT-PCR and chest X-ray.
		P3 – man		Was diagnosed with HIV in 1996. He was discharged home with instructions to self-isolate. After discharged in 1 week, he no longer has any symptoms. Had 2 weeks of non-productive cough and bowel movements. He decided to seek medical attention when he developed a temperature of 100.8°F (38.2°C). In the local emergency	Chest X-ray did not show any consolidation.	Emtricitabine, tenofovir alafenamide, and dolutegravir. rosuvastatin and losartan.	RT-PCR, laboratory test and chest X-ray.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				room, the temperature was 100°C, blood pressure was 113/65, heart rate was 75, breathing did not work, and oxygen saturation was 97% in ambient air.			
		P3 – man		Was diagnosed in 2006. He went to the emergency room, temperature was 102.9°F (39.4°C), pulse 83, oxygen saturation 93% on 2 L nasal cannula, blood pressure was 136/71. He was awake, alert, and not showing signs of respiratory distress.	Chest X-ray did not show any consolidation	Oseltamivir 75 mg twice a day for 5 days. Emtricitabine, tenofovir alafenamide, elvitegravir, and cobicistat. Losartan, metformin, atorvastatin, and Coumadin.	RT-PCR, laboratory test and chest X-ray.
Müller et al.[25] (2020)	We described patient with covid-19 and HIV.	01 man	55	In the 1970s, he acquired hepatitis C virus (HCV) infection, probably via factor VIII supplementation, and in 1985, HIV infection. Interferon-based HCV therapy resulted in a sustained virological response. Liver cirrhosis was diagnosed in 2017. In 2018, a solitary hepatocellular carcinoma with a diameter of 55 mm was detected. After successful downstaging by transarterial chemoembolization, the patient underwent uneventful liver transplantation (LT) in January 2019. One year after LT, HIV-PCR was negative. On March 2020, he developed fatigue and fever up to 39.6°C. On March 26, he went to the local hospital in order to be checked for COVID-19. Following worsening symptoms and a positive result for SARS-CoV-2 PCR, he was hospitalized on April 2. The patient presented with fever (39.4°C), fatigue, cough, and tachycardia.	Chest X-ray showed diffuse bilateral infiltrates.	Emtricitabine/tenofovir alafenamide/rilpivirine for HIV is ongoing since 2016. Oxygen and ampicillin/sulbactam.	RT-PCR, laboratory test and chest X-ray.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
Modi et al.[26] (2020)	We presented a case of an orthotopic liver transplant recipient with well-controlled HIV who successfully recovered from a mild, flu-like illness attributed to SARS-CoV-2.	01 man	32	He developed fatigue, fever, headache, and a dry cough. He presented to the emergency department (ED) and was found to have a temperature of 101°F. The patient was initially instructed to engage in supportive care measures at home; however, the development of chest tightness and shortness of breath prompted presentation to the hospital the following day. He complained of aggravating dry cough, but denied any abdominal symptoms. His vital signs were within normal limits. The patient's respiratory symptoms gradually improved, and he never demonstrated fever or hypoxia. He was discharged home on the sixth day of admission and instructed to maintain isolation for 14 days.	Chest X-ray did not demonstrate any infiltrates. CT imaging was not obtained.	Efavirenz, emtricitabine, and tenofovir disoproxil fumarate. His maintenance immunosuppression consisted of mycophenolate mofetil (MMF), prednisone, and tacrolimus. His ART was changed to raltegravir, emtricitabine, and tenofovir disoproxil fumarate posttransplantation; prednisone was maintained, and tacrolimus was dosed to target a lower trough of 5–9 ng/mL. Hydroxychloroquine was administered outside of a clinical trial for 5 days.	RT-PCR
Riva et al.[27] (2020)	We reported three HIV-positive subjects on antiretroviral (ARV) regimen containing darunavir with good immunovirological status, diagnosed with COVID-19.	P1 – man	62	HIV-positive man was admitted at our ED referring dry cough and fever up to 38.8°C for at least 7 days. In the following days, the patient's respiratory function quickly worsened despite Venturi mask and continuous positive airway pressure therapy, and 1 week after admission, the patient required mechanic ventilation. At the last available follow-up (April 1), the patient is still inpatient with no fever and requiring only low-flow oxygen delivery.	Chest X-ray evidenced a bilateral reticular interstitial thickening.	His ARV regimen consisted of darunavir/cobicistat and lamivudine; doxazosin, metoprolol and amlodipine; lopinavir/ritonavir and hydroxychloroquine. In the ICU, lopinavir/ritonavir and hydroxychloroquine were replaced by tocilizumab and remdesivir.	RT-PCR and chest X-ray.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
		P2 – man	63	On March 18, the patient was admitted to the ED reporting fever up to 38.0°C for at least 11 days with no signs of respiratory distress. On March 28, he was successfully discharged.	The chest X-ray evidenced a bilateral reticular interstitial thickening.	On darunavir-based (given at 800 mg co-formulated with cobicistat, tenofovir alafenamide, and emtricitabine). At hospital admission, darunavir/cobicistat was replaced with lopinavir/ritonavir and hydroxychloroquine, irbesartan.	
		P3 – woman	57	Developing SARS-CoV-2 infection was admitted to our hospital on March 24 reporting fever and cough from at least 10 days. At the last available follow-up (April 1), she was still inpatient waiting for the results of the nasopharyngeal swab to confirm SARS-CoV-2 absence before her discharge.	The chest X-ray evidenced reticular interstitial thickening at the right lung.	On darunavir-based (given at 800 mg combined with cobicistat and raltegravir) and on nebivolol and atorvastatin; hydroxychloroquine.	
Nakamoto et al.[28] (2020)	We described a case was coinfected with SARS-CoV-2 and HIV.	01 man	28	His immune status from HIV infection was not well-controlled due to a lack of ART. Underlying condition: smoker, HBV infection; Day of admission of the disease: 8; Saturation at admission: 97	CT findings at admission: multiple GGO.	ART and hydroxychloroquine.	RT-PCR and chest CT.
Gervasoni et al.[29] (2020)	We described our experience with HIV-positive patients regularly followed by our hospital who were infected with SARS-CoV-2.	36 men and 11 women	The median age of patients was men 51 ± 11 years and women 53 ±	A total of 28 patients tested positive for SARS-CoV-2, including one female asymptomatic patient who was tested because she was a healthcare provider. The COVID-19 diagnosis of the untested patients was based on their clinical symptoms and the presence of risk factors. A total of 13 of the 28 SARS-CoV-2 positive patients were hospitalized; 6	Interstitial pneumonia was diagnosed by means of an X-ray in three cases, and GGO was identified by means of CT in one.	Approximately 80% of the identified patients were receiving integrase inhibitor-based antiretroviral treatment and 11% a protease inhibitor-based regimen (11%); 42% were receiving a tenofovir-based	RT-PCR, chest X-ray, and chest CT.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
			12 years old.	had severe lung disease (respiratory rate ≥30 breaths/min, resting percutaneous oxygen saturation ≤93% in room air); 2 of whom required mechanical ventilation: 1 recovered and was discharged and the other died. Another patient with cardiovascular disease and a recent diagnosis of lung cancer died during hospitalization. For comparative purposes, the crude mortality rate of the HIV-negative COVID-19 patients in our hospital (n=502, 67% males, mean age 61±16 years) is currently ~17%. Nearly 64% had at least one comorbidity (82% of the males and 58% of the females), mainly dyslipidemia (32%), arterial hypertension (30%), and hepatitis B or hepatitis C coinfections (11%).		regimen. Fewer than 50% of the patients were given potential anti-SARS-CoV-2 treatments, specifically hydroxychloroquine (17%), azithromycin (15%), lopinavir/ritonavir (11%); one was treated with tocilizumab and remdesivir, and one with tocilizumab alone.	
Iordanou et al.[30] (2020)	We described a case of was coinfected with SARS-CoV-2 and HIV.	01 man	58	The patient had malaise, fever, and dry cough on illness day 1. Breathing difficulty developed on day 4, which led him to seek medical attention. The patient was transferred to hospital. On admission, the patient had a fever (38°C). The oxygen saturation was 92% while the patient was breathing ambient air, the respiratory rate 22 breaths/min, the blood pressure 117/72 mmHg, and the heart rate 105 beats/min. The patient was awake, alert, and fully oriented. He had no comorbidities. The mechanical ventilation aimed at minimizing ventilator-induced lung injury (VILI). Initially, we targeted a tidal volume	Chest radiography was performed, which showed bilateral air space pacifications.	Levofloxacin and oseltamivir. Azithromycin and Chloroquine. Piperacillin-tazobactam and vancomycin. Meropenem and gentamicin, and upon failure to respond, empirical antifungal treatment with caspofungin.	RT-PCR and chest X-ray.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				of 6 ml/kg (Predicted Body Weight), a plateau pressure lower than 30 cm H2O, PaO2 55–80 mmHg, or SpO2 88–95% and pH ≥ 7.25. The oxygenation ratio was the worst on hospital day 9 (PO2/FiO2 185) and gradually improved from that day forward. The patient did not need prone positioning. On hospital day 14, the patient demonstrated a marked elevation of D-dimer to 70,386 ng/mL (from 8,854 ng/mL on day 6), accompanied by a rise in pCO2 and demand for ventilation. Upon initiation to wean the patient from the mechanical ventilation, he developed severe hyperventilation, with high respiratory drive, large tidal volumes, and potentially injurious transpulmonary pressure swing, increasing the risk of Patient Self-Inflicted Lung Injury (P-SILI). Sedation and controlled mechanical ventilation were re-initiated, allowing the lung more time to recover. In that perspective, percutaneous dilatational tracheostomy was performed on hospital day 24 after bronchial secretions resulted in negative for SARS-CoV-2. He was weaned off the ventilator on hospital day 29, and decannulation was performed on hospital day 31. The patient was discharged from the ICU the following day and transferred to a clinic for rehabilitation.			

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
Wu et al.[31] (2020)	We described the clinical characteristics, clinical manifestations, treatments, and clinical outcomes of both patients.	P1 – man	60	Presented with generalized myalgia for 2 weeks and intermittent fever around 38.3°C for 5 days and was admitted in our hospital. He was diagnosed with stage IV diffuse large B-cell lymphoma and pulmonary tuberculosis in January 2018, for which he received chemotherapy with one cycle of CHOP regimen and seven cycles of EPOCH regimen from April 9 to September 10, 2018. The pulmonary tuberculosis was cured and the lymphoma was significantly regressed. Notably, the patient also had a history of type 2 diabetes for 8 years and received insulin to control blood glucose. During the hospitalization, the patient continued anti-HIV treatment and glucose control with insulin. Fever disappeared 2 days after admission. A total of 5 days later, myalgia, fatigue, and shortness of breath were also significantly mitigated. The patient was considered clinically cured for COVID-19 and was discharged.	A chest CT scan that showed bilateral multiple GGO, prominent on the right lower lobe.	Oxygen, anti-viral (oseltamivir), and antibiotics treatments (moxifloxacin, ceftriaxone, and tazobactam) were given.	RT-PCR, chest CT, and laboratory test.
		P2 – man	47	Attended our hospital after 7 days of fever and non-productive cough. He had a highest body temperature of 39.8°C and generalized myalgia, sore throat, cough, intermittent shortness of breath, and diarrhea. Contrary to case 1 who had known and treated HIV infection, this patient was a newly diagnosed HIV-infected case that was only. He had no fever, cough, and myalgia but still had some dyspnea after labor.	He had performed chest CT scan in local hospital which revealed bilateral multiple GGO.	The patient received oxygen, antibiotic (moxifloxacin), and anti-viral (ribavirin and umifenovir) treatments.	

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
Patel et al.[32] (2020)	We reported a recovered case of SARS-CoV-2 infection in a HIV-positive.	01 man	58	Medical history of chronic bronchitis, hypertension, and HIV presented to the ED complaining of unresolved symptoms of weakness, anorexia, and diarrhea for 2 weeks. He denied shortness of breath, fever, cough, chest pain, or abdominal pain. His fever spike lasted up to 94 h and maximum body temperature during this time was 39.4°C. After 4 days of hospitalization, he became afebrile and had complete resolution of symptoms. He was discharged on the fifth day of hospitalization after the clinical picture showed marked improvement and was advised to self-isolate at home for a minimum of 14 days. Vital signs taken on admission revealed a blood pressure of 145/68 mmHg, the pulse of 94 beats/min, the body temperature of 37°C, and oxygen saturation of 99% in ambient air. Within 12 h of admission, the patient's temperature went up to 39.3°C.	A chest X-ray done on admission showed clear lungs and no significant abnormalities.	Emtricitabine and tenofovir every 24 h, atazanavir and ritonavir. Oral hydroxychloroquine and oral azithromycin, and zinc sulfate.	RT-PCR
Suwanwongse et al.[33] (2020)	We presented the case series of hospitalized HIV patients with COVID-19 in a single hospital in the South Bronx.	07 men and 02 women	The median age of patients was 58 years old (31–76).	All patients had multiple comorbidities. HIV viral load was very low to undetectable. Active ART (HAART) was discontinued during hospital admission in four patients. Fever, cough, and dyspnea were the most common presenting symptoms among all patients. One patient initially presented with gastrointestinal tract symptoms, including nausea, vomiting, and watery diarrhea. A total of 7 patients eventually died (78%), of which	Chest X-ray abnormalities compatible with COVID-19 pneumonia were found in eight patients and correlated with disease severity.	HAART = DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; EFV, efavirenz; FER (mg/dL), ferritin; FTC, emtricitabine; HCV, hepatitis C infection; HCQ, hydroxychloroquine. HAART regime: P1 – FTC, TAF, DTG, RTV, DRV; P2 – EVG,	RT-PCR, chest X-ray.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				4 due to hypoxemic respiratory failure and 3 from septic shock and multiorgan failures.		FTC, TAF, cobicistat; P3 – FTC, TDF, RAL; P4 – FTC, TAF, ATV, cobicistat; P5 – FTC, TAF, DTG; P6 – EVG, FTC, TAF, cobicistat; P7 – Do not take; P8 – FTC, TDF, DTG; P9 – EFV, FTC, TAF.	
Shalev et al.[34] (2020)	We described the characteristics of 31 people living with HIV hospitalized for severe acute respiratory syndrome coronavirus 2 infection.	24 men and 07 women	The median age of patients was 60.7 years old (23–89).	At least 1 comorbidity was identified in 22 patients. The most common were hypertension in 21, diabetes mellitus 13, and obesity 9. Thirteen patients were current or former smokers and 8 were diagnosed with asthma or chronic obstructive pulmonary disease. Twenty-three patients presented with fever (defined as a temperature of >38.0°C) or developed fever during admission. Twenty-eight patients received supplemental oxygen and 8 required invasive mechanical ventilation. Disease severity was distributed as follows: mild, 1; moderate, 2; severe, 2; and critical in 7 patients. At the time of analysis, 8 patients had died, 21 were alive and discharged, and 2 were alive and hospitalized. Thirteen patients were discharged home and 8 to a care facility.	Chest radiography was performed in 30 patients, 20 of whom displayed abnormalities consistent with viral pneumonia.	All subjects were taking ART at the time of admission. Hydroxychloroquine used in 24 patients, followed by azithromycin in 16. Corticosteroids were used in 8 and the interleukin 6 receptor (IL-6R) antagonist tocilizumab in 2 patients. 1 used drug remdesivir and another patient sarilumab. ART regimens containing tenofovir prodrugs or protease inhibitors were prescribed in 17 and 7 patients, respectively.	RT-PCR, chest radiography.
Kumar et al.[35] (2020)	We described the clinical course of a symptomatic kidney transplant recipient with	01 man	50	Presented to the ED complaining of fevers for two days, with temperatures to 101°F, chills, nasal congestion, and mild cough. The past medical history also	NA	He received induction immunosuppression with basiliximab and steroid-sparing maintenance	RT-PCR

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
	HIV who tested positive for SARS-CoV-2.			includes hypertension, asthma, steatohepatitis, and resolved hepatitis B infection. The patient denied shortness of breath, chest or abdominal pain, diarrhea, or vomiting. The patient was diagnosed with HIV infection in 1997, initiated ART at that time, and has had long-term viral suppression. In the ED, the patient was hypertensive with blood pressure 172/95 mmHg and tachycardia with heart rate 108 beats/min, but he appeared well and had temperature 98.9°F and oxygen saturation 100% on room air. The patient had ongoing symptoms reported through the monitoring program including anosmia and ageusia one day after discharge, fatigue, and fevers.		immunosuppression with tacrolimus and mycophenolate mofetil. At and since time of transplant, the ART regimen consisted of dolutegravir, emtricitabine, and tenofovir alafenamide. He was also receiving maraviroc v. placebo as part of a randomized clinical trial (NCT02741323).	
Toombs et al.[36] (2020)	We described patient with covid-19 and HIV.	P1 – man	62	He had received a renal transplant and also had type 2 diabetes (T2DM) and hypertension. He was intubated and ventilated on ITU and died from multi-organ failure precipitated by COVID-19 pneumonitis.	NA	Raltegravir; lamivudine; sbacavir + tazocin. It was immunocompromised from tacrolimus and mycophenolate treatment.	NA
		P2 – man	46	With glucose-6-phosphate dehydrogenase (G6PD) deficiency, had been ART naïve until 5 days prior to admission after he had been lost to follow up since diagnosis in 2013.		Atovaquone in view of G6PD deficiency. truvada; dolutegravir + levofloxacin.	NA
		P3 – woman	57	With a history of stroke, T2DM, hypertension and obesity, was a nurse in an older persons care home with confirmed COVID-19 infections at the time of admission. She also was covered for added bacterial infection and was discharged in a good condition.		Descovy; nevirapine + doxycycline.	

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
Li et al.[37] (2020)	We reported COVID-19 patients coinfected with HIV and analyzed the clinical and laboratory features of them.	P1 – man	37	Physical examination of the patient revealed a body temperature of 38.8°C, respiratory rate of 40 breaths/min, pulse of 119 beats/min, and blood pressure of 145/93 mmHg. The patient had an intermittent fever and chest pain, and the highest body temperature was 39.4°C. Most importantly, the patient presented fluctuating dyspnea symptoms for a long time. The clinicians evaluated the symptoms and examinations comprehensively and speculated that the patients might suffer from immunodeficiency diseases. Then HIV detection results showed that the patient was HIV-positive. At last, the patient was transferred to a special hospital for infectious diseases and received further therapy.	CT scan images of the lung showed that the high-density area was gradually increased.	Was given symptomatic supportive treatment such as intermittent low flow oxygen, lianhua qingwen capsule, and antiviral therapy with abidor.	RT-PCR, chest CT, and laboratory test.
		P2 – man	24	The patient stated that he had got an intermittent fever accompanied by cough, fatigue, poor appetite, dizziness, chest tightness, and shortness of breath after activity since 8 February. Physical examination of the patient revealed a body temperature of 36.5°C, respiratory rate of 22 breaths/min, pulse of 102 beats/min, and blood pressure of 125/88 mmHg. The patient had an intermittent fever and cough, and the highest body temperature was 40.2°C. Most importantly, the symptom of dyspnea had gradually worsened. At last, the patient was transferred to a special hospital for infectious diseases and received further therapy.	CT scan of the lung showed that the high-density area was gradually increased.	Was given symptomatic supportive treatment such as intermittent low flow oxygen, antiviral therapy with abidor, and antibodies therapy toward to interleukin 6 (IL-6) receptor with tocilizumab.	RT-PCR, chest CT, and laboratory test.

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Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
Ridgway et al.[38] (2020)	We reported a case series of five PLWH with COVID-19.	P1 – man	38	HIV positive presented to the ED with 7 days of fever, dry cough, shortness of breath (SOB), headache, and myalgias. He also had 3 days of diarrhea. Medical history included diabetes mellitus type 2 with a hemoglobin A1C of 9.9%, obstructive sleep apnea, hyperlipidemia, hypertension, and obesity. On presentation, he was febrile to 39.3°C and tachycardia. His oxygen saturation was 94% on room air (RA). He was admitted due to evidence of viral pneumonia, elevated LFTs, and uncontrolled diabetes mellitus.	Chest X-ray showed peripheral patchy opacities and chest CT showed bilateral GGO.	Empiric ceftriaxone and azithromycin; hydroxychloroquine.	RT-PCR, chest X-ray, and chest CT.
		P2 – woman	50	HIV positive presented to the ED with 1 week of cough productive of white sputum, daily fevers, and progressive SOB as well as 1 day of headache. Her only significant comorbidity was obesity. On presentation, she was afebrile with a temperature of 36.6°C, and had an oxygenation saturation of 88% on RA, which improved to 93% with 2 L nasal cannula (NC). On HD 2, her oxygenation status slightly worsened and she required 3–4 L oxygen by NC. Her oxygenation improved and she was discharged on HD 4.	Chest X-ray showed mild multi-focal patchy airspace consolidation in the left lower lobe.	Azithromycin and ceftriaxone, cefdinir.	RT-PCR, chest X-ray.
		P3 – woman	51	HIV positive presented to the ED with 1 week of cough productive of yellow sputum, myalgias, SOB, 4 days of fever, and 1 day of watery diarrhea. Her only medical history was a remote history of latent tuberculosis treated with isoniazid	Chest X-ray showed bilateral perihilar and basilar patchy airspace and interstitial opacities.	ART regimen of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide. Ceftriaxone and azithromycin for empiric CAP treatment,	RT-PCR, chest X-ray.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				for 9 months. On presentation, her oxygen saturation was 93% on RA, and she was given 2 L oxygen by NC. She was admitted to rule out acute coronary syndrome. Her temperature was 36.4°C on admission, but increased to 39.3°C the second day of admission.		with ceftriaxone transitioned to cefdinir on HD 2. Hydroxychloroquine.	
		P4 – woman	53	HIV positive and a history of esophageal strictures status post stenting complicated by bronchoesophageal and tracheoesophageal fistulas presented with 1 week of nausea, vomiting, intermittent diarrhea, dehydration, and cough of productive sputum. She endorsed chills, but denied any fever. She denied any sick contacts. On presentation, she was febrile to 39°C and had oxygen saturation of 97% on RA.	Chest X-ray was unremarkable.	ART regimen of bictegravir, emtricitabine, tenofovir alafenamide, ritonavir, and darunavir; cefdinir and azithromycin for empiric.	RT-PCR
		P5 – woman	47	HIV positive presented to the abdominal pain with nausea and vomiting, intermittent chest pain, dyspnea on exertion, and chills. Heart failure with ejection fraction of 15% with implantation of implantable cardioverter defibrillator (ICD), chronic obstructive pulmonary disease, hypertension, and morbid obesity.	Chest X-ray showed cardiomegaly but no infiltrate. Abdominal CT showed wedge-shaped splenic infarction.	ART regimen of tenofovir disoproxil fumarate, emtricitabine, darunavir, ritonavir, and raltegravir.	RT-PCR, chest X-ray, and chest CT.
Childs et al.[39] (2020)	We reported the clinical characteristics of 18 PWH who were hospitalized with confirmed COVID-19.	12 men and 06 women	52 (49–58).	The commonest presenting symptoms were fever, shortness of breath, and cough. Seven patients reached the composite endpoint; these patients had similar HIV and demographic characteristics	Most (78%) had bilateral chest radiograph changes consistent with viral pneumonitis and required oxygen therapy.	Two patients were treated with remdesivir, and in 2 patients, ART was switched to lopinavir/ritonavir. Protease inhibitor;	RT-PCR, chest X-ray, and laboratory test.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				compared to those who did not reach this endpoint. At the time of writing, 5 patients had died, 12 patients were successfully discharged from hospital, and 1 patient remains an inpatient. There was a trend toward more common use of protease inhibitor-containing antiretroviral regimens among those with COVID-19.		integrase strand-transfer inhibitor; Non-nucleoside reverse-transcriptase inhibitor; nucleoside reverse-transcriptase inhibitor; tenofovir b.	
Okoh et al.[40] (2020)	We reported a case series of 27 PLWH with COVID-19.	15 men and 12 women	58	The top 4 common symptoms at presentation were fever, cough, dyspnea, and fatigue, which had started over a median duration of 3 days before presentation. More than half of the patients had a history of systemic hypertension and about one-third reported diabetes mellitus or chronic kidney disease. After a median hospital course of 10 days, 3 patients required intensive unit level of care and 2 of them had died. The deceased subjects were elderly patients, with multiple coexisting conditions whose course was complicated by septic shock and multiorgan dysfunction syndrome.	NA	A total of 7 received hydroxychloroquine and 6 were managed with empiric antibiotics for suspected community-acquired pneumonia. ART was held during hospitalization.	RT-PCR and laboratory test.
Haddad et al.[41] (2020)	We reported a case of a middle-aged man with COVID-19 who developed acute encephalopathy and tonic-clonic seizure activity.	01 man	47	Well-controlled HIV. Maintained on dolutegravir-lamivudine with last CD4 count of 604 cells/cu mm and an undetectable viral load 2 months prior to presentation and recurrent HSV on chronic suppressive therapy presented with abdominal pain,	CT chest revealed diffuse patchy nodular ground-glass infiltrates. The remainder of imaging studies including CT head	Hydroxychloroquine, azithromycin, cefepime, ampicillin, and vancomycin.	RT-PCR, CT, and MRI brain with and without contrast and EEG.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				intractable vomiting, and confusion. He became ill 6 days prior to presentation when the patient started experiencing a dry cough and intermittent fever relieved by antipyretics. On day 2 of hospitalization, the patient was found to have worsening encephalopathy, agitation, and new-onset left-sided ptosis. He subsequently developed witnessed tonic-clonic seizure complicated by a tongue laceration leading to respiratory arrest requiring intubation and sedation. Hospital course was further complicated by acute kidney injury which resolved after discontinuation of acyclovir on day 6 of presentation when HSV PCR was negative. On day 6 of hospitalization, the patient's level of consciousness improved off sedation, and he was successfully extubated.	was unremarkable. CT scan of the chest with coronal (left) and cross-sectional (right) views showing diffuse patchy peripheral ground-glass infiltrates most consolidative within the right lower lobe.		
Sun et al.[42] (2020)	We reported here a case of HIV and SARS-CoV-2 coinfection in a PLHIV on long-term ART in Singapore.	01 man	37	Fever (38.6°C at maximum), sore throat, dry cough, and headache for the duration of 6 days. The CD4+ T-cell count was 201 cells/μL (12%) on diagnosis (2010). His viral load has been undetectable since February 2011, and the CD4+ T-cell count increased to 900 cells/μL (36%) by 2015. On presentation, the patient looked clinically well	His chest radiograph was clear with no infiltrates or consolidation.	Tenofovir, lamivudine, and efavirenz.	RT-PCR and laboratory test.

Continue...

Table 1. Continuation.

Author	Objective	N	Patients' Age	Patient Outcome	Chest Imaging	Treatment	Diagnosis
				and was afebrile (37.2°C) with normal blood pressure and heart rate. His oxygen saturation was 100% on room air, and his respiratory rate after admission was 20 breaths per min.			
Chen et al.[43] (2020)	This report provided reference for the diagnosis and treatment of HIV-infected patients with COVID-19.	01 man	24	Was admitted to our hospital with a 1-day history of fever (37.8°C) and dry cough.	CT showed multiple high-density patchy shadows with unclear boundaries in the sub-pleural regions of the middle and lower lobes of the right lung, with involvement of adjacent interlobar pleura.	ART (tenofovir; lamivudine; efavirenz) for 2 years. After COVID-19 diagnosis, he was given lopinavir/ritonavir combined with interferon inhalation for treatment.	RT-PCR, chest CT, and laboratory test.
Di Giambenedetto et al.[44] (2020)	We reported the case of a 75-year-old male patient, with a history of 23 years since HIV diagnosis.	01 man	75	A 7 days history of high fever, diarrhea, and cough. In the days immediately following, clinical conditions worsened, with persistent fever and worsening dyspnea, requiring a progressive increase in oxygen supplementation up to a FiO2 of 0.6, two distinct episodes of hemoptysis. After some days, we observed a progressive improvement in clinical conditions, with the resolution of fever and improvement of respiratory parameters and gas exchange.	CT scan of the lungs was showing bilateral consolidations and GGO, in the absence of signs of bleeding or signs of pulmonary embolism	ART STR with darunavir/cobicistat/emtricitabine/tenofovir alafenamide. Hydroxychloroquine, azithromycin, sarilumab.	RT-PCR, chest CT, and laboratory test.

NA: not applicable.

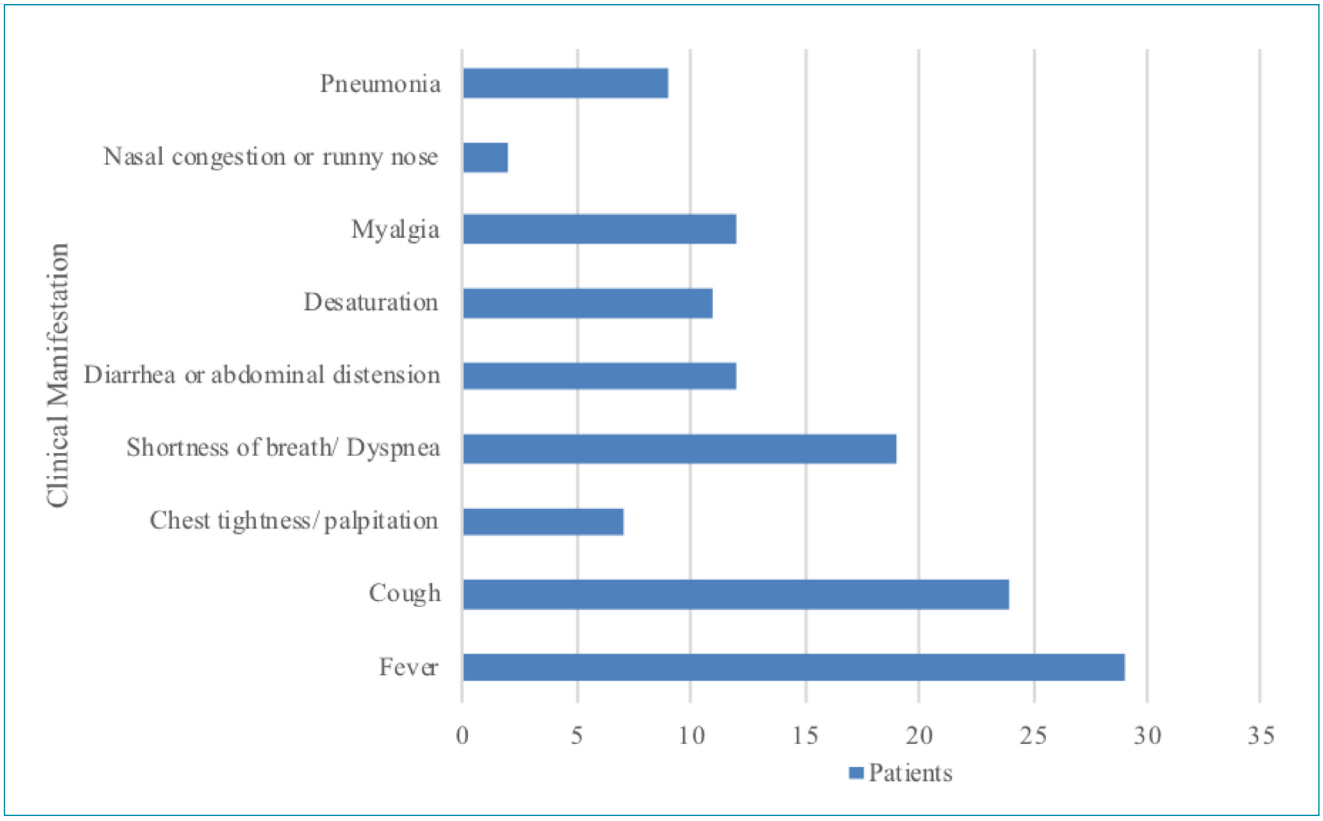

Figure 2. Clinical manifestation of patients with COVID-19 and HIV/AIDS.

- One patient developed encephalopathy and complicated tonic-clonic seizures[41];
- Four patients were transplanted, two of them for liver[25,26] and other two for kidney[35,36];
- One patient developed severe SARS-CoV-2 pneumonia[30].

DISCUSSION

Coronavirus disease 2019 (COVID-19) has spread rapidly around the world since the first reports from Wuhan, China, in December 2019, and the outbreak was characterized as a pandemic by the WHO on March 12, 2020[13]. Approximately 37.9 million people living with HIV-2 are at risk of infection with SARS-CoV-2, which causes COVID-19 infection[45].

Several studies have summarized the clinical characteristics of COVID-19, and some studies have reported that the primary chronic diseases, such as hypertension, atherosclerosis, and diabetes, the patients have had previously, may relevant to the severity of the disease[7-10]. However, until now, none of the study has been conducted to evaluate the morbidity and severity of COVID-19 in HIV/AIDS. Assuming that patients are with compromised immunity and also in a chronic disease state, HIV/AIDS patients were presumed to be at a higher risk of getting infected by the novel virus for their susceptibility to even opportunistic pathogens[17].

Recently, Zhao et al.[16] reported the first case of COVID-19 with HIV-1 and HCV coinfection. Although the test of SARS-CoV-2 RNA was persistently negative on the different specimens at various times, the plasma anti-SARS-CoV-2 antibody was positive. The authors believed that one potential explanation is that the patient who was taking anti-HIV-1 agents had been reported to have anti-SARS-CoV-2 effects[46]. These data are consistent with the notion that some anti-HIV-1 agents may have preventive and/or therapeutic effects against SARS-CoV-2. Another possibility is that the activated type I interferon (IFN-I) may help suppress SARS-CoV-2[16].

Zhu et al.[15] also reported on an identified unique severe case involving coinfection of SARS-CoV-2 and HIV. CT indicated SARS-CoV-2 pneumonia with findings of multiple GGO in bilateral lungs, after oral therapy with an anti-HIV drug, LPV/r 400/100 mg per dose twice daily for 12 days, as was advised by the Chinese health authority for the treatment of SARS-CoV-2 infection, and moxifloxacin 400 mg once daily for 7 days, γ-globulin 400 mg/kg once daily for 3 days, and

methylprednisolone 0.8 mg/kg once daily for 3 days through the intravenous route. The patient showed a marked clinical and radiological improvement, and the patient was in stable condition and discharged.

Guo et al.[17] conducted a more extensive study to find out the risk factors of COVID-19 in HIV/AIDS patients and evaluated the role of antiretroviral therapy (ART) in preventing or treating COVID-19. This study found that in the HIV/AIDS population, all of those combined COVID-19 patients had relatively normal CD4 counts, which indicated a relatively normal immune function, factors such as the gender, of the CD4 counts, or the HIV-VL, or the ART regimen did not show any relevance with the occurrence of COVID-19. None of those COVID-19/HIV patients took remdesivir, LPV/r-based ART regimen, which seemed to support the use of LPV/r in pre-exposure prophylaxis (PrEP) and cope with COVID-19[17].

The results of these findings are conflicting, on the one hand, some authors suggested that an immune system debilitated probably facilitates the dominant infection, or more accurately, causes the pathological changes to give rise to the symptoms. On the other hand, other authors also indicated that a compromised immune system with a lower CD4 count levels might waive the clinical symptoms. Considering that there were a lot of asymptomatic SARS-COV-2-infected individuals being reported, although we do not have effective strategies to screening all of the HIV/AIDS patients, we may speculate that some of them may be infected but present with no symptoms. This finding probably supports the hypothesis that a lower active immune status might protect the human body from a severe viral attack other than the immune storm, such as SARS and MERS[17].

The elaboration of this review evidenced that few studies exist on this topic and that lot of gaps still need to be filled. The fact is that the studies point out one possible influence of HIV-1-induced immune dysfunction on the immune responses to and clearance of SARS-CoV-2; at the same time, HIV did not show any relevance with the occurrence of COVID-19. On the contrary, some studies have shown that HIV-1 infection through the induction levels of IFN-I may, to some extent, stop the apparent SARS-CoV-2 infection, thus leading to persistently undetectable RNA. Besides that, some authors suggested that retroviral drugs routinely used to control HIV infection could be used to prevent the infection by COVID-19. Future studies are needed to prove these possibilities[15-17].

Remdesivir, LPV/r, ribavirin, arbidol, and chloroquine, and others have already been tried in COVID-19 treatment, and remdesivir is now under a registered clinical experiment. The combination of protease inhibitor, LPV/r, was proved to target both HIV and coronaviruses, and the national guidelines for diagnosis and treatment of COVID-19 (from the 1st to 6th) also suggested to treat patients with LPV/r. The exact effect of LPV/r in treating the SARS-CoV-2-caused disease still needs more observation. Nevertheless, since HIV/AIDS patients might take LPV/r as a routine of the ART, it provides a natural study object to observe whether LPV/r can be used as PrEP for SARS-CoV-2, like the PrEP for HIV. These people were not infected by HIV, but were at high risks and suggested to take the antiretroviral drugs every day to prevent the infection[11,12].

However, in 2018, only 62% of adults and 54% of children living with HIV in low- and middle-income countries were receiving lifelong ART. Besides that, not everyone can access HIV testing, treatment, and care. Therefore, this is worrying[47].

The potential limitations of the present study include few number of cases, the shorter follow-up time, and lack of clinical trials proving that the use of retroviral drugs as prophylaxis for COVID-19 is safe. The latter limitations serve as an incentive for the production of clinical trials with a larger number of patients and with a longer follow-up time, as well as the production of randomized clinical trials that assess the safety and the effectiveness of antiretroviral drugs.

CONCLUSION

This review points to the existence of conflicts regarding the results obtained in the studies evaluated in this study. Some authors pointed out one possible influence of HIV-1-induced immune dysfunction on the immune responses to and clearance of SARS-CoV-2, although the HIV did not show any relevance directly with the occurrence of COVID-19. Some studies suggested that HIV-1 infection through the induction levels of IFN-I may, to some extent, stop apparent SARS-CoV-2 infection, thus leading to persistently undetectable RNA. Besides that, there is an assumption that retroviral drugs routinely used to control HIV infection could be used to prevent the infection by COVID-19.

AUTHORS' CONTRIBUTIONS

Medeiros KS, Sarmento AC, Silva LASS and Macêdo LTA were responsible for the study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, and critical revision. Eleutério Jr. J and Costa APF were responsible for the manuscript critical revision. Gonçalves AK was responsible for the study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript and critical revision.

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REVIEW ARTICLE
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Diabetes in the COVID-19 pandemic era

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SUMMARY

OBJECTIVE: To analyze the association between patients with diabetes mellitus and the increased severity and its complications that arise with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

METHODS: This is a complementary review of literature in which 14 articles published in 2020 were selected. These reviewed articles were written in both Portuguese and English available in the SciELO and PubMed databases. This review also involved searching on websites of international and national organizations in order to gather information published by these bodies about diabetic population and coronavirus disease (COVID-19)-infected individuals.

DISCUSSION: The presence of comorbidities in SARS-CoV-2-infected individuals causes an increase in the expression level of angiotensin-converting enzyme 2, facilitating the entry of the virus into the cell. Diabetes causes metabolic and vascular changes, thus weakening the immune system through the inhibition of the innate immune system and the secretion of various inflammatory cytokines. This hyperinflammation can lead to multiple organ failure. The interaction between this comorbidity and COVID-19 can worsen pre-existing diabetes or predispose the onset of diabetes in non-diabetic individuals.

CONCLUSIONS: Diabetes mellitus is related to the increased severity and complications of COVID-19. The association between diabetes and COVID-19 creates a devastating double pandemic, as it worsens the prognosis of COVID-19.

KEYWORDS: Diabetes mellitus. Coronavirus infections. Chronic disease. Pandemics. Betacoronavirus.

INTRODUCTION

At the end of 2019, a viral disease called coronavirus disease (COVID-19), caused by a coronavirus defined as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged. Since March 2020, COVID-19 has been a major threat to public health worldwide, affecting more than 188 countries and resulting in a global pandemic. The first case of this virus was identified and isolated in Wuhan, Hubei Province, China[1]. According to a report published by the World Health Organization (WHO)[2] as of August 17, 2020, there were 21,732,472 confirmed cases worldwide, with 770,866 deaths.

In Brazil, more than three million cases and a hundred thousand deaths have been confirmed and these numbers have been progressively increasing since early March 2020[3]. The high power of dissemination of this new virus and its ability to cause death, associated with insufficient knowledge of the virus, have created major obstacles in controlling the disease[4].

Since the first reports, many severe and fatal COVID-19 cases have occurred in older patients or people with comorbidities, especially those with diabetes *mellitus* (DM), hypertension, cerebrovascular diseases, and chronic kidney and lung diseases.

Currently, there is no explanation for patients with chronic diseases, particularly hypertension and diabetes, who are more severely affected by COVID-19. However, one of the theories is based on the involvement of the angiotensin-converting enzyme 2 (ACE2) that is present in several tissues, such as

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cardiac, pulmonary, renal, intestinal, and blood vessels. The new coronavirus binds to the ACE2, which is present on cell surfaces and enter cells[5].

METHODS

This is a complementary literature review of articles published in 2020. The reviewed articles were written in Portuguese and English and they were based on the SciELO and PubMed scientific databases. The descriptors used were 'diabetes mellitus', 'coronavirus infection', 'chronic disease', 'betacoronavirus', and 'pandemics'. The review also involved searching on websites of international and national organizations in order to gather information regarding recommendations published by these bodies for the diabetic population and people affected by COVID-19. These organizations included the World Health Organization (WHO), the International Diabetes Federation (IDF), state health departments, and Brazilian Diabetes Society.

DISCUSSION

The COVID-19 pandemic reached Latin America around the end of February 2020. The countries, such as Brazil and Mexico, presented a high number of cases and high death rates not only because of their large populations but also because of their conflicting policies regarding travel restrictions and social contact. Other countries, such as Chile, Ecuador, and Peru, were also highly affected by the virus, since they presented great difficulty adjusting to social distancing, due to the high percentage of poor population in these countries. About 50–70% of jobs in Latin American are informal, which leads people to seek their income on the streets[6].

Individuals with chronic diseases present a more severe form of COVID-19. Recently, researchers from Universidade de São Paulo have published a study explaining the possible reasons for increased mortality in patients with chronic diseases. The comorbidities, such as hypertension, DM and asthma, change the metabolism by increasing the expression of ACE-2 gene in the cells of patients affected by the virus[7]. ACE-2 encodes the protein to which the virus binds to enter the cell, i.e. it facilitates the entry of the virus as seen in Figure 1. The increased expression of ACE-2 in patients with chronic diseases facilitates lung cell infection by the coronavirus, thereby increasing the risk of COVID-19 symptom aggravation. This is due to the binding of SARS-CoV-2 with ACE-2 that deregulates its cellular expression, leading to the onset of acute lung injury[7,8].

The relationship between being diabetic and having an increased susceptibility to COVID-19 is not fully proven, but there is evidence that patients with diabetes show an increased risk for both infection and severe disease. The first three coronavirus-related deaths in Hong Kong occurred in patients with diabetes. A Chinese study has showed that the prevalence of diabetes in infected people was 16% in patients with more severe forms of the disease and 5.7% in patients with lighter forms of the disease. In addition, 24% of individuals with severe COVID-19 had hypertension, compared to 13% of people with mild COVID-19, highlighting the increased risk of adverse outcomes in infected ones with other chronic diseases[5].

As diabetes is a chronic inflammatory disorder associated with high rates of glucose, patients with diabetes present metabolic and vascular changes that weaken the body defenses and prevent the immune system from responding properly to viral and bacterial infections in general. It increases the risk of infections, particularly pneumonia and influenza, due to multiple innate immune disorders. Diabetes, especially when poorly controlled, presents impaired phagocytosis, as neutrophils, macrophages, and monocytes as well as neutrophil chemotaxis and complement activation that impact the body negatively[5,9]. Micro and macrovascular complications are also associated with DM, affecting the patient's overall survival[10].

The human pathogenic coronavirus SARS-CoV and SARS-CoV-2 connect to the target cells through ACE-2, which is expressed by the lung, intestine, kidney, and blood vessel epithelial cells. Patients with both type 1 and type 2 diabetes have an ACE-2 production increased due to frequent treatment with ACE-2 inhibitors and angiotensin II type 1 receptor blockers (ARB), which have antihypertensive and nephroprotective effects. Treatment with ACE-2 and angiotensin-receptor blockers inhibitors increases ACE-2 production, which facilitates COVID-19 infection consequently. Therefore, treating diabetes and hypertension with ACE-2 stimulant drugs may increase the risk of developing severe COVID-19, which can be fatal; thus, patients with chronic diseases who use these drugs for treatment should be closely monitored[8,11].

The virus invades the cells and induces apoptosis or necrosis, triggering inflammatory responses characterized by pro-inflammatory cytokine or chemokine activation, resulting in the recruitment of other defense cells. SARS-CoV-2 infects the circulating immune cells and increases lymphocyte apoptosis, thereby affecting clusters of differentiation (CD) 3, 4, and 8 T-cells, among other lymphocyte cells, and, consequently, causing lymphocytopenia. Therefore, the severity of SARS-CoV-2 infection is directly associated with the degree of lymphocytopenia. Innate immune system inhibition occurs when T-cell action decreases, triggering the secretion of many inflammatory cytokines and generating a phenomenon called "cytokine storm," characterized by a significantly increased level

of circulating cytokines, such as interleukins (IL-6), (IL-17), (IL-21), (IL-22); tumor necrosis factor (TNF); and chemokines. This hyperinflammation in the body can lead to multiple organ failure as seen in Figure 2[8].

Besides decreasing immune system response (delayed T-helper 1 and T-helper 17 responses), diabetes also contributes to several specific factors that predispose patients to infections in general, resulting in a worse prognosis of COVID-19 in these patients. Some of these factors are: increased expression of ACE-2; increased furin, which is a membrane-bound protease involved in allowing coronavirus entry into the cell, facilitating viral replication; T-cell impairment that generates lymphocytopenia; and increased IL-6 levels that result in an increased susceptibility to hyperinflammation[9,12].

As diabetes is a chronic inflammatory disease, patients with diabetes have a significantly higher level of IL-6 and increased pro-inflammatory cytokines in their bodies. A treatment that has been widely used, especially in autoimmune diseases, for blocking IL-6 receptors. For example, the monoclonal antibody Tocilizumab, which improves insulin resistance and decreases glycated hemoglobin (HbA1c), has been used in rheumatoid arthritis. This medicine has been suggested for use in the treatment of COVID-19 pneumonia. Some Italian centers are conducting a randomized study on the use of Tocilizumab for treating patients with diabetes infected with COVID-19[13].

In 2019, a study analyzed the data collected from 5,266 patients with diabetes over a period of 6.2 years in the United States to assess the mortality of patients with chronic lower respiratory diseases and the use of metformin. It was reported that the use of metformin, an anti-diabetic with anti-inflammatory and antioxidant properties, significantly decreased the mortality of patients with respiratory diseases[12].

Diabetes is one of the leading chronic non-transmissible pandemic diseases worldwide, affecting over 463 million people[13]. The interaction between diabetes and SARS-CoV-2 infection can follow a two-way model as SARS-CoV-2 worsening pre-existing diabetes or predisposing non-diabetic people to diabetes. The mechanism that allows the entry of the virus into the cell involves ACE-2, which is highly expressed in the liver and pancreas as seen in Figure 3. SARS-CoV-2 infection in pancreatic beta cells can generate insulin resistance and decreased insulin secretion, worsening hyperglycemia in the acute phase of infection, whereas in the chronic phase, it may trigger autoimmunity of these pancreatic cells in predisposed patients. COVID-19 in patients with DM worsens the glycemic profile, thereby intensifying the impairment of innate

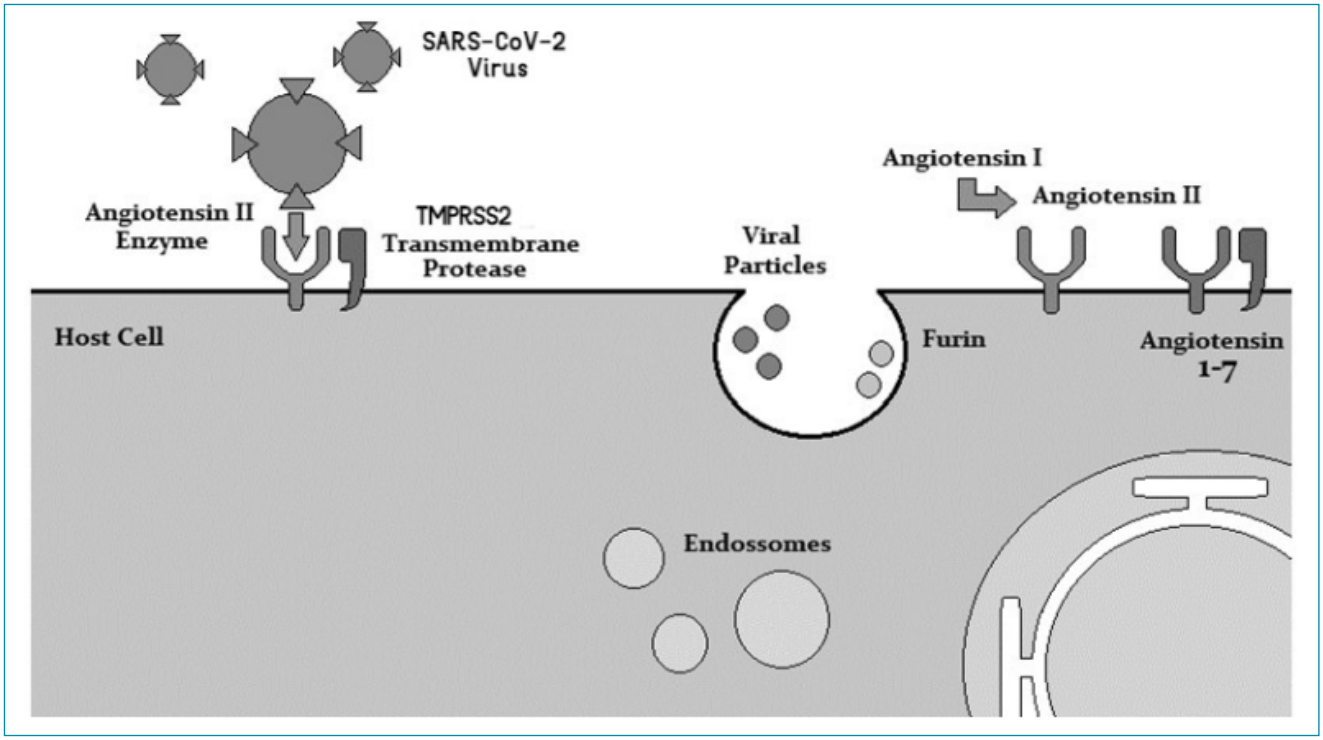

Figure 1. SARS-CoV-2 entry into the cell[8]. The virus needs to bind to the angiotensin-converting enzyme 2, which is present on the cell surface, to get into the cell. Proteases, such as transmembrane serine protease 2 and furin, also help the virus merges with the cell. After being absorbed by the endosomes, the viral particles use the endogenous cellular machinery to multiply. Angiotensin-converting enzyme 2 degrades angiotensin II and I (to a lesser extent) into minor peptides, namely angiotensin 1–7 and angiotensin 1–9, respectively.

immune response and generating pro-inflammatory cytokines that provoke a vicious cycle. Therefore, the complex interaction between these two pandemics produces an extremely high risk of developing severe diseases, such as acute respiratory distress syndrome (ARDS) or even death[14-16].

Hyperglycemia and insulin resistance, as a result from diabetes, induce increased synthesis of advanced glycation end products (AGEs) and pro-inflammatory cytokines that generate oxidative stress. An *in vitro* study, conducted in 2013, showed that the exposure of pulmonary epithelial cells to high glucose concentrations provokes increased influenza virus infection and replication, suggesting that the hyperglycemia state could increase *in vivo* viral replication[9]. In addition, patients with hyperglycemia in type 1 diabetes have a high chance of developing diabetic ketoacidosis (DKA) as well as metabolic complications during an infection[9].

Hyperglycemia can cause endothelial dysfunction, either by diabetes or by increased inflammatory cytokines, resulting in the formation of thrombi, which may damage other organs and result in a fatal disease outcome. This hypothesis was considered after reviewing evidence that high D-dimer levels were found in patients with diabetes, especially those with poor blood glucose control[6].

A study called "CORONADO" was conducted in France in the period between March and April 2020 to evaluate patients with diabetes who were diagnosed with COVID-19. A nationwide multicentric observational study was conducted to evaluate the phenotypic characteristics and prognosis associated with the early severity of patients with diabetes who had been hospitalized with SARS-CoV-2, as well as to estimate the primary outcome that associates death and orotracheal intubation for mechanical ventilation in the first seven days of hospitalization. The study showed that about 20.3% of the population analyzed underwent orotracheal intubation for mechanical ventilation, with 10.6% mortality in the first seven days after admission[17].

Type 2 DM, commonly present in obese people, also aggravates the expressed inflammatory cytokine response, increasing insulin resistance. In addition, vitamin D is another factor that interferes with the amount of blood glucose. The need of social isolation by confining people to their homes, as well as restricted physical activity, result in limited sunlight exposure and vitamin D deficiency. Hypovitaminosis D is characterized as a risk factor for insulin resistance since it worsens the glycemic profile in patients infected with COVID-19 as vitamin D supplementation, on the other hand, improves insulin sensitivity[15].

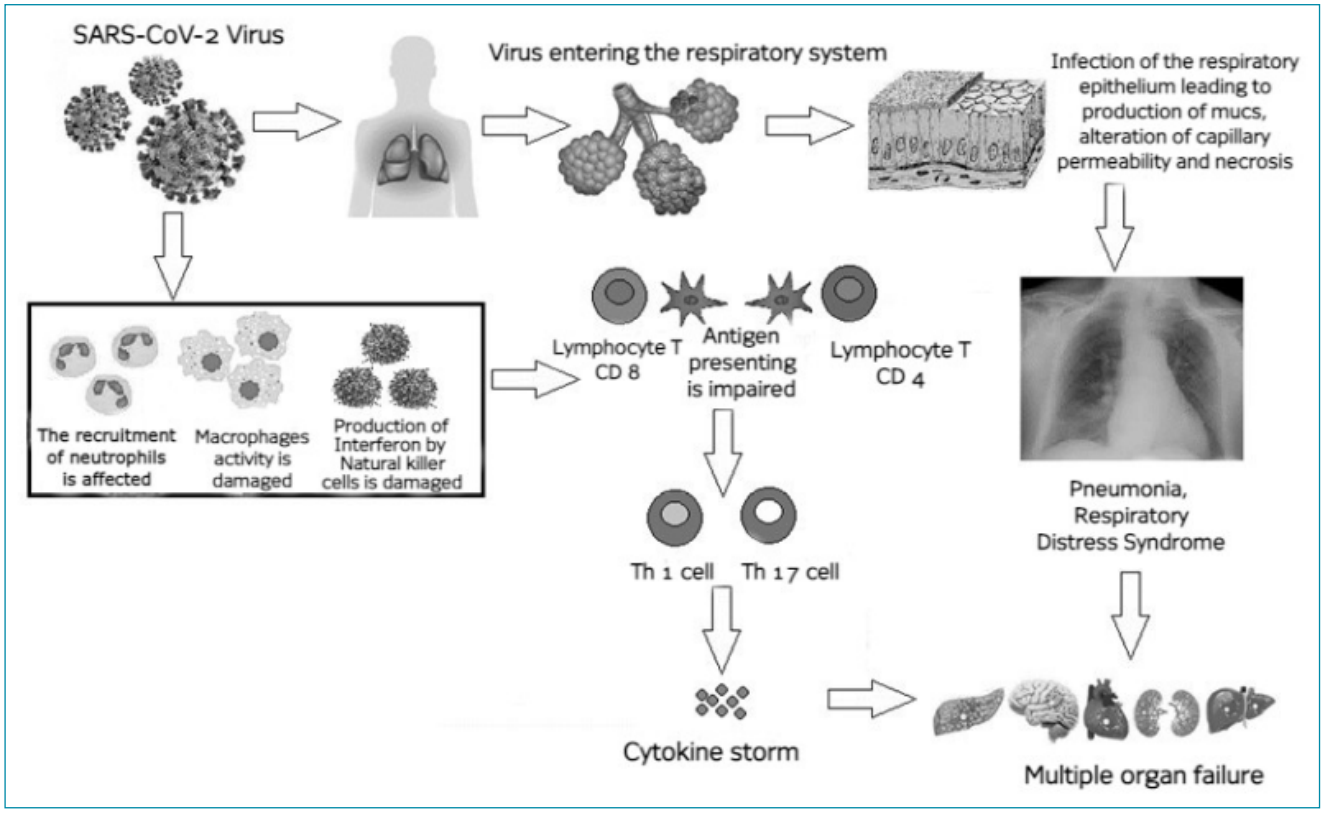

Figure 2. Mechanism that contributes to the increased susceptibility to COVID-19 in patients with diabetes mellitus[8]. Patients with diabetes have increased angiotensin-converting enzyme 2 levels, which may facilitate the existence of a more efficient cell connection and consequently the virus entry into the cells. Multiple innate immune disorders hinder early neutrophil recruitment and macrophage function. The delayed onset of adaptive immunity and cytokine response deregulation in diabetes mellitus can initiate the cytokine storm. Hyperinflammation can lead to multiple organ failure.

Treating diabetes in this current pandemic scenario is a challenge, since most people are confined to their homes with limited physical activity. In addition to this physical barrier, there is psychological stress due to unpredictability of disease and mobility restrictions. New routines imposed by the pandemic can change food intake. In most cases, access to fruits and vegetables has become limited, leading people to choose processed food that presents high calories and saturated and trans fats[12].

Besides the SARS-CoV-2 infection in patients with diabetes, another problem, resulting from the COVID-19 pandemic, has been the lack of access to medication. The outbreak and infection caused by COVID-19 have inhibited people from going to clinics, making it impossible to treat diabetes-related problems. As the supply of health services has been increasingly interrupted and fragmented, there has been enormous difficulty in getting access to basic medical supplies such as insulin. The concern about not having access to medication has generated anxiety and sleep disturbances, which, in turn, affect glucose control. Glucose deregulation may predispose people to complications, such as infections, hyperosmolar coma, ketoacidosis, or even acute cardiac events[5,12].

The treatment during this pandemic period should include medication and non-medication factors. It is necessary to maintain a regular daily diet, focused on not increasing caloric intake. An adequate and balanced diet, with high protein and fiber content and low in saturated fat, helps to maintain glycemic control. Regular physical exercises and the use of antidiabetics and insulin should be maintained. Additionally, if patients have questions about the treatment, they can use telemedicine, a practice widely used in this pandemic period. However, it is necessary to clarify to patients that they should seek medical service urgently in emergency situations as soon as they feel symptoms, such as vomiting, drowsiness, shortness of breath, chest pain, limb weakness, or sensory change[12].

CONCLUSIONS

Diabetes plays a role in increasing the severity and complications of COVID-19. The association between diabetes and COVID-19 creates a devastating double pandemic by increasing the chances of having a severe form of COVID-19. In addition, concerns about SARS-CoV-2 virus contamination hinder glycemic control in patients with diabetes, as they avoid

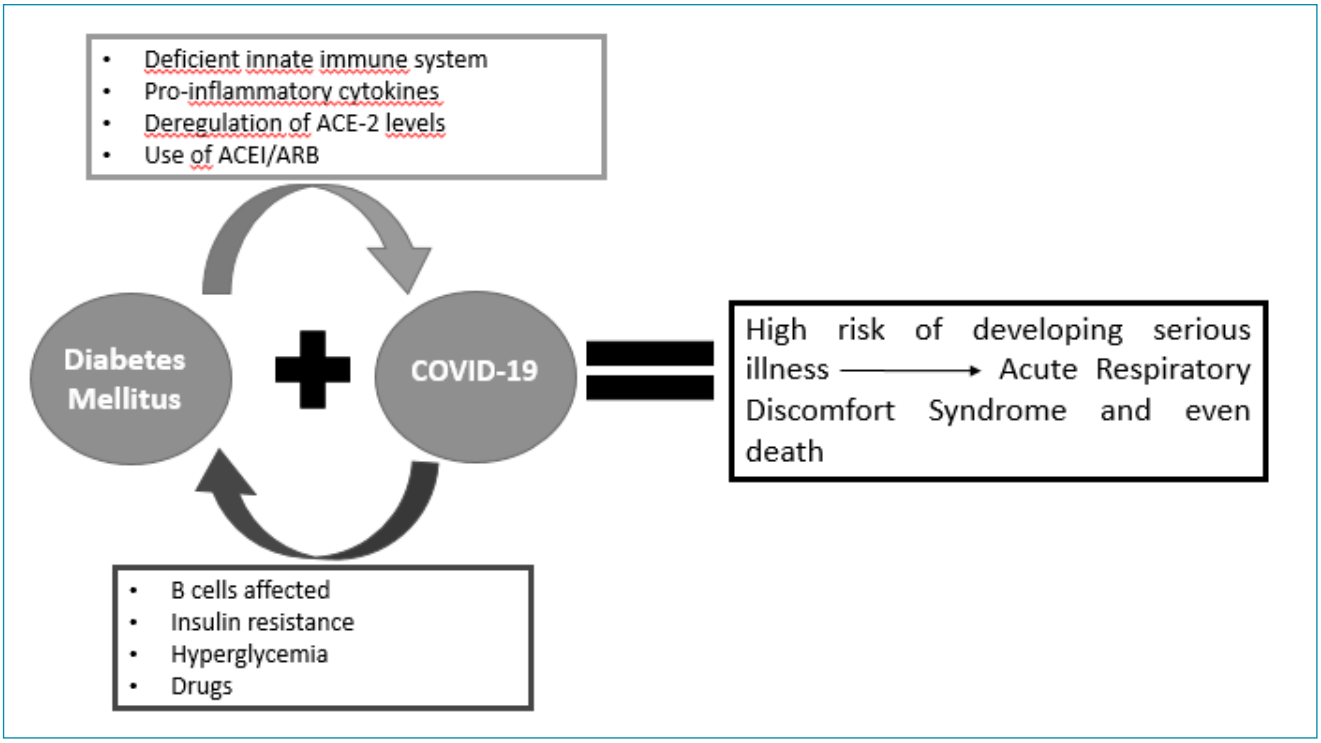

Figure 3. Schematic diagram of the bidirectional interaction between the new coronavirus disease (COVID-19) and diabetes mellitus[15]. Diabetes mellitus worsens COVID-19 prognosis by affecting innate immunity, pro-inflammatory cytokine overreaction, and angiotensin-converting enzyme 2 deregulation. In addition, the use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers in individuals with diabetes mellitus can increase COVID-19 severity. On the other hand, COVID-19 leads to a worsened glucose control in individuals with diabetes mellitus, due to pancreatic beta cell damage and increased insulin resistance through cytokines and fetuin-A, causing hyperglycemia. In addition, medicines used to treat COVID-19, such as corticosteroids and lopinavir/ritonavir, can also change blood glucose levels.

seeking healthcare assistance, generating, consequently, additional metabolic and vascular complications. Finally, patients with DM need to maintain regular physical exercise, proper nutrition, and hygiene and exert rigorous blood glucose control during the pandemic.

AUTHORS' CONTRIBUTIONS

ACSS: Conceptualization, Writing – Review & Editing.
KZ: Conceptualization, Writing – Review & Editing.
LPS: Conceptualization, Writing – Review & Editing.
TCPB: Conceptualization, Supervision, Data Curation.

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REVIEW ARTICLE
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The Impact of COVID-19 on the Cardiovascular System

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SUMMARY

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces coronavirus-19 disease (COVID-19), has affected many people in Brazil and worldwide. This disease predominantly affects the organs of the respiratory system, but it also damages the brain, liver, kidneys and especially the heart. In the heart, scientific evidence shows that this virus can damage the coronary arteries, generating microvascular dysfunction, favoring acute myocardial infarction. Furthermore, with the increased expression of pro-inflammatory cytokines, it can lead to myocarditis and cardiac fibrosis, inducing changes in the electrical conduction system of the heart, generating cardiac arrhythmias. All these factors mentioned are protagonists in promoting the increase in the mortality outcome. This outcome may be even higher if the individuals are elderly, or if they have other diseases such as type 2 diabetes mellitus or hypertension, because they may already have cardiomyopathy. In this context, this review focused on the impact that COVID-19 can have on the heart and cardiovascular system and the association of this impact with aging, type 2 diabetes mellitus, cardiac arrhythmias and arterial hypertension

KEYWORDS: Coronavirus. Infection. Betacoronavirus. Cardiovascular System.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease that was first identified at the end of 2019 in the city of Wuhan, China. The causative agent is severe acute respiratory syndrome (SARS-CoV-2), a single-stranded RNA virus[1,2] with different replication kinetics, depending on the type of host cell[3]. According to the data from the World Health Organization (WHO)[4], until May 14, 2021, the number of confirmed positive cases for COVID-19 were 160,813,869 and confirmed deaths were 3,339,002 due to COVID-19.

Clinically, the main symptoms are fever, cough, myalgia or fatigue, sputum, and dyspnea. In a meta-analysis of 10 studies involving 1,994 patients, a higher prevalence among men (60%) and a mortality rate of 7% were observed, with 43% of deaths affecting the patients aged over 60 years, or those with cancer, comorbidities, or other infections[5].

Different organ systems, such as heart, lung, liver, brain, and kidneys, are severely affected by the COVID-19 virus. This virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor, causing damage to these organs, and specifically in the coronary arteries, pericytes have high ACE2 expression. These cells are damaged inducing endothelial and microvascular dysfunction[6]. Among cardiovascular complications, infection can lead to myocardial damage with elevated troponin and electrocardiographic abnormalities, as well as outcomes such as cardiogenic shock, arrhythmias, myocarditis, pericarditis, and death[7] (Figure 1).

In view of the possible cardiovascular complications evidenced in COVID-19 patients, this study performed a literature review with

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the aim to investigate the COVID-19 complications related to the myocardium. We also tried to associate the ratio of age and mortality, the data over acute myocardial infarction (AMI), diabetes mellitus, cardiac arrhythmias, and hypertension related to COVID-19.

STUDY VARIABLES

For this review, acute myocardial infarction (AMI) was defined as myocardial injury, with necrosis, through an increase in cardiac troponin values, in a clinical context consistent with cardiac ischemia[7]. As defined by the American Diabetes Association, diabetes is a metabolic disorder characterized by persistent hyperglycemia, resulting from deficiency in the production of insulin or in its action[8], or in both mechanisms[9]. Chronic and acute heart failure was defined as a complex clinical syndrome, which occurs when the heart is unable to meet the tissue demand for blood supply due to the incompetence of its pump activity, or when it does so only under high filling pressures[10]. From definition of JNC 8 guidelines for hypertension, systolic blood pressure levels >130 mmHg or diastolic blood pressure levels >80 mmHg was considered[11].

RELATIONSHIP BETWEEN AGE AND MORTALITY

Lian et al.[12] divided their study population into over and above 60 years old and less than 60 years old. It was demonstrated that there was a higher discharge rate for patients in the younger group compared with those in the older group (44.6 vs. 22.8%, p<0.001), with no deaths recorded. Age above 60 years was associated with the symptoms of severity and intensive care unit (ICU) admission (9.56 vs. 1.38%, p<0.001). Deng et al.[13] pointed out that the mean age of the group of deaths was higher than that of the group of survivors (69 [range, 62–74] years vs. 40 [33–57] years, Z=9,738, p<0.001), which corroborates with the findings of He et al.[14] Also, Wang et al.[15] compared patients in relation to the need for admission to the ICU and showed that this variable was associated with a higher mean age (66 years [IQR, 57–78] vs. 51 years [IQR, 37–62]; p<0.001), as well as other associated comorbidities such as hypertension, diabetes, and cardiovascular disease.

AMI, TROPONIN, AND BNP

Huang et al.[16] found a significant relationship between COVID-19 and the elevation of ultrasensitive troponin >28 pg/mL (99th percentile) in 12% of patients, and this was even higher for those admitted to ICU (31%). Wang et al.[15] pointed out that 7.2% of the patients evolved with AMI, of which 80% required admission to the ICU, totaling 22% of the population. A higher mean troponin value was found for patients admitted to ICU compared with those without ICU admissions (11.0 [5.6–26.4] vs. 5.1 [2.1–9.8]). Shi et al.[17] described

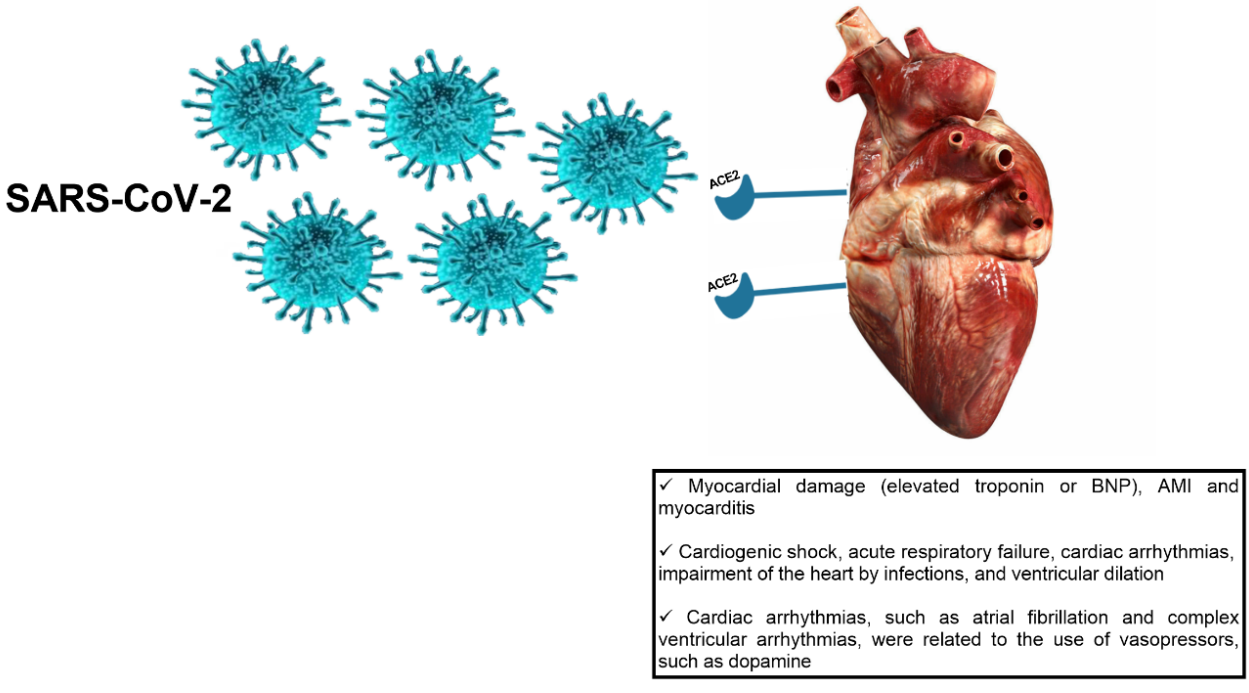

Figure 1. Impact of SARS-COV-2 and COVID-19 on cardiac structure and function.

the clinical characteristics of 82 patients (19.7%) who developed AMI. These patients were older with an average age of 74 years [34–95] vs. 60 years [21–90] (p<0.001), and more hypertensive 49 [59.8] vs. 78 [23.4%] (p<0.001). The mean value for ultrasensitive troponin in these patients was 0.19 (0.08–1.12). Deng et al.[13] showed that AMI was a more frequent complication among nonsurvivors than survivors (59.6 vs. 0.8%, c2=93,222, p<0.001). Chen et al.[18] compared the patients who underwent ultrasensitive troponin testing (only 203) and reported the relationship between increased troponin and a higher number of deaths (68/94 [72%] vs. 15/109 [14%]), in addition to the higher values of this marker (concentration) among patients who died (40.8 pg/mL) in relation to those who recovered (3.3 pg/mL). In this line, he also described the serum brain natriuretic peptide (BNP) levels and their relationship with mortality and cardiovascular diseases, finding more patients with high BNP among the group who died (68/80 [85] vs. 17/93 [18%]), and also higher BNP values (800.0 pg/mL vs. 72.0 pg/mL).

He et al.[14] found that 44.4% of the patients had myocardial injury and separated their population from this condition. Patients with myocardial injury had significantly higher BNP (p<0.01) and higher mortality rate (75 vs. 26.7%, p=0.001). Guo et al.[19] reported that there was a statistical significance in the elevation of troponin T level in patients with diabetes mellitus when compared with patients with normal troponin T level (30.8 vs. 8.9%, p<0.001) hospitalized with COVID-19 disease. Zhou et al.[20] found elevated serum troponin in 17% of the study cohort, and that the proportion of patients with high troponin was higher in nonsurvivors vs. survivors (46 vs. 1%). AMI was observed in 59% of patients who died, but in only 1% of survivors. Zhou et al.[21] reported an association between elevated serum troponin levels and disease severity. In the very severe group (respiratory failure and the need for mechanical ventilation, shock, or other organ dysfunction), 100% had elevated troponin, while in the severe group (respiratory rate >30; O_2 saturation <93%; PaO_2/FiO_2 <300 mmHg), this was 3.84%. Chen et al.[22] summarized the patients as critical and noncritical and observed that 62.5% of the critical patients had high serum troponin and 79.2% had elevated BNP.

Patients with respiratory symptoms resulting from viral infections often have pulmonary tomographic changes such as ground-glass interstitial infiltrates, a finding that is similar to pulmonary congestion in congestive heart failure. This may present diagnostic difficulties in these affected patients[15,23,24]. We observed that the elevation of cardiac enzymes, such as troponin, is associated with the clinical status and electrocardiographic abnormalities[25-28].

DIABETES MELLITUS

The prevalence of diabetes ranged from 7.2[12] to 24.1%[14] with an overall rate of 12.5%. Lian et al.[12] demonstrated that a significant difference in prevalence between older and younger groups (5 vs. 17.65%). Deng et al.[13] found that the mortality rate was similar between older and younger groups (15.6 vs. 7.8%, p=0.066). A proinflammatory state is usually noted in all diabetic patients who did not present COVID-19 infection symptoms.

The SARS-COV-19 pandemic in 2020–2021 has placed severe burdens on different health systems worldwide. In addition to high viral infectivity, this virus generates a systemic inflammatory process[16], due to the high replication kinetics and damage to host cells, increasing the expression of proinflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1-beta (IL-1β), interferon-gamma (IFNγ), and monocyte chemoattractant protein 1 (MCP-1), inducing the state of hyperinflammation or cytokine storm[29-34], which can promote complications from cardiogenic shock leading to mortality, and acute respiratory failure with extensive pneumonic conditions and impairment of the heart by infections, ventricular dilation, and cardiac arrhythmias[19,22,26,35,36].

CARDIAC ARRHYTHMIAS

Cardiac arrhythmias were not reported frequently in the studies observed, having been reported only in two studies. Wang et al.[15] reported that 23% of the observed patients had arrhythmias, of which 69.5% required intensive care, corresponding to 44.4% of the total ICU stay (p<0.001). Guo et al.[19] observed that malignant arrhythmias (ventricular tachycardia and ventricular fibrillation) were more frequent in patients with previous cardiovascular disease and elevated troponin T (9 [17.3] vs. 2 [1.5%], p<0.001).

HYPERTENSION

Liu et al.[37] described the prevalence of comorbidities of 20%, but only 9.5% of patients were hypertensive with an average age of 57 years [20–83]; however, the overall mortality rate was elevated at 11.7%. Lian et al.[12] demonstrated that older adults had more comorbidities compared with young people (55.15 vs. 21.93%, p<0.001), e.g., hypertension (38.97 vs. 11.20%, p< 0.001). Deng et al.[13] found that a higher number of deaths were associated with previous comorbidities (72.5 vs. 41.5%, c2=22,105, p<0.001), e.g., hypertension (36.7 vs. 15.5%, c2=14,184, p<0.001). On the other hand, despite finding a high prevalence of hypertension in the population studied (44.4%), He et al.[14] did not observe a statistical significance

between survivors with hypertension and nonsurvivors (46.2 vs. 42.9%). As an unfavorable clinical outcome, the variable "ICU stay," Huang et al.[16] found no association between hypertension vs. ICU stay (15 vs. 14%). However, hypertension was documented in 15% of the sample with an average age of 49 years. Thus, arterial hypertension is an important and very common risk factor, affecting 30% of the adult population[10]. Hypertension was a common comorbidity with a prevalence between 17 and 40%, and was a significant risk factor of mortality. Together with age, other cardiovascular risk factors such as diabetes mellitus (16%) and arterial hypertension contribute to greater disease severity, ICU admission, and mortality[15,23,38-40].

CONCLUSIONS

There is a high prevalence of cardiovascular involvement in patients with COVID-19 with conditions such as myocardial damage (elevated troponin or BNP), AMI, and myocarditis. This subset of patients was at a significantly higher risk of mortality. Cardiac arrhythmias, such as atrial fibrillation and complex ventricular arrhythmias, were related to the use of vasopressors, such as dopamine. COVID-19 often affects various organ systems including the liver, lungs, kidneys, brain, and heart. The mortality due to COVID-19 infection is higher for the elderly people (>60 years) and in patients with cardiovascular comorbidities, elevated troponin, and cardiac arrhythmias.

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COMMENTARY

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Comment on "Can the neutrophil/lymphocyte ratio (NLR) have a role in the diagnosis of coronavirus 2019 disease (COVID-19)?"

Cihan Bedel[1]*, Mustafa Korkut[1], Hamit Hakan Armağan[2]

We read with great interest the article "Can the neutrophil/lymphocyte ratio (NLR) have a role in the diagnosis of coronavirus 2019 disease (COVID-19)?" by Nalbant et al[1]. They aimed to evaluate the role of neutrophil/lymphocyte ratio (NLR), an inflammation marker in the diagnosis of COVID-19. They concluded that NLR is an independent predictor for the diagnosis of COVID-19. First of all, We congratulate the authors for their invaluable contribution to the literatüre. However, we think that some points should be discussed about the study.

White blood cell count, CRP, and immature granulocyte are useful inflammatory biomarkers in clinical practice[2,3]. An easily measurable laboratory marker is used to evaluate systemic inflammation, particularly the WBC subtypes NLR and platelet/lymphocyte ratio (PLR)[4]. However, these parameters are affected by many factors such as acute coronary syndromes, local or systemic infection, previous history of infection, inflammatory diseases, renal or hepatic dysfunction and known malignancy[2-5]. For these reasons, it would be better if the authors had mentioned these factors.

It is well known that some drug use, such as corticosteroids, can increase neutrophils and decrease lymphocytes. For this reason, more accurate results can be obtained by excluding or identifying patients with drug use that may cause an increase in NLR in patients in the groups. In addition, plasma inflammatory biomarkers and NLR are time sensitive variables. It is known that ischemic events can increase NLR[6]. Therefore, it is important to define the time from the first symptom to sample collection. As a result, NLR can be affected by many factors. We think that there are still gaps in the clinic regarding the routine use of these parameters in critically ill patients. Larger prospective studies are needed to demonstrate the importance of NLR in COVID-19 on this topic.

AUTHORS'CONTRIBUTION

CB: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **MK:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **HHA:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

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COMMENTARY

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Comment on "Current evidence of SARS-CoV-2 vertical transmission: an integrative review"

Jianghui Cai[1]*, Hongxi Zhang[1], Mi Tang[2], Xiaoqin Gan[2]

Dear Editor,

We read with great interest the study by Oliveira et al.[1]. In their article, the authors have reviewed the current scientific evidence of vertical transmission related to coronavirus disease 2019 (COVID-19). However, some concerns should be addressed.

First, only MEDLINE (via PubMed) and LILACS databases were searched for potential articles, which resulted in a significant reduction in the number of search results. Currently, they were more than 15 studies with available clinical characteristics of pregnant women and detailed neonatal outcomes. Other articles published up until 17th June 2020 meeting inclusion criteria can be seen in Table 1[2-20].

Second, the authors stated that "This review was performed according to a standard protocol for systematic reviews, which was based on the methodological manuals of the Preferred

Table 1. Other published reports with available clinical characteristics of pregnant women and detailed neonatal outcomes until 17th June 2020.

Study	Date of publication	Country	Study design	Language of publication	Admission date	No. of pregnant women confirmed with COVID-19 (n)
Zhu et al.[2]	Feb. 6, 2020	China	Case series	English	1.20~2.05	9
Wang et al.[3]	Feb. 28, 2020	China	Case report	English	2.05~2.18	1
Khan et al.[4]	Mar. 19, 2020	China	Case reports	English	1.28~3.01	3
Yu et al.[5]	March 24, 2020	China	Case series	English	1.01~2.08	7
Dong et al.[6]	Mar. 27, 2020	China	Case report	English	1.28~2.22	1
Chen et al.[7]	Mar. 28, 2020	China	Case series	English	1.20~2.10	5
Lee et al.[8]	Mar. 31, 2020	Korea	Case report	English	3.06~3.11	1
Gidlöf et al.[9]	Apr. 6, 2020	Sweden	Case report	English	Not mention	1
Breslin et al.[10]	Apr. 9, 2020	USA	Case series	English	3.13~3.27	43
Xiong et al.[11]	Apr. 10, 2020	China	Case report	English	3.7~3.10	1
Khassawneh et al.[12]	Apr. 14, 2020	Jordan	Case report	English	3.23~3.26	1
Zamaniyan et al.[13]	Apr. 17, 2020	Iran	Case report	English	3.7~3.26	1
Al-Kuraishy et al.[14]	Apr. 21, 2020	Iraq	Case report	English	3.13~3.30	1
Wu et al.[15]	May 5, 2020	China	Case series	English	1.31~3.09	13
Perrone et al.[16]	May 11, 2020	Italy	Case reports	English	3.01~4.30	4
Xia et al.[17]	May 17, 2020	China	Case report	English	1.23~2.20	1
Lowe et al.[18]	May 28, 2020	Australia	Case report	English	Not mention	1
Wang et al.[19]	Jun. 8, 2020	China	Case series	English	12.08~4.01	30
Bani Hani et al.[20]	Jun. 12, 2020	Jordan	Case report	English	3.28~4.12	1

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Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[21]". But we can't find the PRISMA checklist in the manuscript or supplementary material.

Third, the authors didn't exclude studies suspected of including duplicate reporting. The data from reference 15 (Yan et al.[22]) in this review were pooled from a national registry including 25 hospitals with study dates overlap. We suggest that when a hospital had published their cases more than once, only the paper with the biggest data was included to minimize the possibility of double counting.

AUTHOR'S CONTRIBUITION

JC: Conceptualization, Writing – Review & Editing. **HZ:** Writing – Original Draft. MT: Data Curation, Writing – Original Draft. **XG:** Data Curation, Formal Analysis.

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COMMENTARY
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Comment on "Comparison of neutrophil lymphocyte ratio, platelet lymphocyte ratio and mean platelet volume and PCR test in Covid-19 patients"

Mehmet Zahid Kocak[1]

Dear Editor,

We read with pleasure the article by Ozsari et al.[1], on the association between lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and mean platelet volume (MPV) levels and PCR test results and thorax tomography (CT) findings in Covid-19 patients. The Covid-19 disease is a pandemic that affects the whole world and causes many deaths. Early diagnosis and start early treatment was very important to prevent deaths due to the Covid-19 disease. PCR test, CT findings, NLR, and acute phase reactants are used in the diagnosis of Covid-19 disease. In this manuscript, the authors assessed the diagnostic value of NLR, PLR, and MPV according to PCR test and CT findings. This cross-sectional study provided varied significant outcomes. For this aim of analysis, we congratulate the authors, and we want to discourse some subjects that deserve more interest.

The diagnostic and prognostic importance of NLR and PLR in Covid-19 patients has been reported in various studies[2,3]. Recently studies have reported that the diagnostic value of NLR and PLR is not certain[4]. However, discordance in PCR test results and CT findings were not mentioned in these studies. In this context, this study is very valuable. On the other hand, we want to mention that; it is not reported that patients who are negative for PCR become positive or remain negative in their repeated tests. The interpretation that the inflammation was severe in the CT positive-PCR negative group was somewhat ambitious. There is no data that the PCR test is negative due to the severity of inflammation. We think that this negativity is due to the sensitivity and specificity of the PCT test.

Consequently, as in this study, hemogram parameters such as NLR and PLR are valuable markers in the diagnosis of Covid-19[2,3]. However, more studies are needed for the relationship between hemogram parameters and PCR test and CT findings.

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