RAMB
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

AMB Associação Médica Brasileira
WMA

Volume **66-2020 Supplemment 2**
ISSN **0104-4230**
ISSN **1806-9282** (On-line)

COVID-19

SECTIONS

ARTICLES

ORIGINAL ARTICLES

REVIEW ARTICLES

RAMB REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

RAMB - REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA (JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION)

EDITORS-IN-CHIEF: *Carlos V. Serrano Jr. and José Maria Soares Jr.*
CO-EDITOR: *Wanderley M. Bernardo*
MANAGING EDITOR: *César Teixeira*
E-MAIL: *ramb@amb.org.br*
WEBSITE: www.ramb.org.br

Address: Rua São Carlos do Pinhal, 324
Bela Vista – São Paulo
Postal Code: 01333-903
Phone no.: (+55 11) 3178-6800 Ext. 177

The RAMB, Journal of The Brazilian Medical Association, *is an official publication of the Associação Médica Brasileira (AMB – Brazilian Medical Association), indexed in Medline, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B2 Capes databases, and licensed by Creative Commons®. Registered in the 1st Office of Registration of Deeds and Documents of São Paulo under n. 1.083, Book B, n. 2.*

Publication norms are available on the website www.ramb.org.br

THE RAMB IS INDEXED IN SCIELO - SCIENTIFIC ELECTRONIC LIBRARY ONLINE.

TIMBRO EDITORA

PUBLISHER: *Rodrigo Aguiar*
AUTHORIZING EDITOR: *Luciano Bauer Grohs*
EDITOR: *Celina Maria Morosino Lopes*
PRODUCER: *Maria Fortes*
EDITORIAL PRODUCER: *Helvânia Ferreira*
ENGLISH TRANSLATION OF ARTICLES: *Alpha & Omega*
REFERENCE REVIEWER: *Rosângela Monteiro*
PROOFREADING: *Hebe Ester Lucas e Alpha & Omega*
GRAPHIC DESIGN: *Angela Mendes, Fernando Zanardo*

Ipse Dixit

Wanderley Bernardo[1,2]

1. Coordenador do Projeto Diretrizes da Associacao Medica Brasileira, São Paulo, SP, Brasil
2. Professor da Faculdade de Medicina da Universidade de Sao Paulo, SP, Brasil

E-mail: wmbernardo@usp.br

http://dx.doi.org/10.1590/1806-9282.66.S2.1

The Latin form of the expression *Ipse dixit*, which means "he said it himself", is attributed to the Roman philosopher Marcus Tullius Cicero (106-43 BC)[1].

It is an affirmation without proof, or a dogmatic expression of opinion, or a fallacy that consists in defending a proposition by stating, without further justification, that it is "exactly as it is" because it is an intrinsic, immutable question, namely: the argumentum ad verecundiam or argumentum magister dixit.

The *argumentum ad verecundiam* or *argumentum magister dixit* is a Latin expression that means an appeal to authority or an argument based on authority that dispenses reasoning or evidence. It is a logical prose that is supported by the word or reputation of some authority or institution in order to validate the argument. And absurdly and conveniently its conclusions are based exclusively on the credibility of the author of the proposition and not on the reasons that he or she presented to support it.

Despite the origins of this expression preceding the birth of Christ, the conflicts generated by its use and abuse pervade the period after Christ as a method to disqualify the proves and to keep "everything as it is", suppressing liberation initiatives, such as the one exemplified in the excerpt which I transcribe from Abraham Lincoln's second debate with Stephen A. Douglas on August 27, 1858 in Freeport Illinois, on page 48[2]:

Lincoln said: "I pass on one or two points that I have because my time will expire very soon, but I must be able to say that Judge Douglas repeats himself again, as he did on one or two other occasions when saying Lincoln, in his *ipse dixit*, accusing a conspiracy of a large number of members of Congress, the Supreme Court and two presidents, to nationalize slavery... I mean that, in the first place, I did not make this type of accusation based on my ipse dixit. I just exposed the evidences tending to prove them, and I presented them to the acknowledgement of others, saying what I think proves them, but giving you the means to judge whether they prove them or not. That's exactly what I did. I didn't incorporate that into my *ipse dixit*. On this occasion, I would like to recall your attention to the evidence I have presented[2].

Abraham Lincoln, the 16th President of the USA, was assassinated 7 years after his speech denouncing a conspiracy against the freedom from human slavery in America. Despite presenting evidences so that these could be freely assessed (the principle of democracy) he was falsely accused of practicing *ipse dixit* by his debater, where in the absence of contrary evidence, it only remained to seek his disqualification.

In the past, the scientific method available for generating evidence was much more limited than at the present time, and therefore concepts were also limited. Even then, there already was the dichotomy between the existence of evidence and the "Because I say so!" speech similar to nowadays. The involvement of politics as well, because evidence and democracy were notably associated, and "politicization" was a positive natural phenomenon of scientific contextualization.

Unfortunately, human nature and its self-preservation and survival instincts, as in a medullary reflex, responds immaturely and selfishly towards its self-interests. And even in severe situations of high mortality, it is not capable of simply being transparent and considering the other, who in this case are patients or potential patients of COVID-19.

The available evidence of effectiveness and accuracy is not imperative or dogmatic. It is an additional element to assist in decision making, and there is always the option to not enforce it. On the other hand, we should not ignore the evidence or spend time uselessly trying to disqualify it, especially when there is no evidence to support a different recommendation.

The method of constant criticism and never striving to learn how to technically analyze the "proofs" is convenient, even if you are not able to produce them. But is inexcusable the inconsequential attitude and the lack of commitment in not considering the evidence in decision making, based on the assumption that the risk lies with the patient and not with those who exercise their ipse dixit.

The evidence establishes a parameter and it does not allow an affirmation without a proof simply in the name of autonomy and freedom of choice. The latter may seem more in line with the concept of democracy, but actually translates an obscure and non-reproducible attitude that exposes patients to uncertainties and diversions alike a Roman politics of "medicine and circuses".

We do not need to do anything because we are unable or unwilling to do what is necessary. The transparency concerning our limitations is desirable and has been associated with evidence-based practice since the dawn of democratic and ethical humanity. We always need to exercise what is best for patients based on science that increasingly advances in strengthening fundamental human concepts during this COVID-19 epidemic, because science also learns from its mistakes:

1. We are often powerless;
2. We cannot do everything;
3. We cannot accomplish everything;
4. We strive to do what we owe;
5. If we don't, we admit it;
6. We prepare ou for the future;
7. We do not exercise our *ipse dixit*.

Above all, we must acknowledge the limits in our own humanity during this constant fight against the exercise of *ipse dixit*. In the face of the persistent generation of scientific evidence by a few, there will only be left (or not) for those who exercise *ipse dixit* a sad and useless mea culpa for all the harm caused to patients.

REFERENCES

1. "Ipse dixit." Merriam-Webster.com Dictionary, Merriam-Webster, https://www.merriam-webster.com/dictionary/ipse%20dixit. Accessed 20 Jul 2020.
2. Second debate between Abraham Lincoln and Stephen A. Douglas on August 27, 1858 in Freeport Illinois, page 48. Available in: https://quod.lib.umich.edu/l/lincoln/lincoln3/1:5.1?rgn=div2;singlegenre=All;sort=occur;subview=detail;type=simple;view=fulltext;q1=ipse+dixit

This article was originally written in Portuguese within the medical education initiatives in evidence-based medicine of the Federation of Unimeds of the State of São Paulo (FESP) and is available for access in the digital collection.

Is it safe to delay testosterone replacement therapy in pandemic times?

Fernando Nestor Facio Junior[1]
Luis Cesar Fava Spessoto[1]

1. Professor de Urologia, Departamento de Urologia. Faculdade de Medicina de São José do Rio Preto (FAMERP FUNFARME), São José do Rio Preto, SP, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.3

Unprecedented measures have been adopted by several countries to curb the spread of the virus and control the increase in the number of patients infected with COVID-19, making the population's health more vulnerable[1].

Daily data show that the entire population with SARS-CoV2 is composed of 62% of men[2]. This had a great impact on the quality of life of men aged over 60, as 66.2% can develop severe forms of this disease[3]. Especially in this group, attention should be increased, including social isolation recommended by health authorities.

In this context, men seem to be more susceptible to infection and mortality compared to women[4]. Hormonal effects may have a pathophysiological role in association with SARS-CoV-2; thus, this disease could worsen hypogonadism with depletion of androgenic action, triggering a severe or even fatal course of the disease[4]. Androgen deficiency increases with age and hypogonadism can negatively affect the functions of multiple organs and quality of life, therefore, it is necessary to maintain testosterone replacement therapy[5].

It is known that a low plasma testosterone concentration associated with comorbidities such as obesity, hypertension, diabetes, and respiratory diseases are all highly prevalent in patients with COVID-19. In this context, low levels of testosterone can reduce muscle activity in the respiratory system, general strength, and exercise capacity[6], while normal levels of circulating testosterone show a protective effect on the respiratory system[7].

Evidence indicates that testosterone, capable of modulating the expression of the angiotensin-converting enzyme 2 (ECA2), is activated and negatively regulated by the coronavirus spike protein, which allows its penetration into epithelial cells and the myocardium[8].

From a psychogenic point of view, depression, irritability, and concentration difficulties are some of the side effects that low serum testosterone levels can cause[9]. The deficiency of this hormone in men suggests changes in effective processing and in the regulation of emotional decision making[10]. In such cases, it is essential to maintain adequate patient monitoring, including an effort to avoid treatment abandonment and probable hypogonadism relapse.

DATE OF SUBMISSION: 08-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Fernando Nestor Facio Jr.
Fernando C. Pires Avenue, Faculdade de Medicina de São José do Rio Preto, Departamento de Urologia, SP, Brasil – 3600
E-mail: fnfacio@yahoo.com.br

Therefore, as we face these challenges and the uncertainties regarding the time necessary for social isolation and possible delays in personal visits to clinics, we can offer online appointments to answer questions regarding the acquisition of prescriptions, doses, and maintenance of therapy. During this pandemic, low testosterone levels in men older than 60 years of age can further aggravate the health status of these patients, who require specialized care, social isolation, and emotional support.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China. N Engl J Med. 2019;382(8):727-33.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
3. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al; China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):200547.
4. Salonia A, Corona G, Giwercman A, Maggi M, Minhas S, Nappi RE, et al. SARS-CoV-2, testosterone and frailty in males (PROTEGGIMI): a multidimensional research project. Andrology. 2020. doi: 10.1111/andr.12811.
5. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical practice guideline. J Clin Endocrinol Metab. 2018;103(5):1715-44.
6. Montanõ LM, Espinoza J, Flores-Soto E, Chávez J, Perusquiá M. Androgens are bronchoactive drugs that act by relaxing airway smooth muscle and preventing bronchospasm. J Endocrinol. 2014;222(1):1-13.
7. Mohan SS, Knuiman MW, Divitini ML, James AL, Musk AW, Handelsman DJ, et al. Higher serum testosterone and dihydrotestosterone, but not oestradiol, are independently associated with favourable indices of lung function in community-dwelling men. Clin Endocrinol (Oxf). 2015;83(2):268-76.
8. Pozzilli P, Lenzi A. Testosterone, a key hormone in the context of COVID-19 pandemic. Metabolism. 2020;108:154252.
9. Kumar P, Kumar N, Thakur DS, Patidar A. Male hypogonadism: symptoms and treatment. J Adv Pharm Technol Res. 2010;1(3):297-301.
10. Mueller SC, Grissom EM, Dohanich GP. Assessing gonadal hormone contributions to affective psychopathologies across humans and animal models. Psychoneuroendocrinology. 2014;46:114-28.

Bioethical aspects of artificial intelligence: COVID-19 & end of life

Oswaldo Jesus Rodrigues da Motta[1]
Eugênio Silva[2,3,4]
Rodrigo Siqueira-Batista[5,6]

1. Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brasil.
2. Fundação Centro Universitário Estadual da Zona Oeste do Rio de Janeiro (UEZO), Rio de Janeiro, RJ, Brasil;
3. Centro Universitário Serra dos Órgãos (UNIFESO), Teresópolis, RJ, Brasil.
4. Centro Universitário Carioca (UNICARIOCA), Rio de Janeiro, RJ, Brasil.
5. Universidade Federal de Viçosa (UFV), Viçosa, MG, Brasil.
6. Faculdade Dinâmica do Vale do Piranga (FADIP), Ponte Nova, MG, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.5

KEYWORDS: *Bioethics. Artificial Intelligence. Coronavirus Infections. Decision Making. Decision Support Systems, Clinical. Palliative Care.*

Dear Editor,

The disease caused by the SARS-CoV-2 virus (COVID-19) has brought significant challenges to clinical medicine and public health[1] since its appearance in China during the month of December 2019. In fact, this novel virus — whose transmission mechanisms and natural history are still under investigation — has disseminated and grown exponentially regarding the number of infected people[2], on a global scale. In this scenario, there is, naturally, the need to make decisions when faced with questions such as: (1) defining which patients will be given priority in intensive care units[3,4] and (2) whether or not to submit COVID-19 patients to mechanical ventilation[5]. The answers to these questions — that are closely related to (bio)ethical reflections — can be supported by computational techniques, especially those based on artificial intelligence (AI).

A study by Ouyang *et al.*[4] used mathematical modeling to determine what type of screening policy could be useful in ICUs during the SARS-CoV-2 pandemic. The article — whose aim was to find a heuristic to minimize the average global lethality rate over time — analyzed the circumstances in which patients could be placed in line, for admission to a hypothetical ICU with limited beds, or transferred to a general ward as the condition changes. The proposed heuristic worked satisfactorily in the simulation.

Another possible way of applying these techniques concerns the use of AI in determining personalized sedation and analgesia in the case of mechanical ventilation and extubation. In this context, Prasad *et al.*[5] used a reinforced learning algorithm — known as Q-learning — that suggested better decisions than those proposed by specialists regarding extubation time. AI techniques, especially those belonging to the machine learning area, allow for the construction and

DATE OF SUBMISSION: 09-Jul-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Oswaldo Jesus Rodrigues da Motta
Av. Horácio Macedo, S/N, Rio de Janeiro, RJ, Brasil – 21941-901
E-mail: oswaldojrm@hotmail.com

extraction of behavioral patterns implicit in decision histories, regarding a problem situation.

Assuming the existence of a database of previous decisions that comprise, for example, the type of care to be used at the end of life or the therapy to be prescribed to a patient, the patterns underlying this data can assist in choosing the most appropriate conduct to be adopted in each situation, provided it is properly extracted. In the current COVID-19 pandemic scenario, in which these decisions become even more pressing, this type of support can be of great value for ethically, more responsible, and fair conducts.

Conflict of interest

The authors declare no conflicts of interest.

Funding

All authors have no financial disclosures or support in this work.

Author's Contribution

All authors have made substantial contributions to this work. All authors have seen and approved the manuscript and contributed significantly to the work.

PALAVRAS-CHAVE: *Bioética. Inteligência Artificial. Infecções por Coronavirus. Tomada de Decisões. Sistemas de Apoio a Decisões Clínicas. Cuidados Paliativos.*

REFERENCES

1. Vieira JM, Ricardo OMP, Hannas CM, Kanadani TCM, Prata TDS, Kanadani FN. What do we know about COVID-19? A review article. Rev Assoc Med Bras. 2020;66(4):534-40.
2. Gouveia CC, Campos L. Coronavirus disease 2019: clinical review. Acta Med Port. 2020. doi: 10.20344/amp.13957.
3. Siqueira-Batista R, Gomes AP, Braga LM, Costa AS, Thomé B, Schramm FR, et al. COVID-19 e o fim da vida: quem será admitido na Unidade de Terapia Intensiva? Observatório COVID-19 Fiocruz. Rio de Janeiro: Fiocruz; 2020. 6p. [cited 2020 Jul 2]. Available from: https://portal.fiocruz.br/sites/portal.fiocruz.br/files/documentos/COVID-19_e_o_fim_da_vida_-_quem_vai_para_uti_27-5_.pdf
4. Ouyang H, Argon NT, Ziya S. Allocation of intensive care unit beds in periods of high demand. Operations Research. 2020;68(2):591-608. [cited 2020 Jul 2]. Available from: http://ziya.web.unc.edu/files/2019/04/Allocation_of_ICU_Beds-FINAL.pdf
5. Prasad N, Cheng L-F, Chivers C, Draugelis M, Engelhardt BE. A reinforcement learning approach to weaning of mechanical ventilation in intensive care units. arXiv preprint. arXiv:1704.06300. [cited 2020 Jul 2]. Available from: https://arxiv.org/abs/1704.06300#:~:text=A%20Reinforcement%20Learning%20Approach%20to%20Weaning%20of%20Mechanical,-care%20of%20patients%20admitted%20to%20intensive%20care%20units.

The doctor-patient relationship in the context of the COVID-19 pandemic

Vânia Thais Silva Gomes[1]
Roberto Oliveira Rodrigues[2]
Raimundo Nonato Silva Gomes[3]
Maria Silva Gomes[4]
Larissa Vanessa Machado Viana[5]
Felipe Santana e Silva[6]

1. Departamento de Medicina, Universidade de Gurupi, Gurupi, TO, Brasil
2. Departamento de Medicina, Universidade Estadual do Maranhão, São Luiz, MA, Brasil
3. Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil
4. Força Estadual de Saúde do Maranhão, São Luiz, MA, Brasil
5. Centro de Ciências da Saúde e do Desporto, Universidade Federal do Acre, Rio Branco, AC, Brasil
6. Centro de Ciências da Saúde. Universidade Estadual do Maranhão, São Luiz, MA, Brasil

http://dx.doi.org/10.1590/1806-9282.66.S2.7

KEYWORDS: *Coronavirus Infections. Pandemics. Physician-Patient Relations.*

The novel Coronavirus disease (COVID-19) pandemic has brought up complex and challenging issues in all areas of knowledge and in the social, political, economic, religious, cultural, and medical spheres. An important question to ask ourselves is: are doctors prepared to eliminate suffering and/or save lives in the current context?

The countless advances in biotechnology and biomedical engineering show promise in increasing people's life expectancy. Research is continuously being done in these areas; we learn more and more each day. However, the advances in technology have brought up an important discussion around the doctor-patient relationship (DPR).[1]

In addition to scientific advances, another important agent that affects DPR is telemedicine, which guarantees the possibility of remote assistance, but makes skin-to-skin contact, which is so necessary for medical conduct, impossible.

The implementation of social distancing has forced doctors to guarantee more humane and extremely high-quality care, as the disease has exposed the country to this situation of great suffering. Therefore, it is necessary to discuss the role of human relations, with an emphasis on DPR, in the development of medical practice.[2]

On the other hand, in the context of hospitals, the intensive care unit (ICU) itself is already a widely

DATE OF SUBMISSION: 05-Jul-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Raimundo Nonato Silva Gomes
Av. Carlos Chagas Filho, 373, Bloco L – Prédio do CCS UFRJ, Rio de Janeiro, RJ, Brasil – 21941-590
Tel: +55 21 98329-8123
E-mail: raigomes.ufrj@gmail.com

complex unit and in serious need of technological apparatuses, especially in cases of complex diseases such as COVID-19. Patients with COVID-19 who are admitted to the ICU need extensive biotechnological investment to maintain vitality; additionally, they require great dedication from the doctors. However, DPR in the ICU was already a major challenge and with the outbreak of the COVID-19 pandemic the situation has become even worse, considering that the disease is highly contagious and there is a high mortality rate among "high-risk groups."[3]

The ICU, signaling the critical nature of patients' condition, causes great distress to patients' family members and the medical team itself. In the context of the COVID-19 pandemic, a patient in intensive care creates even more distress for the medical team and the patient's family, since the doctors do not have access to completely effective therapeutic means to alleviate the suffering of the patients and their relatives.

The DPR has always been based on the bond between the doctor and the patient and the doctor's sense of empathy; it is based on the medical oath to "save lives." Today, this principle has become fragile and powerless in the face of a giant that has already claimed many lives due to the collapse of the health system in many countries, including Brasil.[4]

Due to the collapse of the health system, it is up to the physician to decide who will have access to the scarce ICU beds. This situation favors the exponential growth of depressive, anxious, and phobic symptoms in medical professionals, especially among intensivists. Given these facts, we ask if the DPR will remain the same, and if humanized care — seeing the patient holistically — will still be the same in the near future.

Among the various aspects that make up the DPR, empathy deserves the most emphasis. Therapeutic adherence is based on the DPR since trust and mutual collaboration are required for the effectiveness of diagnostic and therapeutic processes, which are essential for good medical practice. As highlighted in Figure 1, DPR is based on multiple intersecting principles.

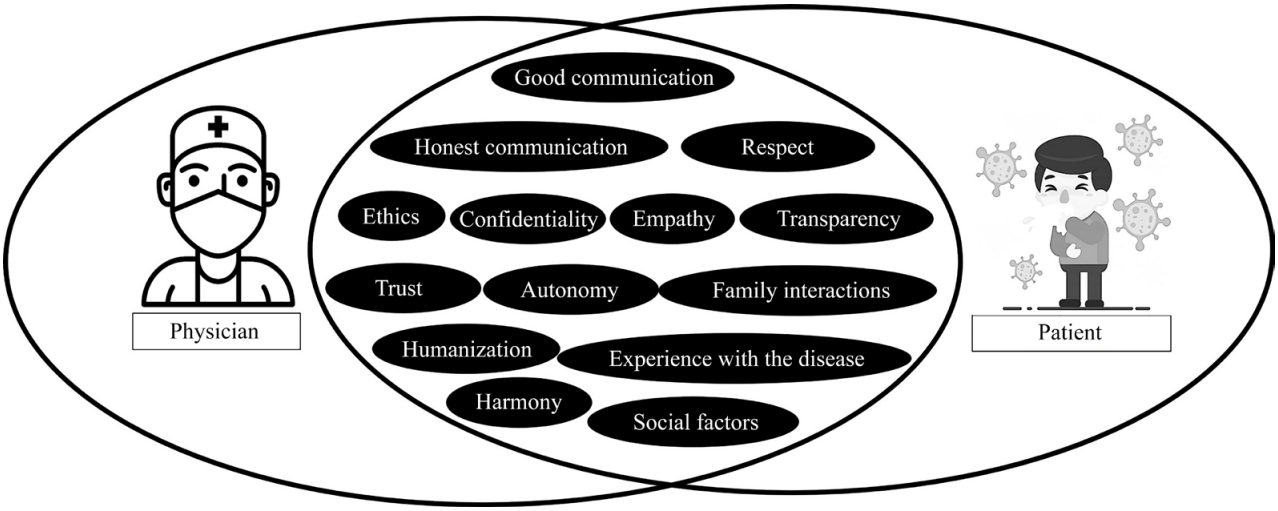
The evolutionary process of medical practice, which occurs naturally, has caused DPR to undergo numerous changes over the years, and empathy has not gone unaffected. Changes in behavior intrinsic to the pandemic constitute a landmark of great importance in DPR.

COVID-19, due to its highly infectious character, has overburdened healthcare systems and human resources, requiring the establishment of new modalities for patient care, such as telemedicine. However, it should be noted that the basic principle of DPR, as postulated by Hippocrates, may not be achieved through telemedicine (an alternative widely used during the pandemic).[5]

In addition to the numerous technical and ethical-legal questions raised by the pandemic, it must be made very clear that there is a great need for common sense in the DPR at present. Numerous alleged prophylactic and therapeutic measures emerge daily, and with them, new challenges to the DPR.[4-5]

The successful use of a technological resource to face this global challenge is likely to increase the

FIGURE 1. ASPECTS OF DPR NEEDED DURING THE COVID-19 PANDEMIC



acceptance of such technologies. And, as already foreseen, any change (such as that caused by COVID-19) causes also evolutionary changes in behavior in society. Therefore, DPR combined with new technologies can guarantee the scientific/humanistic apparatus necessary for the efficient care of patients with COVID-19.

Thus, the DPR continuum must coexist beyond the chaos in the public healthcare system; however, physicians' self-preservation must be an inalienable parameter in the daily practice of medicine.

Author's Contribution

All authors contributed equally to the work.

PALAVRAS-CHAVE: *Infecções por Coronavirus. Pandemias. Relações Médico-Paciente.*

REFERENCES

1. Costa FD, Azevedo RCS. Empatia, relação médico-paciente e formação em medicina: um olhar qualitativo. Rev Bras Educ Med. 2010;34(2):261-9.
2. Gomes AMA, Caprara A, Landim LOP, Vasconcelos MGF. Relação médico-paciente: entre o desejável e o possível na atenção primária à saúde. Physis. 2012;22(3):1101-19.
3. Vallelonga F, Elia F. Doctor-patient relationship at the time of COVID-19: travel notes. Intensive Care Med. 2020;1. doi: 10.1007/s00134-020-06152-w.
4. Gao B, Dong J. Does the impact of COVID-19 improve the doctor-patient relationship in China? Am J Med Sci. 2020;S0002-9629(20)30231-7.
5. Azoulay E, Kentish-Barnes N. A 5-point strategy for improved connection with relatives of critically ill patients with COVID-19. Lancet Respir Med. 2020;8(6):e52.

Speech therapy practice in hospital settings and COVID-19 pandemic

Brenda Carla Lima Araújo[1,2]
Thales Rafael Correia de Melo Lima[3]
Vanessa Tavares de Gois-Santos[2,4]
Victor Santana Santos[5]
Silvia de Magalhães Simões[4,6]
Paulo Ricardo Martins-Filho[2,4]

1. Departamento de Fonoaudiologia, Universidade Federal de Sergipe, Aracaju, SE, Brasil.
2. Laboratório de Patologia Investigativa, Universidade Federal de Sergipe, Aracaju, SE, Brasil.
3. Programa de Pós-Graduação Profissional em Gestão e Inovação Tecnológica em Saúde, Universidade Federal de Sergipe, Aracaju, SE, Brasil.
4. Programa de Pós-Graduação em Ciências da Saúde, Universidade Federal de Sergipe, Aracaju, SE, Brasil.
5. Centro de Epidemiologia e Saúde Pública, Universidade Federal de Alagoas, Arapiraca, SE, Brasil
6. Departamento de Medicina, Hospital Universitário/EBSERH, Universidade Federal de Sergipe, Aracaju, SE, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.10

KEYWORDS: *Coronavirus infections. Speech therapy. Deglutition Disorders. Primary Health Care.*

Dear editor,

Coronavirus disease 2019 (COVID-19), an emerging infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is transmitted mainly by droplets and contact, has become a major health problem and resulted in new challenges for healthcare systems worldwide[1]. Multidisciplinary teams can play a major role in the management of patients with SARS-CoV-2 infections.

In the hospital setting, speech therapists must be involved in the care of patients with complaints and symptoms related to difficulty in swallowing, regardless of the underlying disease. It is necessary to reflect on the changes and challenges faced by these health professionals during the COVID-19 pandemic. The challenges with the emergence of COVID-19 include changes in the service schedule, work process, and the physical and organizational structure of the hospital environment.

Patients with severe symptoms associated with SARS-CoV-2 infections may require respiratory support, including endotracheal intubation and mechanical ventilation, and enteral nutrition by tube feeding. It has been reported that critically ill patients with COVID-19 can present severe muscle weakness, impaired mobility, neurological and psychological disorders, dysphagia, and smell and taste dysfunction[2,3].

The speech therapy service aims to perform a clinical evaluation of swallowing to determine the risk

DATE OF SUBMISSION: 30-Jun-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Brenda Carla Lima Araújo
Universidade Federal de Sergipe - UFS, Pós-Graduação em Ciências da Saúde. Rua Cláudio Batista, s/n. Bairro Sanatório. Aracaju, Sergipe., SE, Brasil – 49060-100. Tel.: +55 79 99954-7094
E-mail: brendaaraujo@yahoo.com.br

of dysphagia and the safest diet route, in addition to defining the need for instrumental evaluation at the bedside. Preliminary results from a recent clinical study on the swallowing performance and safety of COVID-19 patients suggest fewer rehabilitation sessions to return to safe oral feeding when compared to critical Intensive Care Unit (ICU) patients without COVID-19[4].

The COVID-19 pandemic also caused limitations in conducting clinical evaluation, as the procedures performed by speech therapists require proximity to the patients' faces and contact with the oral mucosa and body fluids, such as saliva and respiratory droplets[5]. The available evidence recommends avoiding any type of stimulus that may trigger coughing and vomiting reflexes, including areas of the oral cavity, such as the base of the tongue, fauces, uvula, palate, and posterior pharynx wall[6], in addition to restrictions on the use of cervical auscultation in the assessment of dysphagia[7].

Instrumental assessment including video-fluoroscopy and endoscopic evaluation of swallowing should only be performed after patients test negative for SARS-CoV-2 infection in the previous 48 hours, but there are still controversies about the appropriate time to perform these procedures in the current context. Moreover, the recommendation is to avoid elective treatments since speech therapists are at high risk of contamination during aerosol-generating procedures[8].

Biosafety modifications have been needed for speech therapy in the hospital setting. At present, particular attention has been paid to personal protective equipment (PPE), including the use of face masks and face shields, N95 respirators, eye protection, gloves, goggles, and disposable aprons[9]. Current evidence indicates that N95 respirators provide better protection than surgical masks in the laboratory environment and while aerosol-generating procedures, including speech therapy, coughing, aspiration of saliva or food, and management of tracheostomy. During the management of patients with COVID-19, speech therapists must also follow guidelines on social distancing and frequent handwashing to minimize the risk of infection.

An alternative for speech therapists is monitoring patients via a call center. However, there are still controversies in the literature about the effectiveness of this approach. A systematic review did not demonstrate the effectiveness of telerehabilitation in dysphagic patients compared to face-to-face therapy[10]. Other studies have found benefits in the call center approach, suggesting that it promotes increased access to clinical rehabilitation and guarantees adequate services for patients with swallowing disorders, requiring periods of intensive treatment followed by long-term management[11-13]. In the current scenario, call centers can be an alternative means of providing services, in a complementary way or replacing face-to-face treatments. The focus of speech therapists' work at this time should be to guide the implementation of a new flow of care, both for those hospitalized for other diseases, as well as for suspected cases of COVID-19, in addition to organizing the priority demand for cases of severe bronchoaspiration in dysphagic patients. One of the greatest challenges in the current and post-pandemic speech therapy practice is the difficulty in communicating with patients through expressions and gestures to demonstrate movements, which is impaired due to the use of PPE. Communication favors the professional-patient bond and is important for adherence to the treatment. However, for speech therapists who work in the hospital setting, reducing the risk of contamination and spreading the virus must be a team effort. Speech therapy in a hospital setting faced with this new respiratory virus should be based on rigorous biosafety measures and effective collaboration of professionals in the treatment of COVID-19 patients. Studies on the functional consequences of the disease are needed to understand possible sequelae and specific needs for speech therapists.

Conflict of interest

The authors have no conflict of interest to declare.

Financial source

This study was not funded.

Author's Contributions:

All authors were involved in the drafting of the article or revised it critically for important intellectual content. All authors approved the final version to be submitted for publication as stated by the International Committee of Medical Journal Editors (ICMJE): Ms. Brenda Araújo had full access to all the data and the accuracy of the data analysis. ARAÚJO participated in the concept of the study, data collection, analysis and interpretation, and writing; LIMA, GOIS-SANTOS participated in data collection; SANTOS, SIMÕES AND MARTINS-FILHO participated in guiding, the concept of the study, analysis, interpretation of data, and writing

PALAVRAS-CHAVE: *Infecções por coronavírus. Fonoaudiologia. Transtornos de Deglutição. Atenção Primária à Saúde.*

REFERENCES

1. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection: a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020;9(1):727-32.
2. Kiekens C, Boldrini P, Andreoli A, Avesani R, Gamna F, Grandi M, et al. Rehabilitation and respiratory management in the acute and early post-acute phase. "Instant paper from the field" on rehabilitation answers to the COVID-19 emergency. Eur J Phys Rehabil Med. 2020;56(3):323-6.
3. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020;277(8):2251-61.
4. Lima MS, Sassi FC, Medeiros GC, Ritto AP, Andrade CRF. Preliminary results of a clinical study to evaluate the performance and safety of swallowing in critical patients with COVID-19. Clinics. 2020;75:e2021.
5. American Speech-Language-Hearing Association. SLP Service delivery considerations in health care during coronavirus/COVID-19. Rockville: American Speech-Language-Hearing Association; 2020. [cited 2020 Jun 13]. Available from: https://www.asha.org/SLP/healthcare/SLP-Service-Delivery-Considerations-in-Health-Care-During-Coronavirus/
6. Bolton L, Mills C, Wallace S, Brady MC, Royal College of Speech and Language Therapists (RCSLT) COVID-19 Advisory Group. Aerosol generating procedures, dysphagia assessment and COVID-19: a rapid review. Int J Lang Commun Disord. 2020;10.1111/1460-6984.12544.
7. Associação de Medicina Intensiva Brasileira. Parecer do Departamento de Fonoaudiologia da AMIB referente ao atendimento ao COVID-19 na terapia intensiva e no ambiente hospitalar. São Paulo: Associação de Medicina Intensiva Brasileira; 2020. [cited 2020 Jun 13]. Available from: https://www.amib.org.br/fileadmin/user_upload/amib/2020/marco/22/14_Parecer__FonoaudiologiaCOVID-19.pdf
8. Jotz GP, Voegels RL, Bento RF. Otorhinolaryngologists and coronavirus disease 2019 (COVID-19). Int Arch Otorhinolaryngol. 2020;24(2):e125-8.
9. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. Corrigendum to "World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19)". Int J Surg. 2020;77:217.
10. Nordio S, Innocenti T, Agostini M, Meneghello F, Battel I. The efficacy of telerehabilitation in dysphagic patients: a systematic review. Acta Otorhinolaryngol Ital. 2018;38(2):79-85.
11. Morrell K, Hyers M, Stuchiner T, Lucas L, Schwartz K, Mako J, et al. Telehealth stroke dysphagia evaluation is safe and effective. Cerebrovasc Dis. 2017;44(3-4):225-31.
12. Tedesco A, Lavermicocca V, Notarnicola M, De Francesco L, Dellomonaco AR. Telemonitoring of swallowing function: technologies in speech therapy practice. Recenti Prog Med. 2018;109(2):146-8.
13. Mayadevi M, Thankappan K, Limbachiya SV, Vidhyadharan S, Villegas B, Ouyoung M, et al. Interdisciplinary telemedicine in the management of dysphagia in head and neck. Dysphagia. 2018;33(4):474-80.

Immune status could be associated with severity in COVID-19 patients

Chuan Liu[1,2]
Jiahui Yang[3]
Wancong Wang[1]
Yang Mi[1,2]
Youcai Tang[2,4]
Pengyuan Zheng[1,2]

1.Department of Gastroenterology, The Fifth Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, Henan Province, China.
2.Marshall B.J.Medical Research Center of Zhengzhou University, Zhengzhou, 450052, Henan Province, China.
3.Department of Geriatric, West China Hospital of Sichuan University, Chengdu, 610041, Sichuan Province, China.
4.Department of Children's Rehabilitation Medicine, The Fifth Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, Henan Province, China.

http://dx.doi.org/10.1590/1806-9282.66.S2.13

KEYWORDS: *Coronavirus Infections/immunology. Meta-analysis. Immunocompetence. Immunologic Factors.*

Dear Editor,

Corona Virus Disease 2019 (COVID-19) is a highly contagious disease that has caused outbreaks across the globe. As of May 21, 2020, a total of 5,027,732 confirmed COVID-19 cases have been reported in 188 countries, with an average mortality of 6.54%[1]. The current relationship between COVID-19 disease severity and immune function status is unclear. As far as we know, this study is the first meta-analysis to compare immune status and immunoglobulin efficacy in severe vs. non-severe patients with COVID-19.

An extensive electronic search of PubMed, Embase, and Cochrane Library was conducted without date limitations (until May 6, 2020), using the keywords "COVID-19", "2019-nCoV", "SARS-CoV-2", "Novel Coronavirus", "Feature", "Immune", etc. Two authors independently screened articles, assessed qualities, and performed data extraction. Any discrepancies during these steps were regularly resolved by consulting with a third reviewer. Severe COVID-19 infection was defined as severe pneumonia, acute respiratory distress syndrome (ARDS), treatment with mechanical ventilation or intensive care unit (ICU), and/or death. Dichotomous variables were estimated with Odd Risks (OR) and 95% confidence interval (CI). Continuous data (using mean and standard deviation - SD) were compared and the mean difference (MD) was calculated with 95% CI, and a P-value <0.05 was considered statistically

DATE OF SUBMISSION: 26-Jun-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Pengyuan Zheng
Department of Gastroenterology, The Fifth Affiliated Hospital of Zhengzhou University; Marshall B.J.Medical Research Center of Zhengzhou University, Kangfu Street No. 3, Zhengzhou 450052, China. Tel.: 0371-66902171
Email address: medp7123@126.com

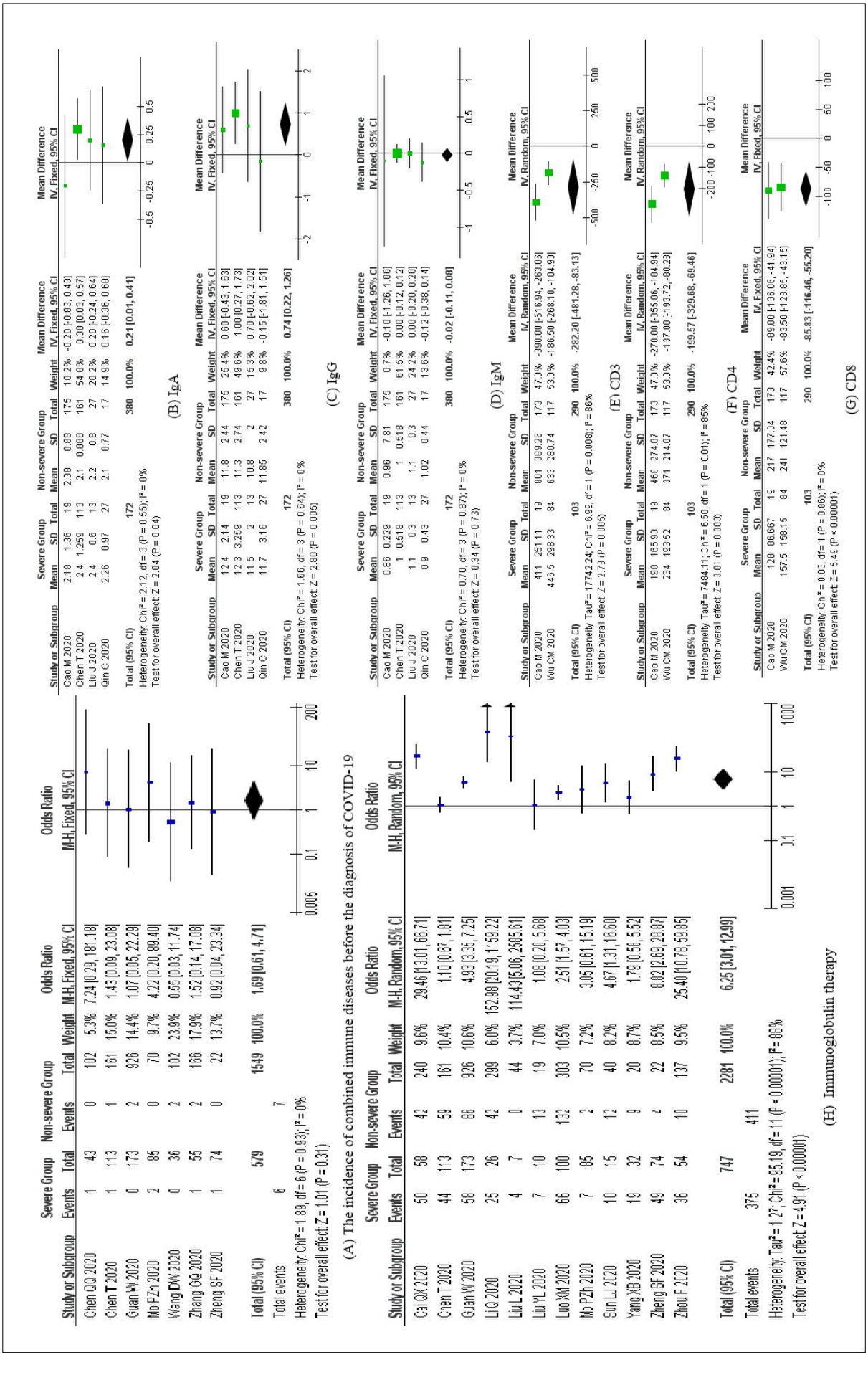


FIGURE 1. META-ANALYSIS RESULTS OF THE OUTCOMES: (A) THE INCIDENCE OF COMBINED IMMUNE DISEASES BEFORE THE DIAGNOSIS OF COVID-19; (B) IGA; (C) IGG; (D) IGM; (E) CD3; (F) CD4; (G) CD8; (H) IMMUNOGLOBULIN THERAPY.

significant. The random-effects model was used if I^2>50%. The publication bias was evaluated by visual inspection of the funnel plot. Our meta-analysis was carried out using Review Manager software version 5.3 (Cochrane Collaboration).

Nineteen studies [2-20] were enrolled in our analysis. All studies originated from China and involved 4,011 confirmed COVID-19 patients in total. The incidence of combined immune diseases before the diagnosis of COVID-19 was not significantly associated with an enhanced risk of severe COVID-19 (OR: 1.69, 95% CI: 0.61-4.71, P=0.31). Immune globulin A (IgA) and immune globulin G (IgG) were found to be increased in COVID-19 patients in the severe group [IgA: MD=0.21, 95%CI (0.01, 0.41), P=0.04; IgG: MD=0.74, 95%CI (0.22, 1.26), P=0.005]. Immune globulin M (IgM) was not found to be correlated with the severity of COVID-19 (MD: -0.02, 95% CI: -0.11, 0.08, P=0.73). Our study revealed that a decrease in the mean cluster of differentiation (CD)3, CD4 and CD8 was significantly associated with an increased likelihood of severity [CD3: MD=-282.2, 95%CI (-481.28, -83.13), P=0.005; CD4: MD=-199.57, 95%CI (-329.68, -69.46), P=0.003; CD8: MD=-85.83, 95%CI (-116.46, -55.20), P<0.0001]. Immunoglobulin therapy is significantly more effective in severe COVID-19 patients (OR: 6.25, 95% CI: 3.01-12.99, P<0.0001). Based on a visual inspection of the funnel plots, no evidence of publication bias was found. More details of our meta-analysis are presented in Figure 1.

This meta-analysis provides evidence that hypoimmune states could be associated with a more severe form of COVID-19, and that immunoglobulins are more effective against severe COVID-19. Our results are consistent with some previous descriptive reviews[21-23]. In addition, this study has important clinical implications. First, it can potentially help in disease assessment as the COVID-19 pandemic continues to affect multiple countries. Second, it reminds us of the relevance of early initiation of immunoglobulin therapy, which is effective in improving the prognosis of severe and critical type patients.

This study has its limitations. First, most of the studies included are retrospective and lack a prospective design. Second, some of the outcomes in this study had a high I2 value, which represents heterogeneity. This might be explained by the small sample size, limited data, and different patient populations.

Based on our results, a hypoimmune status might be an important sign of COVID-19 severity, guiding clinicians to identify severe patients earlier and faster and alerting clinicians that immunoglobulins have better efficacy in critically ill patients. Further, more high-quality literature is needed to better support this conclusion.

Acknowledgments

The National Natural Science Foundation of China (No. 81370494 and No. 31471330) funded this manuscript.

Ethical approval

All analyses were based on previously published studies, thus no ethical approval and patient consent are required.

Author's Contribution

Chuan Liu conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Jiahui Yang, Wancong Wang, and Yang Mi obtained the data, carried out the analyses. Youcai Tang and Pengyuan Zheng critically reviewed the manuscript and approved the final manuscript as submitted.

Conflict of Interest

The authors declare no conflict of interest.

PALAVRAS CHAVE: *Infecções por Coronavirus/imunologia. Metanálise. Imunocompetência. Fatores Imunológicos.*

REFERENCES

1. Johns Hopkins University. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Baltimore: Johns Hopkins University; 2020. [cited 2020 May 21]. Available from: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6
2. Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy. 2020;75(7):1742-52..
3. Chen Q, Zheng Z, Zhang C, Zhang X, Wu H, Wang J, et al. Clinical characteristics of 145 patients with corona virus disease 2019 (COVID-19) in

Taizhou, Zhejiang, China. Infection. 2020;1-9.

4. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. Bmj. 2020;368:m1091.
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. The New England journal of medicine. 2020;382(18):1708-20.
6. Li Q, Zhang J, Ling Y, Li W, Zhang X, Lu H, et al. A simple algorithm helps early identification of SARS-CoV-2 infection patients with severe progression tendency. Infection. 2020;1-8.
7. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763.
8. liu lei GJ-y. Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing-China. medrxiv. 2020.
9. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, et al. Prognostic value of C-reactive protein in patients with COVID-19. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020;ciaa641.
10. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020;ciaa270.
11. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020;71(15):762-68.
12. Sun L, Shen L, Fan J, Gu F, Hu M, An Y, et al. Clinical Features of Patients with Coronavirus Disease 2019 (COVID-19) from a Designated Hospital in Beijing, China. Journal of medical virology. 2020;10.1002/jmv.25966.
13. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama. 2020;323(11):1061-69.
14. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA internal medicine. 2020;180(7):1-11.
15. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory medicine. 2020;8(5):475-81.
16. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. 2020;127:104364.
17. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. Bmj. 2020;369:m1443.
18. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
19. Cao M, Zhang D, Wang Y, Lu Y, Zhu X, Li Y, et al. Clinical Features of Patients Infected with the 2019 Novel Coronavirus (COVID-19) in Shanghai, China. medRxiv. 2020.
20. Liu Y, Sun W, Li J, Chen L, Wang Y, Zhang L, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv. 2020.
21. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection: a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020;9(1):727-32.
22. Kadkhoda K. COVID-19: an immunopathological view. mSphere. 2020;5(2):e00344-20.
23. Jawhara S. Could intravenous immunoglobulin collected from recovered coronavirus patients protect against COVID-19 and strengthen the immune system of new patients? Int J Mol Sci. 2020;21(7):2272.

AMB Guidelines: COVID –19

Lincoln Lopes Ferreira[1]
Diogo Leite Sampaio[2]
Antonio Carlos Palandri Chagas[3]
Hélio Penna Guimarães[4,17,18,19]
Ludhmila Abrahão Hajjar[5]
Suzana Margareth Ajeje Lobo[6]
Carmita Helena Najjar Abdo[7,8]
José Luiz Bonamigo Filho[9,10]
Helio Arthur Bacha[11,12,13]
Robson Freitas de Moura[14,15]
Wanderley Marques Bernardo[16]

Created on: July 2020

1. Presidente da Associação Médica Brasileira, São Paulo, SP, Brasil
2. Vice-Presidente da Associação Médica Brasileira, São Paulo, SP, Brasil
3. Diretor Científico da Associação Médica Brasileira, São Paulo, SP, Brasil
4. Presidente da Associação Brasileira de Medicina de Emergência (ABRAMEDE), Porto Alegre, RS, Brasil
5. Diretora Extraordinária de Ciência, Tecnologia e Inovação – Sociedade Brasileira de Cardiologia, São Paulo, SP, Brasil
6. Presidente da Associação de Medicina Intensiva Brasileira, São Paulo, SP, Brasil
7. Professora Associada do Depto. de Psiquiatria da FMUSP, São Paulo, SP, Brasil
8. Primeira secretária da Associação Médica Brasileira, São Paulo, SP, Brasil
9. Clínico e hematologista. Coordenador do Programa de Residência Médica em Clínica Médica do Hospital Israelita Albert Einstein, São Paulo, SP, Brasil
10. Segundo Tesoureiro da Associação Médica Brasileira, São Paulo, SP, Brasil
11. Infectologista, mestre e doutor Faculdade de Medicina USP, São Paulo, SP, Brasil
12. Membro do Comitê Científico da Associação Médica Brasileira, São Paulo, SP, Brasil
13. Fellow American College of Physicians
14. Especialista em Cirurgia Oncológica, Professor de Clínica Cirúrgica da UNIFACS, Salvador, BA, Brasil
15. 2º Vice Presidente da Associação Médica Brasileira, São Paulo, SP, Brasil
16. Coordenador do Projeto Diretrizes da Associação Médica Brasileira, São Paulo, SP, Brasil
17. Médico do Departamento de Pacientes Graves do Hospital Israelita Albert Einstein, São Paulo, SP, Brasil
18. Coordenador Médico do Instituto de Ensino do Hospital do Coração-HCor, São Paulo, SP, Brasil
19. Professor afiliado da Escola Paulista de Medicina-EPM- Universidade Federal de São Paulo-UNIFESP, São Paulo, SP, Brasil

E-mail: wmbernardo@usp.br

http://dx.doi.org/10.1590/1806-9282.66.S2.17

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

The Brazilian Medical Association comprises various Specialty Societies, interacts with the Health System, public and private, municipal, state, and federal, and actively participates in the international scientific community through the World Medical Association and many other health institutions involved in education, assistance, or research.

These characteristics provide the AMB (board of director, scientific board, and departments) with unique and updated knowledge, a broad and concrete perspective of the facts as they are and not as we are, which along with our willingness to contribute to the national health system, allows our technical body to draw up recommendations that are autonomous,

unbiased, transparent, and based on scientific evidence, mainly and including in emergency, conflict, and serious situations, as is the case with the Coronavirus (COVID-19).

Thinking of these recommendations from a practical point of view to aid in the decision-making by the Brazilian health system, these were divided into 4 main areas: 1. Know where the cases are (early diagnosis and prevalence of COVID-19 patients); 2. Directed hospital or home isolation (early diagnosis) and social isolation (to prevent spread by undiagnosed cases); 3. Protection of healthcare professionals (protect the health of professionals, maintain the workforce, and avoid dissemination by professionals); 4. Develop a health care structure capable of properly handling more severe cases that require hospitalization, particularly in Intensive Care Units (ICU).

The evidence used to support these recommendations is based on the mistakes and successes of the international community in the management of COVID-19 cases and on the assumption of its consequences on the control of the epidemiological spread, the reduction of mortality, and in fighting the course of the disease up until the year 2021.

The seven propositional elements in this assessment expressed in the following sequence support the recommendations. However, it is important to remember that they may suffer changes and incorporations as required by the evidence available and the national context, singe these are undergoing daily dynamic changes:

1. Know where the cases are (early diagnosis and prevalence of COVID-19 patients); 2. Directed hospital or home isolation (early diagnosis) and social isolation (to prevent spread by undiagnosed cases); 3. Protection of healthcare professionals (protect the health of professionals, maintain the workforce, and avoid dissemination by professionals); 4. Pre- and intra-hospital treatment; 5. Shared decision making; 6. Mental health; 7. A health care structure capable of properly handling more severe cases that require hospitalization, particularly in Intensive Care Units (ICU), maintaining proper assistance to non-COVID-19 patients.

Issues related to the return to common activities of everyday life, both of health care or community life, are not the scope of these recommendations given its current degree of uncertainty as measured by the indices of national viral circulation, as well as the different realities in several regions of the country.

RECOMMENDATIONS

The 10 recommendations deal with some of the best practices for diagnosis, treatment, prevention, and protection to the population, patients, doctors, and health professionals, in scenarios of unpredictability, uncertainty and that require rapid decision-making as in primary care, emergency or intensive care, or even in community environments or elective assistance in the care of patients with suspected or confirmed COVID-19, as well as in the general population or with other diseases:

1. The Brazilian health system must adopt and maintain austere, intense and constant measures to minimize the effects that now affect the Brazilian population in the context of the worldwide COVID-19 epidemic (pandemic);

2. Ensure hospital infrastructure with specific and isolated areas to care for suspected and sick patients, with specific hygiene and transport measures, and a guaranteed sufficient number of beds, particularly for critically ill patients in intensive care units associated with a sufficient number of respirators for respiratory care. Ensure the appropriate hospital care, thus minimizing the risk of contagion for non-COVID-19 patients[1-7];

3. Constantly consider the index of system collapse (strain of the beds available, including ICU ones) in strategies for implementing additional beds to fill the gaps[8];

4. Ensure the provision and availability of protective equipment to health professionals, particularly those exposed to suspected or confirmed cases, with the following available for use during procedures: cap, mask (preferably N95), face shield, goggles, disposable and waterproof apron, and respirator[9-23];

5. Actively test patients with suspected COVID-19 by PCR, as well as those close to them who could have been contaminated, isolating (block) and monitoring confirmed patients, whenever possible in a community environment or through hospitalization; community isolation (lockdown) proportional to the mortality and/or number of cases diagnosed in the area, particularly of patients in risk groups[24-40];

6. Organize multi-professional committees to discuss the care priorities and community strategies according to scientific and ethical criteria to assist in decision-making in the context of the national epidemic;

7. There is no evidence to support the use of any pre-hospital treatment, both as a prophylactic (to

reduce the incidence of new cases) or in suspected or confirmed cases (to reduce mortality) [41-50];

8. The use of dexamethasone in hospitalized patients who require oxygen supplementation seems to reduce mortality[51];

9. Provide emotional support for healthcare professionals and patients, as necessary and as symptoms of psychological/psychiatric nature are identified[52-63];

10. The decisions between doctor and patient must follow the principles of shared decision-making, in which the patient is adequately informed of the benefits or absence of benefits, as well as the risks, to actively participate in the medical decision[64-75]. In addition, the AMB stands firmly in favor of the autonomy of doctors and patients, under the terms of the Helsinki Declaration, of which we are signatory[76].

Acknowledgments

Luca Bernardo, Filipe Bernardo, and Fernanda Bley for aiding in the search and selection of evidence and drafting.

REFERENCES

1. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020 Mar 13. pii: S0140-6736(20)30627-9. doi: 10.1016/S0140-6736(20)30627-9. PMID: 32178769.
2. A Estratégia Sul-Coreana de Combate do Surto de COVID-19. Givisiez LGVB, Kim P, Gorito CAC. Páginas 1-9.
3. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair Allocation of Scarce Medical Resources in the Time of COVID-19. N Engl J Med. 2020 Mar 23. doi: 10.1056/NEJMsb2005114. PMID: 32202722.
4. Truog RD, Mitchell C, Daley GQ. The Toughest Triage - Allocating Ventilators in a Pandemic. N Engl J Med. 2020 Mar 23. doi: 10.1056/NEJMp2005689. PMID: 32202721.
5. Estimativa da American Hospital Association sobre o impacto do Coronavírus no Sistema de Saúde dos EUA. Disponível em URL: https://www.businessinsider.com/presentation-us-hospitals-preparing-for-millions-of-hospitalizations-2020-3
6. Cenário dos hospitais o Brasil. Disponível em URL: http://fbh.com.br/wp-content/uploads/2019/05/CenarioDosHospitaisNoBrasil2019_10maio2019_web.pdf
7. Hospital beds (per 1,000 people). Disponível em URL: https://data.worldbank.org/indicator/SH.MED.BEDS.ZS
8. COVID-19 Projections – Institute for Health Metrics and Evaluation (IHME) – Disponível em URL: https://COVID-19.healthdata.org/projections. Acessado em 31 de março de 2020.
9. The Lancet. COVID-19: protecting health-care workers. Lancet 2020; 395(10228):922. doi: 10.1016/S0140-6736(20)30644-9. PMID: 32199474.
10. Coronavirus disease (COVID-19) outbreak: rights, roles and responsibilities of health workers, including key considerations for occupational safety and health. World Health Organization - Interim guidance 19 March 2020. Disponível em URL: https://www.who.int/docs/default-source/coronaviruse/who-rights-roles-respon-hw-COVID-19.pdf?sfvrsn=bcabd401_0. Acessado em 27 de março de 2020.
11. Advice on the use of masks in the community, during home care, and in health care settings in the context of COVID-19. World Health Organization - Interim guidance 19 March 2020. Disponível em URL: https://www.who.int/publications-detail/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak. Acessado em 27 03 2020.
12. Radonovich LJ Jr, Simberkoff MS, Bessesen MT, Brown AC, Cummings DAT, Gaydos CA, et al. N95 Respirators vs Medical Masks for Preventing Influenza Among Health Care Personnel: A Randomized Clinical Trial. JAMA. 2019; 322(9):824-833. doi: 10.1001/jama.2019.11645. PMID: 31479137.
13. Rational use of personal protective equipment (PPE) for coronavirus disease (COVID-19). World Health Organization - Interim guidance 19 March 2020. Disponível em URL: https://apps.who.int/iris/handle/10665/331215. Acessado em 27 de março de 2020.
14. Schwartz J, King CC, Yen MY. Protecting Health Care Workers during the COVID-19 Coronavirus Outbreak -Lessons from Taiwan's SARS response. Clin Infect Dis 2020. pii: ciaa255. doi: 10.1093/cid/ciaa255. PMID: 32166318.
15. Yen MY, Schwartz J, Chen SY, King CC, Yang GY, Hsueh PR. Interrupting COVID-19 transmission by implementing enhanced traffic control bundling: Implications for global prevention and control efforts. J Microbiol Immunol Infect. 2020 Mar 14. pii: S1684-1182(20)30071-2. doi: 10.1016/j.jmii.2020.03.011. PMID: 32205090.
16. Strategies to Optimize the Supply of PPE and Equipment. Centers for Disease Control and Prevention (CDC.gov). Coronavirus Disease 2019. Disponível em URL: https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html. Acessado em 27 de março de 2020.
17. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. World Health Organization. Scientific brief 27 March 2020. Disponível em URL: https://www.who.int/publications-detail/modes-of-transmission-of-virus-causing-COVID-19-implications-for-ipc-precaution-recommendations Acessado em 27 de março de 2020.
18. Parodi SM, Liu VX. From Containment to Mitigation of COVID-19 in the US. JAMA. 2020 Mar 13. doi: 10.1001/jama.2020.3882. PMID: 32167525. Table. Key Elements of a Proposed Plan for Coronavirus Disease 2019 Community Spread Mitigation in Kaiser Permanente Northern California.
19. Adams JG, Walls RM. Supporting the Health Care Workforce During the COVID-19 Global Epidemic. JAMA. 2020 Mar 12. doi: 10.1001/jama.2020.3972. PMID: 32163102.
20. Infection prevention and control during health care when COVID-19 is suspected. World Health Organization. Interim guidance 19 March 2020. Disponível em URL: https://reliefweb.int/report/world/infection-prevention-and-control-during-health-care-when-COVID-19-suspected-interim. Acessado em 27 de março de 2020.
21. The burning building. BMJ 2020;368:m1101 doi: 10.1136/bmj.m1101 (Published 19 March 2020). Disponível em URL: https://www.bmj.com/content/bmj/368/bmj.m1101.full.pdf.
22. COVID-19 Coronavirus Pandemic (Update live): Disponível em URL: https://www.worldometers.info/coronavirus/. Acessado em: 22.04.2020.
23. Bae S, Kim MC, Kim JY, Cha HH, Lim JS, Jung J, et al. Effectiveness of Surgical and Cotton Masks in Blocking SARS-CoV-2: A Controlled Comparison in 4 Patients. Ann Intern Med 2020. doi: 10.7326/M20-1342. PMID: 32251511.
24. Sharfstein JM, Becker SJ, Mello MM. Diagnostic Testing for the Novel Coronavirus. JAMA. 2020 Mar 9. doi: 10.1001/jama.2020.3864. PMID: 32150622.
25. Loeffelholz MJ, Tang YW. Laboratory Diagnosis of Emerging Human Coronavirus Infections - The State of the Art. Emerg Microbes Infect 2020; 20:1-26. doi: 10.1080/22221751.2020.1745095. PMID: 32196430.
26. Pfefferle S, Reucher S, Nörz D, Lütgehetmann M. Evaluation of a quantitative RT-PCR assay for the detection of the emerging coronavirus SARS-CoV-2 using a high throughput system. Euro Surveill 2020; 25. doi: 10.2807/1560-7917.ES.2020.25.9.2000152. PMID: 32156329.
27. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DKW, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020; 25(3). doi: 10.2807/1560-7917.ES.2020.25.3.2000045. PMID: 31992387.

28. Reusken CBEM, Broberg EK, Haagmans B, Meijer A, Corman VM, et al. Laboratory readiness and response for novel coronavirus (2019-nCoV) in expert laboratories in 30 EU/EEA countries, January 2020. Euro Surveill 2020; 25. doi: 10.2807/1560-7917.ES.2020.25.6.2000082. PMID: 32046815.

29. Cohen J, Kupferschmidt K. Countries test tactics in 'war' against COVID-19. Science 2020; 367(6484):1287-1288. doi: 10.1126/science.367.6484.1287. PMID: 32193299.

30. Guo L, Ren L, Yang S, Xiao M, Chang, Yang F, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clin Infect Dis 2020. pii: ciaa310. doi: 10.1093/cid/ciaa310. PMID: 32198501.

31. Konrad R, Eberle U, Dangel A, Treis B, Berger A, Bengs K, et al. Rapid establishment of laboratory diagnostics for the novel coronavirus SARS-CoV-2 in Bavaria, Germany, February 2020. Euro Surveill 2020; 25(9). doi: 10.2807/1560-7917.ES.2020.25.9.2000173. PMID: 32156330.

32. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA 2020 Mar 23. doi: 10.1001/jama.2020.4683. PMID: 32203977.

33. Spiteri G, Fielding J, Diercke M, Campese C, Enouf V, Gaymard A, et al. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. Euro Surveill 2020; 25(9). doi: 10.2807/1560-7917.ES.2020.25.9.2000178. PMID: 32156327.

34. Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. Int J Infect Dis. 2020 Mar; 92:214-217. doi: 10.1016/j.ijid.2020.01.050. PMID: 32007643.

35. Salathé M, Althaus CL, Neher R, Stringhini S, Hodcroft E, Fellay J, et al. COVID-19 epidemic in Switzerland: on the importance of testing, contact tracing and isolation. Swiss Med Wkly. 2020; 150: w20225. doi: 10.4414/smw.2020.20225. PMID: 32191813.

36. Wang CJ, Ng CY, Brook RH. Response to COVID-19 in Taiwan: Big Data Analytics, New Technology, and Proactive Testing. JAMA 2020 Mar 3. doi: 10.1001/jama.2020.3151. PMID: 32125371.

37. Prioridades para realização de testes em pacientes com suspeitas de COVID-19. Disponível em URL: https://www.cdc.gov/coronavirus/2019-ncov/downloads/priority-testing-patients.pdf.

38. The Global Impact of COVID-19 and Strategies for Mitigation and Suppression. Imperial College COVID-19 Response Team. 26 March 2020. Disponível em URL: https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID-19-Global-Impact-26-03-2020.pdf. Acessado em 27 de março de 2020.

39. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. Imperial College COVID-19 Response Team. 16 March 2020. Disponível em URL: https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID-19-NPI-modelling-16-03-2020.pdf. Acessado em 27 de março de 2020.

40. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020 Feb 24. doi: 10.1001/jama.2020.2648. PMID: 32091533.

41. Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Pardo-Hernandez H, et al. Drug treatments for COVID-19: living systematic review and network meta-analysis. BMJ. 2020 Jul 30;370:m2980. doi: 10.1136/bmj.m2980. PMID: 32732190; PMCID: PMC7390912.

42. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw Open 2020; 3(4):e208857. doi:10.1001/jamanetworkopen.2020.8857. PMID: 32330277.

43. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for COVID-19. N Engl J Med 2020: NEJMoa2016638. doi: 10.1056/NEJMoa2016638. PMID: 32492293.

44. Chen L, Zhang ZY, Fu JG, Feng ZP, Zhang SZ, Han QY, et al. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. Disponível em: medRxiv preprint doi: https://doi.org/10.1101/2020.06.19.20136093.this version posted June 22, 2020.

45. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Dandan Y, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Disponível em: medRxiv preprint doi: https://doi.org/10.1101/2020.03.22.20040758.this version posted April 10, 2020.

46. Jun C, Danping L, Li L, Ping L, Qingnian X, Lu X, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). Journal of the University of Zhejiang 2020; 49 (2): 215-19. DOI: 10.3785/j.issn.1008-9292.2020.03.03.

47. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020; 369:m1849. doi: 10.1136/bmj.m1849. PMID: 32409561.

48. Horby P and Landray M. Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June 2020. Disponível em: https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf

49. Interrupção precoce do braço de HCQ no estudo "Solidarity" da OMS. Disponível em: https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-COVID-19.

50. Letter revoking EUA for chloroquine phosphate and hydroxychloroquine sulfate, 6/15/2020. Disponível em: https://www.fda.gov/media/138945/download.

51. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with COVID-19 - Preliminary Report. N Engl J Med. 2020 Jul 17. doi: 10.1056/NEJMoa2021436. Epub ahead of print. PMID: 32678530.

52. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors Associated with Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease. 2019. JAMA Netw Open 2020; 3: e 203976. doi:10.1001/jamanetworkopen.2020.3976. PMID: 32202646.

53. Xiao H, Zhang Y, Kong D, Li S, Yang N. Social Capital and Sleep Quality in Individuals Who Self-Isolated for 14 Days During the Coronavirus Disease 2019 (COVID-19) Outbreak in January 2020 in China. Med Sci Monit 2020; 26: e 923921. doi: 10.12659/MSM.923921. PMID: 32194290.

54. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020; 395: 912-920. doi: 10.1016/S0140-6736(20)30460-8. PMID: 32112714.

55. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

56. Estimated DALYs, YLL and YLD ('000) by cause, sex and WHO Member State (1), 2016. World Health Organization. Department of Information, Evidence and Research. June 2018. Disponível em: https://www.who.int/healthinfo/global burden_disease/estimates/en/index1.html. Acessado em 09 de abril de 2020.

57. Yao H, Chen JH, Xu YF. Patients with mental health disorders in the COVID-19 epidemic. Lancet Psychiatry 2020; 7: e21. doi: 10.1016/S2215-0366(20)30090-0. PMID: 32199510.

58. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. Int J Environ Res Public Health 2020; 17. pii: E1729. doi: 10.3390/ijerph17051729. PMID: 32155789.

59. Li W, Yang Y, Liu ZH, Zhao YJ, Zhang Q, Zhang L, et al. Progression of Mental Health Services during the COVID-19 Outbreak in China. Int J Biol Sci 2020; 16: 1732-1738. doi: 10.7150/ijbs.45120. PMID: 32226291.

60. Yang Y, Li W, Zhang Q, Zhang L, Cheung T, Xiang YT. Mental health services for older adults in China during the COVID-19 outbreak. Lancet Psychiatry 2020; 7: e19. doi: 10.1016/S2215-0366(20)30079-1. PMID: 32085843.

61. Bo HX, Li W, Yang Y, Wang Y, Zhang Q, Cheung T, et al. Posttraumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with COVID-19 in China. Psychol Med 2020; 27:1-7. doi: 10.1017/S0033291720000999. PMID: 32216863.

62. Qiu J, Shen B, Zhao M, Wang Z, Xie B, Xu Y. A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. Gen Psychiatr 2020; 33: e100213.doi: 10.1136/gpsych-2020-100213. PMID: 32215365.

63. Druss BJ. Addressing the COVID-19 Pandemic in Populations with Serious Mental Illness. JAMA Psychiatry 2020. doi: 10.1001/jamapsychiatry.2020.0894. PMID: 32242888.

64. Hoffmann TC; Del Mar C. Patients' Expectations of the Benefits and Harms of Treatments, Screening, and Tests. A Systematic Review. JAMA Intern Med 2015;175(2):274-286.

65. Coylewright M, Montori V, Ting HH. Patient-centered Shared Decision-making: A Public Imperative. The American Journal of Medicine, Vol 125, No 6, June 2012.

66. Bouma AB, Tiedje K, Poplau S, Boehm DH, Shah ND, Commers MJ, et al. Shared decision making in the safety net: where do we go from here? J Am Board Fam Med. 2014 Mar-Apr;27(2):292-4. doi: 10.3122/jabfm.2014.02.130245. PMID: 24610192.

67. Kuppermann M, Sawaya GF. Shared Decision-Making. Easy to Evoke, Challenging to Implement. JAMA Internal Medicine February 2015 Volume 175, Number 2.

68. Gulbrandsen P. What's in shared decision-making for the physician? Patient Education and Counseling 97 (2014) 145–6.

69. Hoffmann TC, Del Mar CB. Shared decision making: what do clinicians need to know and why should they bother? Med J Aust. 2014 Nov 3;201(9):513-4. doi: 10.5694/mja14.01124. PMID: 25358570.

70. Bot AG, Bossen JK, Herndon JH, Ruchelsman DE, Ring D, Vranceanu AM. Informed shared decision-making and patient satisfaction. Psychosomatics. 2014 Nov- Dec; 55(6):586-94. doi: 10.1016/j.psym.2013.12.013. Epub 2014 Jan 3. PMID: 24836165.

71. Durand MA, Moulton B, Cockle E, Mann M, Elwyn G. Can shared decision-making reduce medical malpractice litigation? A systematic review. BMC Health Serv Res. 2015 Apr 18; 15:167. doi: 10.1186/s12913-015-0823-2. PMID: 25927953; PMCID: PMC4409730.

72. Légaré F, Thompson-Leduc P. Twelve myths about shared decision making. Patient Educ Couns. 2014 Sep;96(3):281-6. doi: 10.1016/j.pec.2014.06.014. Epub 2014 Jul 3. PMID: 25034637.

73. Epstein RM, Gramling RE. What is shared in shared decision making? Complex decisions when the evidence is unclear. Med Care Res Rev. 2013 Feb;70(1 Suppl):94S-112S. doi: 10.1177/1077558712459216. Epub 2012 Oct 2. PMID: 23035055.

74. Elwyn G, Fisher E. Higher integrity health care: evidence-based shared decision making. Circ Cardiovasc Qual Outcomes. 2014 Nov;7(6):975-80. doi: 10.1161/CIRCOUTCOMES.114.000688. Epub 2014 Sep 30. PMID: 25271048.

75. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared decision making: a model for clinical practice. J Gen Intern Med. 2012 Oct;27(10):1361-7. doi: 10.1007/s11606-012-2077-6. Epub 2012 May 23. PMID: 22618581; PMCID: PMC3445676.

76. WMA declaration of Helsinki – ethical principles for medical research involving human subjects. Disponível em: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

SPECIAL ISSUE ARTICLE

Risk of venous thromboembolism in users of contraception and menopausal hormone therapy during the COVID-19 pandemic

Andréa Larissa Ribeiro Pires[1]
José Gomes Batista[1]
José Mendes Aldrighi[2,3]
Irineu Francisco Delfino Silva Massaia[2]
Diego Medeiros Delgado[1]
Edson Santos Ferreira-Filho[4]
José Maria Soares-Junior[4]

1. Departamento de Obstetrícia e Ginecologia - Centro de Ciências Médicas - Universidade Federal da Paraíba (UFPB), João Pessoa, PB, Brasil.
2. Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo, SP, Brasil.
3. Faculdade de Saúde Pública da Universidade de São Paulo, São Paulo, SP, Brasil.
4. Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.22

SUMMARY

OBJECTIVES: *The outbreak of coronavirus disease (COVID-19) is a public health emergency of international concern. Inflammatory changes are part of COVID-19 pathophysiology and this might generate a higher thromboembolic risk in patients using combined hormonal contraception and menopausal hormone therapy. We aimed to discuss the main aspects related to this issue and propose management strategies for women affected by COVID-19.*

METHODS: *This narrative review collected information from several articles published since the beginning of the outbreak of the new coronavirus disease about the pathophysiology, stage of the disease, the occurrence of thrombotic events, and the risk of thromboembolism in users of contraception and hormonal therapy.*

RESULTS: *This article consolidates clinical parameters about the risk of venous thromboembolism in users of contraception and menopausal hormone therapy emphasizing the probable increase of that risk in women with suspected or confirmed COVID-19 and bringing safer recommendations.*

CONCLUSIONS: *In this scenario, apart from the fundamental orientations of preventive measures, like social isolation and hygiene, it is important that all female health professionals have knowledge of the new rules and adopt safety measures, especially on the prescription of hormonal therapy and contraception.*

KEYWORDS: *Contraception. Hormone Replacement Therapy. Coronavirus Infections. Betacoronavirus. Venous Thromboembolism/prevention & control.*

INTRODUCTION

The COVID-19 ("coronavirus disease 2019") pandemic caused by the new coronavirus (Sars-CoV-2; severe acute respiratory syndrome corona 2) unveils a new preventive reality regarding the prescription of steroid hormones, involving not only the use of combined hormonal contraception (CHC) during the reproductive

DATE OF SUBMISSION: 04-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Andréa Larissa Ribeiro Pires
Universidade Federal da Paraíba, Campus I, Lot. Cidade Universitária, João Pessoa, PB, Brasil – 58051-900
E-mail: alarissaribeiro@gmail.com

period but also the use of hormone replacement therapy in menopausal transition and post- menopause (MHT). This alert stems from the observation that symptomatic carriers of COVID-19, particularly in its more severe presentation, present hyperactivation of coagulation, which, in combination with the estrogen contained in these formulations, potentially increases the likelihood of thromboembolic[1] events. In addition to the coronavirus, the fact that patients remain bedridden for long periods also can increase the risk of developing deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), and the association of multiple risk factors can aggravate this risk[2].

Sars-CoV-2 is an enveloped virus composed of structural proteins, with emphasis on the *Spike* glycoprotein (*S*), the membrane (*M*), the nucleocapsid (N), and the envelope protein (*E*). The protein, after entering the host cell, connects to the receiver of the angiotensin-converting enzyme (ACE2) and, with the aid of local endosomal proteases, triggers the fusion of the membrane to the virus endosome, and the viral genome is released. As a result, there is an increase in neutrophils and serum leukocytes, a reduction in the lymphocytes CD4+ and CD 8+, and of regulatory (*Tregs*), memory, and natural killer (*NK*) T-cells, and B cells[3].

In more severe stages of COVID-19, there is a true pro-inflammatory "storm", with the excessive and uncontrolled release of cytokines, which evolves with systemic inflammation, endothelial injury, and exposure of thrombogenic structures (collagen, tissue factor, and platelet adhesion molecules), which favors the formation of thrombi[4].

In fact, anatomopathological studies show a probable hypercoagulable and immunethrombotic state[5] due to the unveiling of multiple microthrombi in the pulmonary vasculature[6], thus constituting systemic microangiopathy, which explains the failure of multiple organs (cardiomyopathy, kidney failure, acute liver failure, mesenteric ischemia, and neurological damage). In addition, it should be emphasized that since the vascular endothelium actively expresses ACE2, it becomes an active locale for the multiplication of Sars-CoV-2, as had been previously described for patients with Sars-CoV-1 infections[7].

An alert that should be considered is that coagulation hyperactivation in symptomatic COVID-19 patients with more severe presentations can have an increased risk of thromboembolism when in use of estrogens (CHC and MHT).

METHODS

Our study is a narrative review of the literature available on the coronavirus so far, focusing on its physiopathology, the stages of the disease, and the occurrence of thrombotic events, as well as on the risk of venous thromboembolism (VTE) in CHC and MHT users, aiming to gather information for a safe approach in women with suspected or confirmed COVID-19. For the review, we searched the Medline/PubMed database using specific keywords ("COVID-19"; "coronavírus"; "contraception"; "menopausal hormone therapy"; "thromboembolic disease"). There were no restrictions regarding date or language. Most data on COVID-19 comes from Asia. The electronic databases were searched for the last time on 18 May 2020.

Thromboembolic risk in the COVID-19 pandemic

The Spanish Societies of Menopause, Gynecology, and Obstetrics and the Thrombosis and Hemostasis Society recently published recommendations on the use of combined oral hormonal contraceptives (COHC) and menopause hormonal therapy (MHT) in women in menopausal transition with suspected or confirmed COVID-19, based on the severity of the disease.

In these recommendations, the authors suggest that in women with mild symptoms of COVID-19, who do not exhibit risk factors of greater severity, the use of MHT and CHC may be maintained, provided it is associated with low molecular weight heparin (LMWH), in prophylactic doses; when the use of transdermal MHT is preferred, the recommendation is for maintaining the combined hormonal contraception (CHC) or replacing it for methods with progestogen alone. In women with COVID-19 who develop pneumonia, persistent respiratory symptoms, and have more severe risk factors, and in severe cases, it is recommended to suspend the use of MHT and CHC and associate LMWH in therapeutic doses[8].

It is important that healthcare professionals who guide the use of these hormones know the stages of SARS-CoV-2 infections for an adequate and safe prescription.

A classification of COVID-19 infection severity was proposed by Siddiqi & Mehra (2020) and is characterized by three stages that correlate signs/symptoms, treatment response, and clinical outcomes[9].

There is an initial stage of lesser severity, but that can evolve to an excessive inflammatory response, which characterizes the stage of greater severity

and a worse prognosis (stage III), in which there is a greater production of cytokines and coagulation factors that result in hyperactivation of coagulation, particularly in symptomatic women[9]. In these women, the association of CHC or MHT can increase the risk of thromboembolism.

The risk of VTE is rare in healthy women of reproductive age (5-10 events per 10,000 women yearly), an incidence that increases to 8-10 events per 10,000 women yearly with the use of CHC, a much lower incidence than the risks of VTE observed during pregnancy and the postpartum period[10]. The risk of VTE is associated with the dose of estrogen and the type of progestogen[11].

The CHC, in addition to promoting increased procoagulant factors (fibrinogen, prothrombin, factors VII, VIII, IX, X, XII), reduces the synthesis of the procoagulant factor V and inhibitors of hemostasis that occur naturally, such as antithrombin, protein S, and the tissue factor pathway inhibitor (TFPI), which results in an increased risk of thrombosis[12].

The physiopathological mechanism of hypercoagulability in CHC users occurs by the passage of estrogen through the liver. This prothrombotic effect also occurs with other routes of administration (transdermal, vaginal). Observational studies show that the risk of VTE in users of vaginal rings and transdermal adhesives is, in general, similar to that of users of combined oral hormonal contraception (COHC)[13].

The type of progestogen used associated with ethinylestradiol can modulate these changes. However, when used in isolation, progestogen does not modify the hemostatic system[10]. COHC containing cyproterone, drospirenone, gestodene, and desogestrel present a relative risk (RR) of 3-4 in relation to non-CHC users, while COHC containing levonorgestrel have a RR around 2 in relation to non-CHC users[14].

The use of contraceptive methods that contain only progestogens (oral, IUD, and implants) is not associated with an increased risk of VTE[14].

With respect to MHT, an increased risk two to three times greater has been noted when using the oral route; however, it differs for the transdermal route, which does not seem to increase the risk[15]. A French multicenter case-control study showed that oral estrogen, but not transdermal, is associated with an increased chance of VTE[16].

Recommendation for the management of women in use contraceptives and under menopause hormone therapy

It is recommended that, for users of MHT or CHC who suffer from mild cases of COVID-19 and wish to maintain the use of hormones, is it possible to do so, and, based on the risk factors for VTE, the prophylactic use of heparin must be suggested. However, the use of low molecular weight heparin (LMWH) should not be done indiscriminately, but under medical supervision, aiming to reduce the risk of VTE. In addition, in COVID-19 patients with mild symptoms and without severe risk factors it is also wise to replace CHC by contraception containing progestogen alone. Regarding MHT, when oral, it is recommended to be replaced by transdermal (Figures 1 and 2).

Women who change or suspend MHT and contraception must be instructed to undergo an early revaluation, which can be done by telemedicine or in person after the end of the pandemic. Easy access to communication channels to notify about adverse events

FIGURA 1. RECOMMENDATIONS FOR THE MANAGEMENT OF CHC IN WOMEN WITH SUSPECTED OR CONFIRMED COVID-19

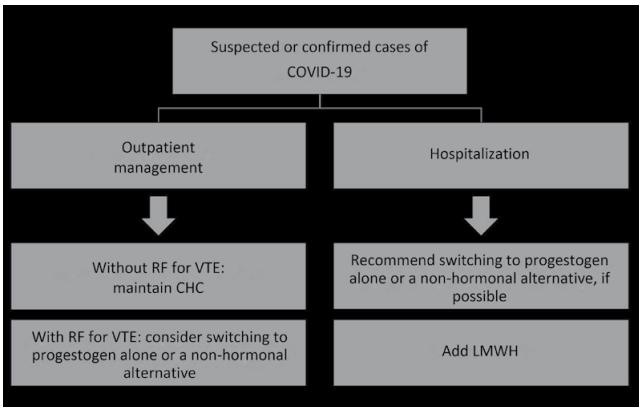
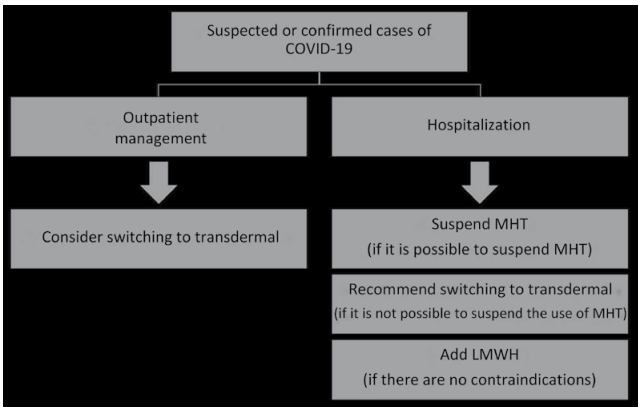


FIGURE 2. RECOMMENDATIONS FOR THE MANAGEMENT OF MHT IN WOMEN WITH SUSPECTED OR CONFIRMED COVID-19



and obtain answers to questions increases women's adaptation to the new method.

Study limitations

Our study has some limitations since we analyzed different types of studies (observational, experimental, reviews, clinical trials); however, the information is consistent between them and have biological plausibility. Moreover, this is a narrative review, which means it does not conform to the technical principles of a systematic review and can confer it some selection bias; however, the search was conducted in a systematic manner to amplify the number of articles included and minimize this risk. These recommendations will probably be reviewed, after some time, considering the growing number of recent publications in the area; even so, this study is urgent, since it is essential to have national recommendations for the safe management of contraception and menopause hormone therapy.

FINAL CONSIDERATIONS

Knowledge about the new coronavirus remains limited; however, SARS-CoV-2 infections are gradually being elucidated by the scientific community, thus contributing to the understanding of the pathophysiology of the disease and the risk of VTE.

According to this review, it is important to highlight that users of contraceptives and women under menopause hormone therapy may have a greater risk of thromboembolism, in the duration of the COVID-19 pandemic, and the assessment regarding the maintenance or modification of the prescription should be individualized, considering the severity of the condition and other risk factors for VTE.

RESUMO

OBJETIVOS: *A pandemia da COVID-19 é um problema de saúde pública emergente e que tem repercussão internacional. As alterações inflamatórias fazem parte da fisiopatologia da COVID-19 e isso pode acarretar um maior risco tromboembólico em mulheres que fazem uso de contracepção e terapia hormonal da menopausa. Discutimos os principais aspectos relacionados a esse risco e propomos uma estratégia de seguimento das mulheres acometidas da COVID-19.*

MÉTODOS: *Esta revisão narrativa coletou informações de vários artigos publicados desde o início da pandemia do novo coronavírus, no que tange à sua fisiopatologia, estágios da doença e ocorrência de eventos trombóticos, bem como sobre o risco de tromboembolismo venoso em usuárias de contracepção e terapia hormonal da menopausa.*

RESULTADOS: *Este artigo consolida alguns parâmetros clínicos sobre o risco de tromboembolismo em usuárias de contracepção e terapia hormonal na menopausa, enfatizando o provável aumento desse risco em mulheres com suspeita ou confirmação do novo coronavírus, e traz uma recomendação de uma conduta mais segura.*

CONCLUSÃO: *Nesse cenário, além das fundamentais orientações de medidas preventivas, como o isolamento social e a higiene, é importante que os profissionais que trabalham na atenção à saúde feminina tenham conhecimentos da nova realidade e adotem condutas seguras, especialmente na prescrição de THM e contracepção.*

PALAVRAS-CHAVE: *Anticoncepção. Terapia de reposição hormonal. Infecções por coronavírus. Betacoronavírus. Tromboembolia venosa/prevenção e controle.*

REFERENCES

1. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost. 2020. doi: 10.1111/jth.14849.
2. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I9-I16.
3. Tufan A, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci. 2020;50(SI-1):620-32.
4. Pereira MP, Lima EG, Serrano Junior CV. Viral infections and atherothrombosis: another caution in the wake of COVID-19? Rev Assoc Med Bras. 2020;66(3):366-9.
5. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin Chim Acta. 2020;507:167-73.
6. Luo W, Yu H, Gou J, Li X, Sun Y, Li J, et al. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). Preprints. 2020; 2020020407.
7. Nicin L, Abplanalp WT, Mellentin H, Kattih B, Tombor L, John D, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. Eur Heart J. 2020;41(19):1804-6.
8. Ramírez I, De la Viuda E, Baquedano L, Coronado P, Llaneza P, Mendoza N, et al. Managing thromboembolic risk with menopausal hormone therapy and hormonal contraception in the COVID-19 pandemic: recommendations from the Spanish Menopause Society, Sociedad Española de Ginecología y Obstetricia and Sociedad Española de Trombosis y Hemostasia. Maturitas. 2020;137:57-62.

9. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplantat. 2020;39(5):405-7.

10. Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T. Combined oral contraceptives: venous thrombosis. Cochrane Database Syst Rev. 2014;(3):CD10813.

11. Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. Int J Gynaecol Obstet. 2018;141(3):287-94.

12. Black A, Guilbert E, Costescu D, Dunn S, Fisher W, Kives S. No. 329-Canadian Contraception Consensus Part 4 of 4 Chapter 9: combined hormonal contraception. J Obstet Gynaecol Can. 2017;39(4):229-68.

13. Tepper NK, Whiteman MK, Marchbanks PA, James AH, Curtis KM. Progestin-only contraception and thromboembolism: a systematic review. Contraception. 2016;94(6):678-700.

14. Mantha S, Karp R, Raghavan V, Terrin N, Bauer KA, Zwicker JI. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. BMJ. 2012;345:e4944.

15. Pinkerton JV, James AH. Management of menopausal symptoms for women who are at high risk of thrombosis. Clin Obstet Gynecol. 2018;61(2):260-8.

16. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER Study. Circulation. 2007;115(7):840-5.

In times of COVID-19, epidemiology is a unifying science

Carlos Dornels Freire de Souza[1]

1. Departamento de Medicina. Universidade Federal de Alagoas, Arapiraca, AL, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.27

SUMMARY

In the end of December 2019, China reported an outbreak of pneumonia in Wuhan, a city with more than 11 million inhabitants, to the World Health Organization. Days later, a new agent (SARS-CoV-2) was identified; since then, it has spread throughout the planet, resulting in one of the most challenging pandemics in recent history. Faced with this scenario, Epidemiology plays an important role, given that its techniques and methods have contributed to generating knowledge, assisting in decision making in healthcare. This text presents a succinct reflection regarding the importance of epidemiology in light of the current pandemic.

KEYWORDS: *Coronavirus Infections. Epidemiology. Public Health.*

INTRODUCTION

On the last day of 2019, China reported an outbreak of respiratory disease in the metropolis of Wuhan, the capital of the province of Hubei, to the World Health Organization (WHO)[1]. It received the name coronavirus disease 2019 (2019-nCOV); the disease is caused by the novel coronavirus SARS-CoV-2, officially identified by Chinese authorities as the cause of the disease[1,2].

On January 30, 2020, the WHO declared the situation a Public Health Emergency of International Concern[2]. By this date, in addition to China, 19 countries already had registered cases of the disease[2]. Notwithstanding the efforts undertaken, 2019-nCoV continued to spread widely, reaching new territories and causing a desolate death toll. On March 11, the WHO declared 2019-nCOV a pandemic[3]. Two days later, on March 13, Europe became the center of the pandemic. Within a few days, the number of deaths in Italy had already exceeded the number registered in China[4]. A few days later, the number of cases exploded in the United States, especially in New York City, and it rapidly reached Latin American countries such as Mexico and Brasil[5].

As of May 5, 2020, the date this text was composed, 3.6 million cases had been confirmed, with 252,346 deaths. The United States (1.8 million cases), Spain (2018,011 cases) and Italy (211,938 cases) were the countries with the highest number of cases, and the United States (69,069 deaths) and Italy (29,079 deaths) had the highest number of deaths[3].

Since the beginning of the outbreak in Wuhan, epidemiology has faced countless questions that needed to be answered within a short timeframe. These questions involve *biological aspects* [What is the origin of the virus? What are its characteristics in relation to infectivity, pathogenicity, virulence, lethality, and immunogenicity? What are its mechanisms of transmission and its potential global spread? What are the most prevalent symptoms?], *quantitative sciences*

DATE OF SUBMISSION: 02-Jun-2020
DATE OF ACCEPTANCE: 02-Jun-2020
CORRESPONDING AUTHOR: Carlos Dornels Freire de Souza
Universidade Federal de Alagoas, Campus Arapiraca, Rodovia AL-115, Bom Sucesso, Arapiraca, AL, Brasil – 57309-005
E-mail: carlos.freire@arapiraca.ufal.br

[What is the disease spread curve like? How can we predict which country will become the next epicenter of the pandemic? What is the global and local magnitude of transmission? How do incidence and mortality behave in different countries?], and even *human and social sciences* [What is the impact of 2019-nCoV in peripheral areas of large cities? How does the disease affect countries' social development? What measures can be taken to mitigate the harmful social effects of the pandemic? How can health systems handle the situation? What is the role of globalization in the spread of the virus and its impact on containing the epidemic?].

It is evident that these are only a few of the many questions that scientists around the world, in different areas of knowledge, are studying at this time, and it will take some years to understand the impact of the pandemic we are facing in the second decade of this century with due clarity.

Is it, then, possible to see a light at the end of the tunnel? If it exists (and we do believe that it exists), it is in epidemiology. For many years, epidemiology has produced knowledge capable of changing the course of human history[6]. It was during the 1854 cholera epidemic in Victorian London that John Snow challenged the scientific principles hitherto used to explain the health-disease process, which was based on miasma theory[7]. After using the scientific method to unveil the causal relation between cholera and the ingestion of contaminated water, science received new momentum, and Snow became the father of modern epidemiology[7]. Since then, it has been a fundamental instrument for understanding disease dynamics in the population. In the 1980s, epidemiology made it possible to understand the HIV epidemic[8]. In the second decade of the 21st century, it was fundamental to understanding the relationship between the Zika virus epidemic and the occurrence of microcephaly in Brasil[9]. Epidemiology is currently facing yet another object to be understood: the 2019-nCoV pandemic.

HOW CAN EPIDEMIOLOGY CONTRIBUTE TO CONTROLLING THE PANDEMIC?

There are reasons to believe that epidemiology may contribute to controlling the 2019-nCoV pandemic. Its very concept has already provided the science with a mission: *Epidemiology is the study of the health-disease process in a population and its determinants/conditions, with the goal of providing knowledge capable of changing the social-health situation*[6]. Accordingly, epidemiological knowledge is founded upon a practical goal, namely, to contribute with solutions to populations' problems. All knowledge produced by epidemiologists should be directed toward a common good, health in its most ontological sense[6].

The problem today is the 2019-nCoV. Faced with this problem, epidemiologists will need to make use of the available methodological framework (*which is not little*) in order to understand the dynamics of the pandemic. With advancements, epidemiology has developed different branches of study on different fronts, namely, classical, molecular, clinical, and social epidemiology, each of which has specific tools for understanding the object of study.

a) *Classical epidemiology* will offer knowledge regarding the magnitude of the pandemic, the main profile of patients, the risk of contracting the disease, the intensity with which the disease spreads, etc.

b) *Molecular epidemiology* will provide information regarding the ways the virus penetrates cells, what molecular markers increase the virulence of the agent, what mechanisms used by the host organism defend against the agent, etc.

c) *Clinical epidemiology* will provide information regarding the best treatment for each patient profile, what clinical conduct is most recommended for patients on mechanical ventilation in comparison with milder cases of the disease.

d) *Social epidemiology* will show the pandemic's impact on families, how social development may be negatively affected, or how the pandemic might increase poverty worldwide. It is evident that these deliberations are merely illustrative and that there are many others.

In addition to the specialization/division of this science, it is worth emphasizing epidemiology's ability to form bonds between the sciences. Studies carried out in different categories need to be articulated for a proper comprehension of the whole, keeping in mind that the whole is not the mere juxtaposition of the parts, but the product of the interaction between them. This is the characteristic that makes epidemiology such a relevant science.

In the pandemic we are currently experiencing, all knowledge produced in different areas must be shared because it will expand the potential comprehension of the pandemic and provide the best evidence for decision making in healthcare. Social sciences, mathematics/statistics, and biology/microbiology are the

three main pillars that sustain the singular character of epidemiology in facing the global pandemic of 2019-nCoV[6]. For this reason, all epidemiological knowledge is always a collective product with a common goal.

WHAT IS THE NOBLE FUNCTION OF EPIDEMIOLOGY IN FACING THE PANDEMIC?

Producing knowledge regarding a phenomenon

As more knowledge is produced, it will become less difficult to control a pandemic; fewer deaths will occur, and the global social impact of the post-pandemic economic crisis will be smaller. It is necessary to emphasize that the knowledge produced must be used for making better decisions; for this reason, it is necessary to pay attention to methodological rigor. Different study designs have specific methodological frameworks, and they should be rigorously followed. Scientific journals must adopt rigorous mechanisms in order to avoid fraud and publication of research without due ethical and scientific scrutiny. Any knowledge produced by dubious mechanisms without the necessary methodological clarity may place millions of people in jeopardy at this moment. On May 5, 2020, the term "SARS-CoV-2" yielded 3,837 publications in PubMed, and the term "COVID-19" yielded 9,225 scientific publications. The volume of publications is intense and necessary, but it requires rigorous monitoring in order to avoid a negative social impact.

To date, epidemiological investigations have shown that the containment of the pandemic must be based on measures targeting professionals, symptomatic individuals, people who have been in contact with symptomatic individuals, and the general population (Table 1). Taken together, these measures may accomplish the following[1,10-12]:

1. Reduce the intensity with which the virus spreads worldwide;
2. Guarantee that healthcare systems have the capacity to attend patients, which involves human and material resources and installed capacity;
3. Reduce mortality due to the disease;
4. Reduce community transmission, flattening the 2019-nCoV spread curve over the course of weeks;
5. Provide time for scientists and health professionals to develop and/or test new therapeutic protocols.

These measures were essential for China to overcome the epidemic and halt local transmission of 2019-nCoV within its territory[13]. Italy neglected these measures and accumulated, as of May 5, 2020, more than 211,000 cases and more than 29,000 deaths[14]. The Italian healthcare system, for instance, was not able to handle the demand of diseased patients, which rapidly increased lethality[14]. It became necessary to decide who would receive mechanical ventilation and who would die in Italian hospitals. The lack of resources and personal protective equipment for

TABLE 1. MEASURES THAT HAVE SHOWN TO BE EFFECTIVE IN CONTAINING THE EXPANSION OF THE PANDEMIC AND AVOIDING DEATHS DUE TO 2019-NCOV.

	Group 1 Health professionals	Group 2 Symptomatic individuals	Group 3 People who have been in contact with symptomatic individuals	Group 4 General population
Measures taken	Provide personal protective equipment; Train health teams to manage patients safely.	Offer rapid testing and systematic clinical follow-up of patients.	Actively search for asymptomatic cases and establish social isolation mechanisms.	Institute social distancing measures; Encourage attitudes of co-responsibility from all parties during the pandemic; Use of masks by the general population.
	Hygiene measure - Washing hands and social etiquette			
Predicted impact	Reduce contamination in professionals who are on the front line; Guarantee quality and safety in the care provided to patients.	Stopping the chain of transmission to other people; Differential diagnosis of other diseases that occur with similar signs/symptoms. Reduce the risk of complications and lethality.	Identification of asymptomatic individuals (80% of patients) and isolation may slow transmission and decrease the intensity of the pandemic.	Attitudes of social distancing and education may reduce disease transmission and avoid overloading healthcare services, due to both mild cases of 2019-nCoV and other diseases that may overload healthcare systems.
Overall results of the measures taken together	Containing the spread of 2019-nCoV; Reducing overload in healthcare systems; Time for countries to prepare their healthcare networks (human and material resources); Time for scientists to develop more effective therapeutic methods.			

healthcare professionals led to the crisis worsening, and news about the death of doctors and nurses became routine in the international media[14].

Good use of epidemiological knowledge

It is fundamental that the knowledge produced reaches the population given that the population is the final beneficiary of epidemiology. It must, however, be passed on to the population clearly and without distortion, in order to avoid situations of social chaos. One example is the study that indicated promising results with the use of hydroxychloroquine for treating 2019-nCoV[15]. In Brasil, when the president Jair Bolsonaro shared this on social media, it led to mass purchasing of the drug, leaving the population *[who in fact needs this drug to continue treatment of other diseases*] without access to it. It was necessary for the Brazilian National Health Surveillance Agency (ANVISA, acronym in Portuguese) to intervene in order to avoid further damage.

Furthermore, fake news and conspiracy theories must be widely combated. False claims arguing that the virus was created in Chinese laboratories or that it is only a "little cold" are merely a few examples of the situation many countries are currently facing, especially those countries that have yet to wake up to the severity of the pandemic, which is the case in Brasil. The WHO has defended the importance of educating society regarding the severity of 2019-nCoV, as well as every citizen's role in preventing the spread of the disease[5].

This text was not intended to answer questions, but rather to propose new points of reflection, therefore, it will conclude with some of the most relevant questions: It is certain that the world, science, and people will not be the same after 2019-nCoV, but what will we become? Will science and scientists be valued to the extent that they deserve, or will governments go back to forgetting about them? Will epidemiology reaffirm its social role or will it once more be pushed to the background in health systems, as is the case in many countries? Will there be a new epidemiology?

Competing interests

The authors declare that they have no competing interests

Funding

None.

Author's Contribution

CDFS reviewed and edited, were responsible for data management, analysis, and quality control. The author(s) read and approved the final manuscript.

PALAVRAS-CHAVE: *Infecções por Coronavirus. Epidemiologia. Saúde Pública.*

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
2. World Health Organization. Novel coronavirus (2019-nCoV) situation report – 11. Geneva: World Health Organization; 2020 [cited 2020 Abr 30]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200131-sitrep-11-ncov.pdf?sfvrsn=de7c0f7_4
3. World Health Organization. Novel coronavirus (2019-nCoV) situation report – 51. Geneva: World Health Organization; 2020 [cited 2020 May 05]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-COVID-19.pdf?sfvrsn=1ba62e57_10
4. Johns Hopkins University CSSE. Coronavirus COVID-19 global cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University CSSE. [cited 2020 May 15] Available from: https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6;
5. World Health Organization. Novel coronavirus (2019-nCoV) situation report – 78. Geneva: World Health Organization; 2020 [cited 2020 Abr 03]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200407-sitrep-78-COVID-19.pdf?sfvrsn=bc43e1b_2
6. Frérot M, Lefebvre A, Aho S, Callier P, Astruc K, Aho Glélé LS. What is epidemiology? Changing definitions of epidemiology 1978-2017. PLoS One. 2018;13(12):e0208442.
7. Fine P, Goldacre B, Haines A. Epidemiology: a science for the people. Lancet. 2013;381(9874):1249-52.
8. Rosenberg C. Explaining epidemics and other studies in the history of medicine. Cambridge: Cambridge University Press; 1992. p.305-17.
9. Albuquerque MFPM, Souza WV, Araújo TVB, Braga MC, Miranda Filho DB, Ximenes RAA, et al. Epidemia de microcefalia e vírus Zika: a construção do conhecimento em epidemiologia. Cad. Saúde Pública. 2018;34:e00069018.
10. Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. J Travel Med. 2020;27(2):taaa020. doi: 10.1093/jtm/taaa020.
11. Leung NHL, Chu DKW, Shiu EYC, Chan KH, McDevitt JJ, Hau BJP, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. Nat Med. 2020;26(5):676-80.
12. Cowling BJ, Ali ST, Ng TWY, Tsang TK, Li JCM, Fong MW, et al. Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong: an observational study. Lancet Public Health. 2020;5(5):e279-88.
13. Azman AS, Luquero FJ. From China: hope and lessons for COVID-19 control. Lancet Infect Dis. 2020;S1473-3099(20)30264-4.
14. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet. 2020;395(10231):1225-8.
15. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;105949.

COVID-19 and health literacy: the yell of a silent epidemic amidst the pandemic

Luana Resende Cangussú[1]
Igor Rafael Pereira de Barros[2]
Carlos Alberto de Lima Botelho Filho[1]
Jarbas Delmoutiez Ramalho Sampaio Filho[1]
Matheus Rodrigues Lopes[1]

1. Universidade Federal do Vale do São Francisco, campus Paulo Afonso, Paulo Afonso, BA, Brasil.
2. Universidade de Pernambuco, campus Serra Talhada, Serra Talhada, PE, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.31

SUMMARY

The emergence of a new form of Coronavirus (SARS-CoV-2) exposed weaknesses of health services in several countries, with overcrowding of hospitals, and lack of supplies and professionals in combating the disease, which sometimes contributed to the installation of social, political, and economic chaos. The critical situation experienced made the subject widely publicized so that the current pandemic also deals with an information epidemic. However, the data received and transmitted require prior critical analysis of its content, although not everyone is able to make the necessary judgment before using or sharing information, partly due to the lack of adequate health knowledge. Health literacy is a broad and important topic in public health but still globally underestimated, thus considered a silent epidemic. The exponential increase in the number of confirmed cases shows the world population's inadequacy and difficulty in understanding basic prevention guidelines. The COVID-19 pandemic warns of gaps in the health literacy levels of the world population and exposes the need for a comprehensive mapping to identify the overall health literacy status in more countries.

KEYWORDS: *Coronavirus Infections. Health Literacy. Pandemics. Betacoronavirus.*

The emergence of a new form of Coronavirus (SARS-CoV-2) in China, in December 2019, has been causing major impacts on medicine, science, politics, and society due to the high infectivity of the virus and morbidity and mortality of the disease. In March 2020, the World Health Organization (WHO) officially declared the COVID-19 disease a pandemic, and since then, several countries have adopted isolation and intervention measures, although overcoming the pandemic still represents a major challenge for science. The exposed weaknesses of health services in several countries, with overcrowding of hospitals, lack of supplies, and professionals in combating the disease, sometimes contribute to the installation of social, political, and economic chaos[1,2].

The catastrophic progression of COVID-19 demanded health agencies to establish rapid intervention measures to curb the spread of the disease[2]. The critical situation experienced made the issue widely disseminated by health organizations, scientific communities, media, and the internet. However, the excess of information does not mean that these

DATE OF SUBMISSION: 21-Jun-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Matheus Rodrigues Lopes
Universidade Federal do Vale São Francisco (UNIVASF), Campus Paulo Afonso
Rua da Aurora, s/n, quadra 27, lote 3, Alves de Souza, BA, Brasil – 48607-190
E-mail: matheuslopesbio@gmail.com / Tel: +55 75 3282-3456

sources invariably present content that is reliable and of quality and sometimes false and inaccurate news are broadcast, being quickly absorbed and propagated[3].

Unlike what happened with the Black Death (14th century) and in the last century with the Spanish Flu, the current pandemic also deals with an information epidemic[4]. Thus, the information received and transmitted requires prior critical analysis of its content, although not everyone makes the necessary judgment before sharing it, partly due to the easiness of spreading news through cell phones, tablets, and computers, and also due to the lack of adequate health literacy[5].

According to the WHO, health literacy is defined as the patient's ability to obtain, process, and understand health information in order to make judgments and relevant decisions regarding their own health, in their daily lives[6]. In a time like this of the COVID-19 pandemic, full of uncertainties, in which information is constantly changing and a rapid behavior change by the world population is required to reduce the risks of infection and spread of this disease, presenting an adequate level of health literacy has never been more important[7].

Health literacy is a broad and increasingly important issue in public health. It is well described in the literature that low health literacy causes difficulties in understanding the health-disease process, increases hospitalization rates and costs to health services, hinders medication adherence, impacts the quality of life, and represents a barrier to self-care[8,9].

However, there are still few studies that identify the level of literacy in different countries. Among some of the places most affected by COVID-19, some studies are highlighted, such as one carried out in Europe through the European Health Literacy Survey (HLS-EU), which identified that about half of the European population presented an insufficient level of health literacy[10]. In Canada, about 60% of adults have inadequate health literacy, something that is even more pronounced in the elderly population, with approximately 80% inadequacy[11]. In the United States, through the National Assessment of Adult Literacy (NAAL) survey, it was found that only 12% of Americans had a proficient level of health literacy[12]. In Brasil, there are no studies of national scope that evaluate health literacy; however, in some regional surveys, it has already been possible to verify a low level of understanding in certain groups of patients[13,14].

Health literacy is a globally underestimated theme, to the point that many authors consider it a silent epidemic[15]. Historically, the impacts of low health literacy have been observed only in the long term, such as in the negative outcomes of patients with chronic non-communicable diseases that do not adhere to treatment[3].

With the pandemic of COVID-19, the impacts of low health literacy are being presented in the short term, and in a frightening way. The exponential increase in the number of confirmed cases evidences the world population's inadequacy and difficulty in understanding basic prevention guidelines[16]. The low rate of social isolation is often a reflection of this lack of understanding regarding the most diverse aspects of the disease and of the individual and collective consequences that contamination may cause[7].

Amidst the growing technological and informational dissemination during the COVID-19 pandemic, an inadequate level of health literacy can expose patients to misunderstanding, especially in communication networks, such as the internet, which exhibit both facts and untruths about the most various subjects[17]. In the face of so much new data, the population suffers from excessive information and consequently has great difficulty in judging the truth of the facts[15]. Thus, it is essential that reliable and relevant guidelines are transmitted in simple language and are easy to access so that they can be widely disseminated and executed. The media must be an ally and not an adversary in this process[18].

In countries with less socioeconomic development, the situation is even more serious: in Brasil, the spread of SARS-Cov-2 started in the middle and upper classes of society; however, with the advance of the spread of the virus in the lower-income segment, the impacts have been more severe, showing the uneven effects of COVID-19 in this part of the population[4].

Several factors make these people more vulnerable to contamination, among them the type of employment relationship, the daily need to use public transport, poor access to healthcare, low rate of social isolation, and low health literacy. In these conditions, the presence of the State, through the provision of the minimum conditions of sustenance, is essential to achieve better adherence to social isolation, thus avoiding the spread of the virus and the overload of the health systems[19].

It is worth noting that the structuring of health services with the increase in the number of intensive

care unit beds, the acquisition of respirators, and the availability of diagnostic tests cannot solve and contain the problem if there are no joint efforts by health professionals, political agents, researchers, and mainly the population whom, guided by reliable sources and fully understanding the dimension of the problem experienced worldwide, manages to fulfill its social role[17].

The COVID-19 pandemic warns of the gaps that exist in the health literacy levels of the world population and exposes the need for a comprehensive mapping to identify the general status of health literacy in more countries, especially in those where the profile of health literacy has not yet been traced[7]. In this sense, amplifying the discussions on this extremely relevant and under-recognized theme is essential. The improvement of literacy has been shown to be an effective strategy in health promotion, disease prevention, and control, and in situations such as the one currently experienced, which require rapid actions, representing a unique tool[20].

Funding

Data sharing is not applicable to this article because no datasets were generated or analyzed during the current study.

Conflicts of interest

The authors have no conflicts of interest that are directly relevant to the content of this article.

Author's Contribution

Luana Resende Cangussú: project idea, design, and writing, final approval of the version to be published; Igor Rafael Pereira de Barros: project design and writing, final approval of the version to be published; Carlos Alberto de Lima Botelho Filho: relevant critical review of the intellectual content, final approval of the version to be published; Jarbas Delmoutiez Ramalho Sampaio Filho: relevant critical review of the intellectual content, final approval of the version to be published; Matheus Rodrigues Lopes: project design, writing, and supervision, relevant critical review of the intellectual content, final approval of the version to be published.

PALAVRAS CHAVE: *Infecções por Coronavirus. Letramento em Saúde. Pandemias. Betacoronavirus.*

REFERENCES

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):105924.
2. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int J Surg. 2020;76:71-6.
3. Paakkari L, Okan O. COVID-19: health literacy is an underestimated problem. Lancet Public Health. 2020;5(5):e249-50.
4. Ahmed F, Ahmed N, Pissarides C, Stiglitz J. Why inequality could spread COVID-19. Lancet Public Health. 2020;5(5):e240.
5. Zarocostas J. How to fight an infodemic. Lancet. 2020;395(10225):676.
6. World Health Organization. Health literacy: the solid facts. Geneva: World Health Organization; 2013. 73p. [cited 2020 May 13]. Available from: https://apps.who.int/iris/handle/10665/326432
7. Sentell T, Vamos S, Okan O. Interdisciplinary perspectives on health literacy research around the world: more important than ever in a time of COVID-19. Int J Environ Res Public Health. 2020;17(9):3010.
8. Parnell TA, Stichler JF, Barton AJ, Loan LA, Boyle DK, Allen PE. A concept analysis of health literacy. Nurs Forum. 2019;54(3):315-27.
9. Bostock S, Steptoe A. Association between low functional health literacy and mortality in older adults: longitudinal cohort study. BMJ. 2012;344:e1602.
10. Sorensen K, Pelikan JM, Röthlin F, Ganahl K, Slonska Z, Doyle G, et al; HLS-EU Consortium. Health literacy in Europe: comparative results of the European health literacy survey (HLS-EU). Eur J Public Health. 2015;25(6):1053-8.
11. LeBrun M, DiMuzio J, Beauchamp B, Reid S, Hogan V. Evaluating the health literacy burden of Canada's public advisories: a comparative effectiveness study on clarity and readability. Drug Saf. 2013;36(12):1179-87.
12. Cutilli CC, Bennett IM. Understanding the health literacy of America: results of the National Assessment of Adult Literacy. Orthop Nurs. 2009;28(1):27-32; quiz 33-4.
13. Chehuen Neto JA, Costa LA, Estevanin GM, Bignoto TC, Vieira CIR, Pinto FAR, et al. Functional health literacy in chronic cardiovascular patients. Cien Saude Colet. 2019;24(3):1121-32.
14. Sampaio HA, Carioca AA, Sabry MO, Santos PM, Coelho MA, Passamai MP. Health literacy in type 2 diabetics: associated factors and glycemic control. Cien Saude Colet. 2015;20(3):865-74.
15. Parker R, Ratzan SC. Health literacy: a second decade of distinction for Americans. J Health Commun. 2010;15(Suppl 2):20-33.
16. Lazcano-Ponce E, Alpuche-Aranda C. Public health literacy in the face of the COVID-19 pandemic emergency. Salud Publica Mex. 2020;62(3):331-40.
17. Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. JAMA. 2020;323(19):1-9.
18. Lima DL, Lopes MAAAM, Brito AM. Social media: friend or foe in the COVID-19 pandemic? Clinics (Sao Paulo). 2020;75:e1953.
19. Bezerra ACV, Silva CEMD, Soares FRG, Silva JAMD. Factors associated with people's behavior in social isolation during the COVID-19 pandemic. Cien Saude Colet 2020;25(suppl 1):2411-21.
20. Nguyen HC, Nguyen MH, Do BN, Tran CQ, Nguyen TTP, Pham KM, et al. People with suspected COVID-19 symptoms were more likely depressed and had lower health-related quality of life: the potential benefit of health literacy. J Clin Med. 2020;9(4):965.

The effects of the COVID-19 pandemic on levels of physical fitness

Cristiano Silva Pinho[1,4]
Alex Cleber Improta Caria[2,3]
Roque Aras Júnior[2]
Francisco José Gondim Pitanga[3,4]

1. Programa de Pós-Graduação em Engenharia, União de Faculdades de Alagoas, Unifal – FIC, Maceió, AL, Brasil.
2. Programa de Pós-Graduação em Medicina e Saúde, Faculdade de Medicina e Saúde, Universidade Federal da Bahia (UFBA), Salvador, BA, Brasil.
3. Departamento de Educação Física em Cardiologia da Sociedade Brasileira de Cardiologia (Defic-SBC), seção Bahia, Salvador, BA, Brasil.
4. Instituto de Saúde Coletiva, Universidade Federal da Bahia (UFBA), Salvador, BA, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.34

SUMMARY

INTRODUCTION: *The COVID-19 pandemic, caused by infections from a novel human coronavirus, has been reported since December 2019 in China but was only made official in March 2020. Since then, it has had an impact worldwide, both due to its aggressiveness and its fast propagation. Society has been facing this pandemic by following the recommendations and determinations of the WHO and the strategies deployed by governmental institutions. Among these, social isolation has been shown to be the most important, because when isolating, society tends to move less, with a consequent increase in physical inactivity and sedentary behavior, affecting its levels of physical fitness. The objectives of this review were: to review the most important effects of physical inactivity and sedentary behavior on the physical fitness levels of the population during the COVID-19 pandemic.*

CONCLUSION: *The role of a regular practice of activities on the levels of physical fitness is fundamental to define the balance of quality of life during a COVID-19.*

KEYWORDS: *Physical Fitness. Coronavirus Infections. Sedentary Behavior. Betacoronavirus.*

INTRODUCTION

The pandemic caused by infections from a new virus, known as new human coronavirus (COVID-19), was notified in December 2019, in China, but only formalized in March 2020 and, since then, has impacted nations throughout the world, both due to its aggressiveness and its speed of propagation[1]. The figures are alarming: on 3 June 2020, the World Health Organization confirmed 6,317,450 cases and 376,320 deaths worldwide[2].

Society, still without a vaccine, has been handling the COVID-19 pandemic through various strategies, trying to strictly follow the recommendations by the World Health Organization (WHO) and the determinations of governmental measures, through extendable decrees focusing on: proportional emergency care, cleaning, disinfection, compulsory use of masks, social distancing, social isolation and, in certain cases, quarantine, and lockdown[2].

DATE OF SUBMISSION: 11-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Cristiano Silva Pinho
R. Basílio da Gama, s/n, Canela, Salvador, BA, Brasil – 40110-040
Tel: +55 71 99145-9283
E-mail: cristiano.pinho@gmail.com

Among these measures, social isolation determines that population should mainly at home, ceasing, thus, their working life, as well the regular practice of physical activity in their daily routine, leading to an increase in physical inactivity and sedentary behavior and its consequences.

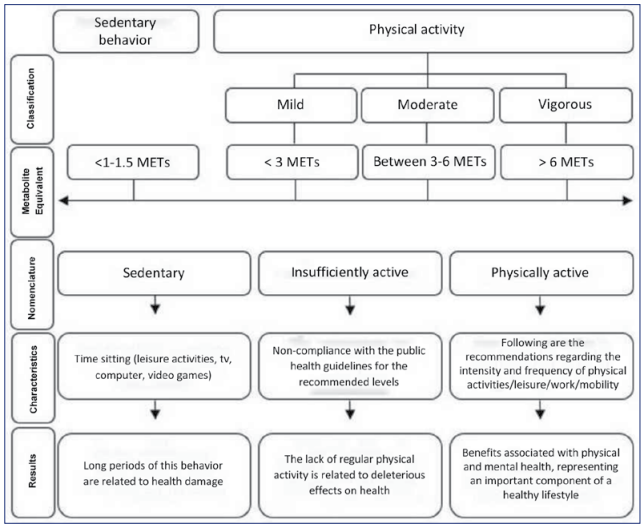
Physical inactivity is characterized by a condition under which the recommended levels of physical activity of moderate and vigorous intensity (MVPA)[3] are not reached, while sedentary behavior is characterized by the practice of activities with low energy expenditure: ≤1.5 metabolic equivalents (METs) (Figure 1), for example, remaining in a sitting, leaning, or lying position over 8 hours per day, except for the period of sleep[4-6]. Both are harmful to health and reduce the levels of physical fitness.

The importance of maintaining in of physical fitness, through the practice of regular physical activity, needs to be better understood in its dimensions so that it can be properly recognized as an activity that is essential for health, in a consensus between society, science, and the government bodies since it is an excellent strategy for its positive effects on cardiovascular, metabolic, immunological, and mental health[7,8]. Therefore, the objectives of this review were: to review the most important effects of physical inactivity and sedentary behavior on the levels of physical fitness of the population during the COVID-19 pandemic.

Levels of physical fitness

The levels of physical fitness have been analyzed by the American College of Sports Medicine, and in cases of its reduction or decline, the effects of aging accelerators would be revealed[9]. Based on these studies, Table 1 gives an idea of what these adaptations would look like in conditions of physical inactivity during the COVID-19 pandemic:

FIGURE 1. DIFFERENCE BETWEEN SEDENTARY, PHYSICALLY INACTIVE, AND PHYSICALLY ACTIVE BEHAVIOR. ADAPTED FROM MENEGUCI ET AL.[4]



The increase in physical inactivity and sedentary behavior during the COVID-19 pandemic can be explained by two important reasons. The first relates to the fact that there were already existing cases of physical inactivity pre-pandemic, and the second is the transitory cases caused by the imposition of a essentially confined life, both converging in the decline of physical fitness[7].

These two reasons together may increase cases of complications and even deaths, both from reasons other than COVID-19. This may even lead to cardiovascular and respiratory complications, considering that physical inactivity is considered a risk factor for cardiovascular and metabolic diseases[10] due to its correlation with increased blood pressure, blood glucose, and lipid profile[11]. The increase in physical inactivity associated with longer periods of sedentary behavior

TABLE 1. RELATIONSHIP OF ELEMENTS OF PHYSICAL FITNESS, ORGANIC EFFECTS, AND FUNCTIONAL IMPACTS OF PHYSICAL INACTIVITY.

Physical Fitness	Effect observed	Functional impact
Strength and Power of muscles	The levels of isometric and concentric strength decrease quickly during periods of physical inactivity. Power declines faster than Strength.	Deficits of strength and power are predictors of disability and increased risk of mortality
Endurance, Fatigability and Cardiorespiratory function	Endurance decreases. The maintenance of strength becomes difficult. The maximum aerobic power (MAP) decreases.	It can affect the recovery from repetitive daily activities; Cardiorespiratory system overload
Balance and Mobility	Changes in the sensory, motor, and cognitive patterns that would affect the biomechanics (sitting, standing, moving, etc.). These elements, added to the matter of environment limitations, would affect balance and mobility	Loss of balance causes fear of falling and may lead to a rejection of the practice of physical activity.
Performance and Motor control	Increases the reaction time (may lead to accidents). The speed of simple and repetitive movements may decrease Change in the control of gesture precision. Difficulty in performing complex tasks.	Impact on instrumental activities of daily living (IADL). Increases the likelihood of accidents and injuries.
Flexibility and Amplitude of Joint Movement	There is a marked decrease in the flexing degree of joints such as the hips, spine, and ankle	Little flexibility, increase risk of injury, decreased mobility, backache, and falls.

can also induce cardiovascular morbidity and mortality due to all the causes[12]. However, individuals who are physically active have significantly reduced mortality due to cardiovascular diseases, even with long periods of sedentary behavior[13], because they improve their cardiorespiratory fitness and prevent various chronic diseases[14].

Thus, being physically active and reducing sedentary behavior during the COVID-19 pandemic are essential to maintain levels of physical fitness, aiding in the balance and improvement of several physical valences, promoting a better quality of life and general health[15], in addition to reducing the risk of cardiovascular and metabolic diseases, at any time, including during the COVID-19 pandemic[16].

It is important to highlight that the elderly population is at a greater risk of complications and death during the COVID-19 pandemic, no matter how well preserved it is in social isolation, because the increase in physical inactivity and sedentary behavior, which reduces their levels of physical fitness, can make them more prone to cardiovascular events, and they may suffer from an accelerated organic and cognitive decline, including the possibility of falls due to postural imbalance.

In this context, in times of difficulty, with the goal of trying to maintain a normal behavior of physical activity practice to improve physical valences and physical fitness, the technologies normally associated to hypokinesia, currently, would have a beneficial and strategic role of virtually bringing together Physical Education professionals and their clients. Both groups are trying to adapt to this model of distant instruction, through applications, for the remote practice of physical activities and exercises, gathering in virtual social networks, through lives, pre-recorded lectures, audio classes, and various media elements[17].

However, the screen time, an important variable in the study of sedentary behavior[18], presents itself, at this moment, as a factor for future studies because individuals who spend too much time using devices such as laptops, phones, or TVs increase a component of sedentary behavior which is harmful to health and is associated with a risk of developing obesity[19]; on the other hand, technology can also be a tool to promote health and improve physical fitness, because games combined with movement and motivational elements, as already seen in the concept of exergaming[20,21] applied to technological exercise equipment, promote competitive games, racing simulations, among others, in the form of videogames or digital neurocognitive games known as brain games[22]. Although both are composed of simultaneous elements of motivation and data monitoring, the latter would have more characteristics to reduce sedentary behavior.

Therefore, several strategies can be adopted to inhibit physical inactivity and reduce sedentary behavior during the COVID-19 pandemic, thus minimizing the risk of chronic-degenerative diseases, as well as of morbidity and mortality.

CONCLUSION

Practicing physical activities has a key role in the levels of physical fitness and is essential to balance and improve health and quality of life during the COVID-19 pandemic because it reduces the levels of physical inactivity and sedentary behavior.

Thus, the practice of regular physical activity is essential because it minimizes harmful effects on physical and emotional health during the pandemic, particularly by maintaining and/or improving the clinical condition of individuals who have chronic diseases.

Author's Contribution

All authors contributed equally to this study.

RESUMO

INTRODUÇÃO: *A pandemia de COVID-19, causada pela infecção por novo coronavírus humano, foi notificada desde dezembro de 2019, na China, mas apenas oficializada em março de 2020 e, desde então, tem impactado nações do mundo inteiro, tanto pela sua agressividade quanto pela sua velocidade de propagação. A sociedade enfrenta a pandemia seguindo as recomendações e determinações da OMS e das instituições governamentais. Entre as estratégias de enfrentamento, o isolamento social se destaca como o mais importante, porque, ao se isolar, a sociedade tende a se mover menos, obtendo aumento da inatividade física e do comportamento sedentário, reduzindo seus níveis de aptidão física. Os objetivos dessa revisão foram: revisar os efeitos mais importantes da inatividade física e do comportamento sedentário sobre os níveis de aptidão física da população durante a pandemia de COVID-19.*

CONCLUSÃO: *O papel da prática regular de atividades físicas sobre os níveis de aptidão física se revela fundamental para estabelecer o equilíbrio na qualidade de vida durante a COVID-19.*

PALAVRAS-CHAVE: *Aptidão física. Infecções por coronavírus. Comportamento sedentário. Betacoronavírus.*

REFERENCES

1. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al; Washington State 2019-nCoV Case Investigation Team. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929-36.
2. World Health Organization. Coronavirus disease (COVID-2019) situation reports. 2020. [cited 2020 May 28]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
3. Hallal PC, Bauman AE, Heath GW, Kohl 3rd HW, Lee IM, Pratt M. Physical activity: more of the same is not enough. Lancet. 2012;380(9838):190-1.
4. Meneguci J, Santos DAT, Silva RB, Santos RG, Sasaki JE, Tribess S, et al. Comportamento sedentário: conceito, implicações fisiológicas e os procedimentos de avaliação. Motricidade. 2015;11(1):160-74.
5. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. Exerc Sport Sci Rev. 2010;38(3):105-13.
6. Pate RR, O'Neill JR, Lobelo F. The evolving definition of "sedentary". Exerc Sport Sci Rev. 2008;36(4):173-8.
7. Pitanga FJG, Beck CC, Pitanga CPS. Atividade física e redução do comportamento sedentário durante a pandemia do coronavírus. Arq Bras Cardiol. 2020. DOI: https://doi.org/10.36660/abc.2020023
8. Pitanga FJG, Beck CC, Pitanga CPS. Should physical activity be considered essential during the COVID-19 pandemic? Int J Cardiovasc Sci. 2020. DOI: https://doi.org/10.36660/ijcs.20200072.
9. Matsudo SMM. Envelhecimento, exercício e saúde: guia prático de prescrição e orientação. 3ª ed. São Paulo: Midiograf; 2013.
10. Carnethon MR. Physical activity and cardiovascular disease: how much is enough? Am J Lifestyle Med. 2009;3(1 Suppl):44S-9.
11. Rissardi GGL, Cipullo JP, Moreira GC, Ciorlia LAS, Cesarino CB, Giollo Junior LT, et al. Prevalence of physical inactivity and its effects on blood pressure and metabolic parameters in a brazilian urban population. Int J Cardiovasc Sci. 2018;31(6):594-602.
12. Young DR, Hivert MF, Alhassan S, Camhi SM, Ferguson JF, Katzmarzyk PT; et al. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. Circulation. 2016;134(13):e262-e79.
13. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. Med Sci Sports Exerc. 2010;42(5):879-85.
14. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blair SN. Sedentary behavior, exercise, and cardiovascular health. Circ Res. 2019;124(5):799-815.
15. Chen P, Mao L, Nassis GP, Harmer P, Ainsworth BE, Li F. Coronavirus disease (COVID-19): the need to maintain regular physical activity while taking precautions. J Sport Health Sci. 2020;9(2):103-4.
16. Zhu W. Should, and how can, exercise be done during a coronavirus outbreak? An interview with Dr. Jeffrey A. Woods. J Sport Health Sci. 2020;9(2):105-7.
17. Raiol RA. Praticar exercícios físicos é fundamental para a saúde física e mental durante a Pandemia da COVID-19. Braz J Hea Rev. 2020;3(2):2804-13.
18. Robinson TN, Banda JA, Hale L, Lu AS, Fleming-Milici F, Calvert SL, et al. Screen media exposure and obesity in children and adolescents. Pediatrics. 2017;140(Suppl 2):S97-S101.
19. Biddle SJH, García Bengoechea E, Pedisic Z, Bennie J, Vergeer I, Wiesner G. Screen time, other sedentary behaviours, and obesity risk in adults: a review of reviews. Curr Obesity Rep. 2017;6(2):134-47.
20. Oliveira B, Nesteriuk S, Queiroz P. Exergames: amostragem da produção acadêmica entre 2010 e 2015. Proceedings of XV Simpósio Brasileiro de Jogos e Entretenimento Digital; 2016. p.714-7.
21. Viana RB, Vancini RL, Andrade MS, Vieira CA, Lira CAB. O uso dos exergames nos protocolos de reabilitação em diversas populações clínicas. Rev Bras Pesq Saúde. 2018;20(3):132-40.
22. Cardoso NO, Landenberger T, Argimon IIL. Jogos eletrônicos como instrumentos de intervenção no declínio cognitivo: uma revisão sistemática. Rev Psicol IMED. 2017;9(1):119-39.

Science of consciousness: reflections on the Pandemic by COVID-19

Marco Osini[1,2,3]
Carlos Henrique Melo Reis[4]
Marco Antônio Alves Azizi[5]
Jacqueline Fernandes do Nascimento[6]
Nicolle dos Santos Moraes Nunes[6]
Janie Kelly Fernandes do Nascimento[6]

1. Médico, PhD pela Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil
2. Professor titular na Universidade Iguaçu – UNIG, Nova Iguaçu, RJ, Brasil
3. Professor titular na Universidade de Vassouras – UniV-RJ, Vassouras, RJ, Brasil.
4. Médico, Neurologista, Mestre pela Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil
5. Médico, Professor titular da faculdade de medicina em Universidade Iguaçu – UNIG, RJ, Nova Iguaçu, RJ, Brasil.
6. Acadêmica de medicina na Universidade Iguaçu – UNIG, RJ, Nova Iguaçu, RJ, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.38

KEYWORDS: *Science. Coronavirus Infections. Scientific Research and Technological Development.*

Uncertainty around the unknown and fascination with the world as it is perceived have accompanied humans from the very start of their journey on this blue planet, in the adventure in search of grasping and understanding the unknown. Knowledge emerges as a result of the creation experience, driven by thought as the consequence of brains in rapid expansion and development. This is the major role of thought, to facilitate the dynamic and ongoing transition from unknown to known. As time passed, with new knowledge at their disposal, humans were inserted in history and culture that were the driving force behind new creations, new horizons[1].

Amazing constructions were built through different types of thinking in an attempt to give meaning to the unknown and new. Initially, many answers were provided by their own experiences, which allowed them to build a set of thoughts from individual opinions, which then became common sense. However, creativity and common thinking were not sufficient to answer their various questions around the unknown[2].

Plato, in Greece, according to the western perspective of the history of humanity, proposed a method to distinguish knowledge from opinions. Episteme is a knowledge whose validity can be demonstrated, unlike an opinion (*doxa)*, which is unfounded and

DATE OF SUBMISSION: 26-Jun-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Nicolle dos Santos Moraes Nunes
Rua Pedro Álvares Cabral 118, Casa 01, XV de novembro, Araruama, RJ, Brasil – CEP: 28970-000
E-mail: nicolle.nunes_@hotmail.com.br

easily disposable, subject to changes in time and without a set of rules of its own. This differentiation applies to the current time, due to the flood of opinions that seek authority in these bleak times. It is urgent, therefore, that we are able to differentiate knowledge from opinions[3].

Opinions or beliefs are not devoid of value, because they belong to an individual's content, to their own heritage; they are true in the intimate sphere. However, to become true knowledge they must be justified by a set of validation rules[4].

It is worth remembering other magnificent paths that are important for the enrichment of human experience, all necessary for human life: art, philosophy, spirituality, religion, or simply human experience[5].

In a context of modern history, scientific thought is defined as the need for a system of verifiable and objectively controlled trials. There was an important addition to the Platonic concept with the presence of more efficient and effective controls. Therefore, considering this important difference, it is unthinkable to have science without philosophy![6]

In 1620, with the *Novum Organum*, by Francis Bacon, a model was proposed for the experimental scientific method, which, based on observation, seeks to explain natural phenomena; thus, theories are derived from, related to, and supported by the phenomena observed. Science ceases to be a contemplation of reality and becomes transformative of reality, and research becomes the foundation for science[7].

Scientific knowledge deals with observable problems that are subjected to various scientific methods, unlike other types of knowledge that address the major themes of human existence (religious thoughts), which are not the object of natural sciences[8].

Therefore, science aims to pursuit knowledge that is verifiable and subject to the rules of the scientific method; those passionate about practicing it honestly look for questions, which can sometimes be accompanied by answers. Answers may come or not in our time, but this certainly will not stop us from formulating thoughts and theories around our intellectual restlessness. In science, truths are always temporary since they are subject to the principles of fallibility, relativity, and debatability; therefore, there is no pretension of absolute validities. Only that which is debatable can be debated. That which is not debatable is a dogma. If it is a dogma, it has nothing to do with science. Everything is debatable in science. Science proposes an open debate. According to Habermas, the truth is the pretense of validity; nothing is indefinitely valid[9].

Therefore, the results of certain published publish papers cause us great concern given their disobedience of the scientific rigor rules, postulating hasty information on therapies recommended for COVID-19 patients, which are subsequently reviewed and withdrawn with justifications of methodological inaccuracies. In science, the instituted authorities are the method used for a particular purpose; reasoning and ethics. The only way to preserve this process is by applying the scientific method and, most importantly, believing in the critical review by our peers, because everything is debatable in science. All of us, when designing and analyzing a study, must follow the principles of impartiality, of cumulative increase of knowledge, and of the logical structure of investigations and results. Let us remember that the scientific method does not always lead us to meritorious and reliable results - although it is the best path to be taken. We emphasize the hard work of some scientists in combating the improper use of information on COVID-19. "When science is lost, reason goes with it; when it is crushed, nothing else makes sense"[10].

Conflict of interest

There is no potential conflict of interest relevant to this article.

Author's Contribution

All authors contributed equally to this study.

PALAVRAS-CHAVE: *Ciência. Infecções por Coronavirus. Pesquisa Científica e Desenvolvimento Tecnológico.*

REFERENCES

1. Ioannidis JPA. Coronavirus disease 2019: the harms of exaggerated information and non-evidence-based measures. Eur J Clin Invest. 2020;50(4):e13222.
2. Alfano V, Ercolano S. The efficacy of lockdown against COVID-19: a cross-country panel analysis. Appl Health Econ Health Policy. 2020;18(4):509-17.
3. Malecki K, Keating JA, Safdar N. Crisis communication and public perception of COVID-19 risk in the era of social media. Clin Infect Dis. 2020;ciaa758. doi: 10.1093/cid/ciaa758.
4. Woodside AG. Interventions as experiments: connecting the dots in forecasting and overcoming pandemics, global warming, corruption, civil rights violations, misogyny, income inequality, and guns. J Bus Res. 2020;117:212-8.
5. Tarazona-Santabalbina FJ, Martínez-Velilla N, Vidán MT, García-Navarro JA. COVID-19, older adults and ageism: mistakes that should never happen again. Rev Esp Geriatr Gerontol. 2020;55(4):191-2.
6. Wu X. Materialism and dialectics of epidemic prevention and control: only by respecting science can we do more with less. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2020;32(3):259-60.
7. Lippi G, Simundic AM, Plebani M. Potential preanalytical and analytical vulnerabilities in the laboratory diagnosis of coronavirus disease 2019 (COVID-19). Clin Chem Lab Med. 2020;58(7):1070-6.
8. Data error in viewpoint on COVID-19 in Italy. JAMA. 2020;323(16):1619.
9. Ellis R, Hay-David AGC, Brennan PA. Operating during the COVID-19 pandemic: how to reduce medical error. Br J Oral Maxillofac Surg. 2020;58(5):577-80.
10. Gandhi TK, Singh H. Reducing the risk of diagnostic error in the COVID-19 era. J Hosp Med. 2020;15(6):363-6.

Allocation of pharmaceutical resources in maternal and child healthcare institutions during the COVID-19 pandemic

Jianghui Cai[1]
Wenwen Chen[1,2]
Xiao Yang[1]
Xiuqing Yang[1]
Gen Li[1]

1. Department of Pharmacy, Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu 610041, China;
2.School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China

http://dx.doi.org/10.1590/1806-9282.66.S2.41

SUMMARY

Since the outbreak of a cluster of patients with pneumonia of unknown cause in Wuhan, Hubei Province, China, in December 2019, the disease was later officially named coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2), quickly spreading globally. Pregnant women and children are particularly vulnerable during disasters and emergencies. Comprehensive and applicable emergency preparedness and response are definitely important methods to prevent and contain the COVID-19 pandemic. The rational allocation of pharmaceutical resources plays an important role in the medical emergency plan. This paper aimed to share experiences for the allocation of pharmaceutical resources in hospitals focusing primarily on women and children during the COVID-19 pandemic.

KEYWORDS: *Coronavirus Infections. Pregnancy. Child. Pharmaceutical Services.*

INTRODUCTION

Since the outbreak of pneumonia of unknown cause in Wuhan, China in December 2019, the disease was later named Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) and quickly spreading throughout China and other countries[1]. The World Health Organization (WHO) declared the sixth public health emergency of international concern over the global outbreak of COVID-19 on January 30, 2020. To date, COVID-19 has affected more than 180 countries or regions with 5,204,508 confirmed and 337,687 deaths, and WHO[2] has warned countries that the crisis is generating stress worldwide. On March 11, 2020, the WHO declared the COVID-19 outbreak a global pandemic. The COVID-19 pandemic has put enormous pressure on public health systems around the world and highlights the importance of emergency preparedness and response (EP&R). The rational allocation of pharmaceutical resources plays an important role in public health to prevent and stop the

DATE OF SUBMISSION: 21-Jun-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Gen Li
Department of Pharmacy, Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu city 610041, China
E-mail: 393155450@qq.com

spread of the COVID-19 pandemic. Pregnant women and children are generally susceptible to COVID-19 considering they are in a special state of immune suppression[3]. Pregnant women might be more prone to have more rapid clinical deterioration due to COVID-19 because of decreased lung volumes caused by the increase in uterus size during pregnancy. As for children, the youngest patient received confirmation of the COVID-19 infection just 2 hours after birth[4]. According to a study from China, it appears that children have a lower prevalence, only 1% of confirmed cases were aged 9 years or younger, 1% of confirmed cases were aged 10 to 19 years. Most confirmed cases were classified as mild (i.e., non-pneumonia and mild pneumonia)[5]. Unfortunately, there have already been death reports in children[6]. Despite a lack of data on the consequences of COVID-19 infections during pregnancy, coronaviruses are responsible for severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV), and have the potential to cause severe adverse outcomes during pregnancy[7-9]. Asymptomatic infections were common in pregnant women and children[10,11]. Thus, the continued vigilance of women and children affected by COVID-19 is warranted.

An effective medical emergency plan is important to respond to the COVID-19 pandemic, and the rational allocation of pharmaceutical resources is an indispensable part of an effective medical emergency plan. Until now, all of the medical emergency plans are for general hospitals, but no articles were found specific to maternal and child health care institutions[12-15]. To the best of our knowledge, this is the first article on the allocation of pharmaceutical resources in maternal and child healthcare institutions when a public health emergency happens. Our hospital is the designated site for women and children with suspected COVID-19 in Chengdu city. On February 20, 2020, an international team of experts led by the WHO visited our hospital to learn about measures and recommendations for the management of pregnant women and children during the COVID-19 pandemic.

This article aimed to share experiences for the rational allocation of pharmaceutical resources in hospitals focusing primarily on women and children during the COVID-19 pandemic to protect their safety faster and better.

Here, we propose seven recommendations for the allocation of pharmaceutical resources in maternal and child healthcare institutions during the COVID-19 epidemic. Each of these components is discussed in more detail below (Figure1).

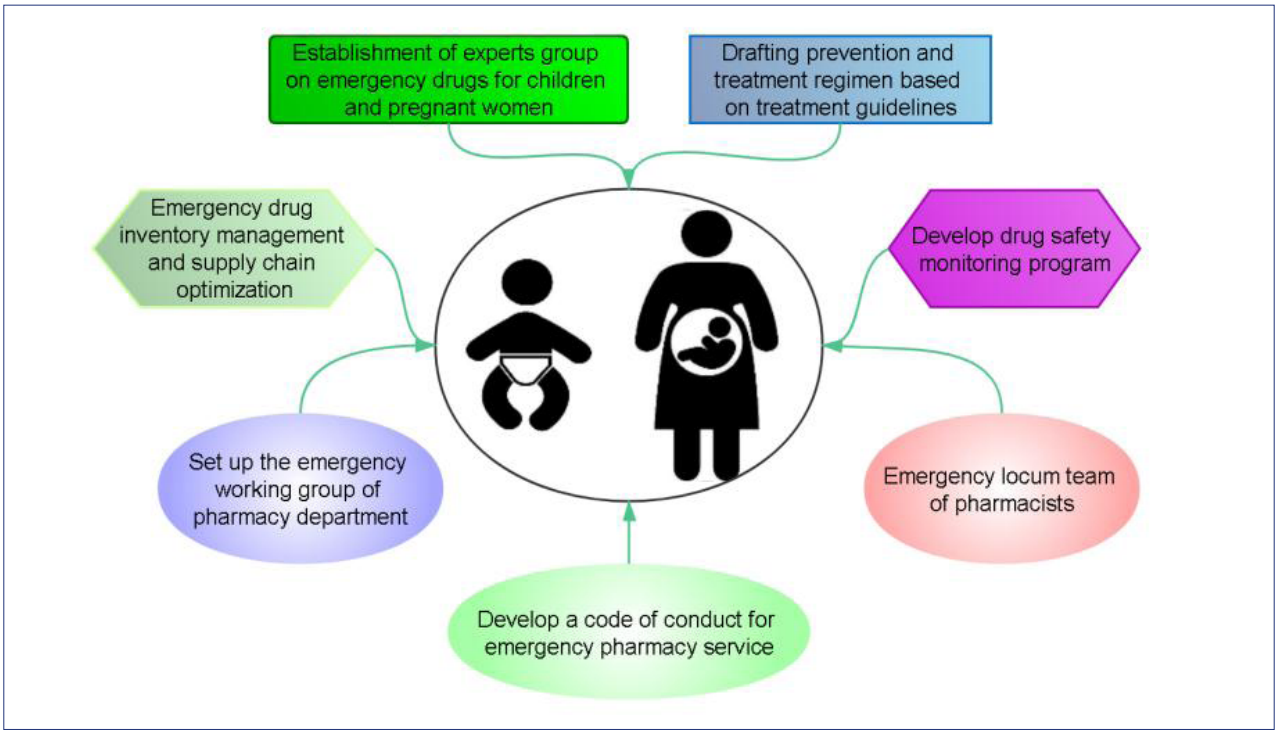


FIGURE 1. THE COMPONENTS FOR THE ALLOCATION OF PHARMACEUTICAL RESOURCES IN MATERNAL AND CHILD HEALTHCARE INSTITUTIONS IN THE COVID-19 PANDEMIC

1. Establishment of a group of experts on emergency drugs for children and pregnant women

Special attention should be given to pregnant women and children during the COVID-19 pandemic. It is well known that the pharmacokinetic characteristics, safety, and efficacy of medication during pregnancy were significantly different from that of the general population. At the same time, most drugs and their metabolites can cross the placenta and have some effect on human fetuses[16]. The effects of drugs on both mother and fetus should be taken into consideration, assessing the benefit-risk ratio, and drugs should only be used if the benefits to the mother outweigh the potential risks to the fetus. Furthermore, the effects of drugs on the fetus are not the same at different stages of pregnancy. In general, the first trimester of pregnancy is most susceptible to drugs, especially during the teratogenically sensitive period. It is noteworthy that children are not miniature adults when it comes to rational drug use, but a special medication group. Because their organs are under development, glomerular filtration rate, tubular secretory capacity, and liver drug-metabolizing enzyme are known to be immature, thus the response to drugs is also different from adults. Children have important physiological and developmental needs that are distinct from adults, and in the event of an emergency situation, they need specialized care involving personalized medicine. Simply placing children under medication as a smaller version of the adult drug use may cause more harm than good to children. Thus, it is urgent to establish a multidisciplinary expert group on emergency drugs for children and pregnant women in the first place. Experts should include: clinical pharmacists, pediatricians, obstetricians, respiratory physicians, infectious disease physicians, and medical staff from the hospital infection control departments.

2. Drafting prevention and treatment regimen based on treatment guidelines

There is an urgent need for an effective treatment for COVID-19. However, until now, there is no vaccine or proven effective specific antiviral drug treatment for COVID-19. The "Diagnosis and Treatment Guidelines for the New Coronavirus Infected Pneumonia (7th edition)" was released by the China National Health Commission focusing primarily on adults[17]. An expert group drafted a prevention and treatment regimen for pregnant women and children based on the treatment guidelines. Some drugs should not be considered because of the teratogenic effect on the fetus, such as ribavirin. In parallel, the dosage should be determined according to the patient's weight, age, and body surface area. Considering most drugs recommended in the guidelines are of off-label use, pharmacists should assist physicians in in evaluating the efficacy and safety of these drugs and inform patients of potential adverse drug reactions (ADR).

3. Emergency drug inventory management and supply chain optimization

Healthcare organizations need inventory and shortage management strategies to address the rapidly escalating demand for medications due to the COVID-19 pandemic. Emergency drug inventory should include not only drugs for the direct treatment of the disease but also drugs for supportive care because the current management of COVID-19 consists mostly of symptomatic supportive treatment[18]. The clinical characteristics of the COVID-19 infection during pregnancy are similar to those observed in non-pregnant adult patients confirmed with COVID-19[11], and children appear to have a milder clinical course[19]. Common signs and symptoms including fever and cough in pregnant women and children indicate there is an increasing demand for antipyretics and antitussives, such as Paracetamol and dextromethorphan[11,19]. Other drugs such as chloroquine, hydroxychloroquine, azithromycin, and antivirals can also be in short supply. Drugstores in China ran out of their antipyretics stock within days of the first COVID-19 case being identified. To curb the hoarding of antipyretics and antitussives, China adopted unprecedented nationwide measures such as requiring an identification card for the purchase of antipyretics drugs during the early phase of the COVID-19 pandemic. The time of the COVID-19 outbreak in Wuhan coincided with the Chinese New Year Festival, with a 7-day long holiday for working professionals. Some manufacturers had difficulties to resume production due to short raw materials stocks. Transportation and logistics in all cities were limited in China, which delayed the transporting time domestically. Having foreseen that emergency situations can disrupt access to medications, our hospital established an emergency drug inventory in the initial days since the closedown of Wuhan on January 23, 2020. As mentioned previously, hospitals must plan to rely on their own assets for at least 7 days. We began filling a 2-week emergency drug supply in anticipation of the

COVID-19 pandemic possibly disrupting our normal filling schedule. Pharmacists could play an important role in estimating supplies during emergencies and ensure adequate stocks of medications for chronic illnesses, anti-infectives, and commonly used Over-The-Counter (OTC) products are available. At the same time, pharmacists should establish surveillance and warning mechanisms to address drug shortages in a timely manner. An essential assessment to calculate the current supply and when it will be used up should be done daily.

Challenges in procurement are likely to result from disruptions to supply chains. Thus it is essential to track the drug inventory level and coordinate with major manufacturers to ensure an uninterrupted supply chain and accurately forecast inventories for existing medications and supplies. Uninterrupted drug supply of critical medications should be ensured and collaborations established with other maternal and child healthcare institutions to procure essential medications and supplies. Clinical pharmacists should give advice on therapeutic exchanges and substitutions and optimize medications based on evidence-based medicine if drug shortages happen.

4. Develop a drug safety monitoring program

Clinical pharmacists collaborate with physicians to monitor the use of drugs in pregnant women and children in various ways. Such as providing information on the dosage, known risks, and drug interactions to patients or their family members using booklets or through medication education. Obtain up-to-date information of patients from the electronic medical record system, patients with complications such as renal and hepatic impairment are the primary focus because they are more prone to adverse drug reactions; if adverse drug reactions happen, medication use should be withdrawn or switched to evidence-based treatment alternatives. Therapeutic Drug Monitoring (TDM) can be used to monitor the use of critical care drugs and selected anti-infectives, optimize medication usage, and reduce the side effects. Other drug safety monitoring measures include providing stewardship on antimicrobial resistance to addressing the abuse of antibiotics, individualizing medication instructions that help improving medication adherence, interpreting and discussing with patients when there are no available alternatives, offering comprehensive medical services to pregnant women and children including evaluating potential drug safety events and monitoring health outcomes to limiting inappropriate use of drugs.

5. Set up an emergency working group with the pharmacy department

In order to ensure the normal operation of the pharmacy department, it is necessary to set up an emergency working group. The members of the emergency working group should include the director of the pharmacy, manager of the drug depot, manager of the outpatient and inpatient pharmacy, manager of the emergency pharmacy, pharmacovigilance director, and division director of clinical pharmacy. Pharmacy services have always been considered essential services during an emergency. Emergency working groups need to take a series of measures aimed at minimizing disruptions in pharmacy services during the COVID-19 pandemic. Each member has a different role and performs their duties to provide critical access to medications (Figure 2). The manager of the drug depot must be responsible for formulating the drug purchase plan according to the treatment guidelines

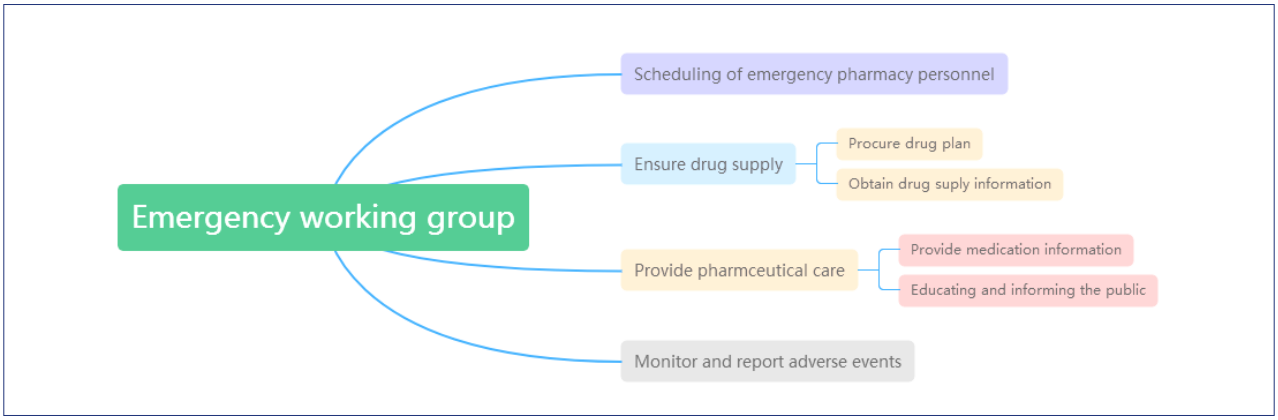


FIGURE 2. THE ROLES AND DUTIES OF THE EMERGENCY WORKING GROUP DURING THE COVID-19 PANDEMIC

or expert group opinions formulated by the hospital, obtaining drug supply information from multiple channels, considering the mutual substitution of drugs, grasping the allocation channel, supply, and allocation information of the hospital's emergency rescue drugs, and ensuring the rapid purchase and transportation to facilitate medication refills. Special personnel should be assigned to be responsible for the management of emergency drugs, and ensure that medications are effectively received, stored, and dispensed properly. The manager of the outpatient and inpatient pharmacy must be responsible for the organization and scheduling of emergency pharmaceutical personnel. A special pharmacy needs to be set up for infectious diseases and disinfection should be done. They should provide medication information for the clinic, ensure drug supply, educate, and inform the public. The pharmacovigilance director should monitor and report adverse events, highly focused on adverse drug reactions, overdoses, misuse, abuse of drugs, and drug exposure during pregnancy and breastfeeding. The members of the emergency working group should keep mobile phones on 24 hours to ensure that emergency services can be launched timely.

6. Emergency locum team of pharmacists

There is no doubt that pharmacists around the world have significant roles to play and contribute to the overall emergency management, especially during pandemics like that of the COVID-19. Community and hospital pharmacies are improving public health by expanding services and hours to provide essential services, putting pharmacists and their colleagues at the frontlines for patient care and safety[20]. Pharmacy professionals have been highly responsive to the crisis in China since the outbreak, either at hospitals and community pharmacies or at the square cabin hospitals in Wuhan[21]. Pharmacists are one of the most accessible healthcare professionals with the potential to provide pharmaceutical care and health information. As one of the frontline healthcare professionals, pharmacists focused on continuing to provide pharmacy services to patients while they were at high risk for COVID-19 infection, and adequate equipment and supplies should be available for physicians, nurses, and pharmacy staff, including students, interns, and part-time workers to protect them from infections with SARS-CoV-2. Extending working hours and the heavy workload for dealing with supply shortages and resource allocations made pharmacists exhausted, stressed, and fatigued. One of the early reported deaths of healthcare workers during the COVID-19 pandemic involved a 28-year-old pharmacist, Dr. Song Yingjie, who died of sudden cardiac death after working for ten days straight[22]. Since the first day of the lunar New Year, Dr. Song Yingjie had been on duty and was responsible for the distribution of medical supplies in the warehouse of the hospital. He died at the end of the midnight shift after he returned to the dormitory on February 3. In response to emergencies, we set up an emergency locum team and hired pharmacy interns for emergency personnel augmentation. The emergency locum team consists of six pharmacists with more than 3 years of work experience and arranged according to three shifts daily. Meanwhile, another six pharmacists in the second tier must be reserved to cope with the abnormal reduction of staff. If any pharmacy staff become sick, sick leaves are granted not only for them to rest and recover, but also to avoid infecting patients and coworkers. All staff must be rotated for 14 days to reduce the pressure on the front-line pharmacy staff.

7. Develop a code of conduct for emergency pharmacy services

A concise and practical manual that contains easy to follow instructions on how to handle an emergency like COVID-19 is needed. Employees of the pharmacy need to be familiar with the manual. The manual needs to be printed and placed in a prominent position in the workplace to aid employees in knowing their roles and responsibilities. Regularly disinfecting pharmacy areas to guarantee that the pharmacy is safe for people to work and visit. A COVID-19 emergency training program provided by the hospital can educate the pharmacy team on how to protect themselves during patient interactions and be better prepared for COVID-19 through emergency preparedness drills. Emphasize hand sanitization and social distancing as strategies for infection control and provide accurate information to patients and communities on mask selection and use. A pharmaceutical clinic and online pharmaceutical services were offered for medication counseling, chronic disease self-management, providing reliable and evidence-based information during the pandemic. Telepharmacy is important for patients in rural areas and to avoid direct contact, reducing risks of contagion. The COVID-19 pandemic increased focus and emphasis on mental health among patients[23],

thus the medical staff needs to take care of people who have been confirmed with or are suspected of having COVID-19, pregnant women might particularly worry about transmitting the virus to the fetus, although whether mother-to-infant transmission is possible remains controversial[11,24], any suspected COVID-19 infection during pregnancy needs a systematic screening.

CONCLUSIONS

On the basis of the allocation of pharmaceutical resources in maternal and child healthcare institutions, we saw no scarcity of medical resources or medication errors in our hospital during the COVID-19 pandemic. Our experience could serve as a reference for other hospitals focusing primarily on women and children. It is noteworthy that every country's situation and medical resources are varied, the experience shared here needs to be tailored according to differences in health-care settings and the policies of specific governments.

Acknowledgments

Not applicable.

Author's Contribution

Cai JH and Chen WW contributed to the work equally and should be regarded as co-first authors. Li G had the idea for the article. Yang X and Yang XQ had roles in the literature search. All authors reviewed and approved the final version.

Funding

Not applicable.

Declaration of interests

All authors declare no competing interests.

RESUMO

Desde o aparecimento de um aglomerado de doentes com pneumonia de causa desconhecida em Wuhan, província de Hubei, China, em dezembro de 2019, a doença foi mais tarde oficialmente nomeada doença do coronavírus 2019 (Covid-19), causada pelo novo vírus da síndrome respiratória aguda grave coronavírus (Sars-CoV-2), que rapidamente se espalhou em nível mundial. As mulheres grávidas e as crianças são particularmente vulneráveis durante catástrofes e emergâncias. A preparação e a resposta de emergência abrangentes e aplicáveis são métodos definitivamente importantes para prevenir e conter a pandemia de Covid-19. A alocação racional dos recursos farmacêuticos desempenha um papel importante no plano de emergência médica. Este documento objetivou compartilhar experiências para a alocação de recursos farmacêuticos em hospitais focando principalmente mulheres e crianças durante a pandemia de Covid-19.

PALAVRAS-CHAVE: *Infecções por coronavírus. Gravidez. Criança. Assistência farmacêutica.*

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
2. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation Report – 125. Geneva: World Health Organization; 2020. [cited 2020 May 24]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200524-COVID-19-sitrep-125.pdf?sfvrsn=80e7d7f0_2
3. Liu H, Wang LL, Zhao SJ, Kwak-Kim J, Mor G, Liao AH. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. J Reprod Immunol. 2020;139:103122.
4. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020;323(18):1846-8.
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020. doi: 10.1001/jama.2020.2648.
6. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145(6):e20200702.
7. Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: report of two cases & review of the literature. J Microbiol Immunol Infect. 2019;52(3):501-3.
8. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol. 2004;191(1):292-7.
9. Favre G, Pomar L, Musso D, Baud D. 2019-nCoV epidemic: what about pregnancies? Lancet. 2020;395(10224):e40.
10. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal screening for SARS-CoV-2 in women admitted for delivery. N Engl J Med. 2020;382(22):2163-4.
11. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395(10226):809-15.
12. Bhavsar TR, Kim HJ, Yu Y. Roles and contributions of pharmacists in regulatory affairs at the Centers for Disease Control and Prevention for public health emergency preparedness and response. J Am Pharm Assoc (2003). 2010;50(2):165-8.
13. Murphy JK. After 9/11: priority focus areas for bioterrorism preparedness in hospitals. J Healthc Manag. 2004;49(4):227-35.
14. Awad NI, Cocchio C. Assessment of hospital pharmacy preparedness for mass casualty events. P T. 2015;40(4):264-7.
15. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair allocation of scarce medical resources in the time of COVID-19. N Engl J Med. 2020;382(21):2049-55.

16. Prouillac C, Lecoeur S. The role of the placenta in fetal exposure to xenobiotics: importance of membrane transporters and human models for transfer studies. Drug Metab Dispos. 2010;38(10):1623-35.

17. National Health Commission of the People's Republic of China. Diagnosis and treatment guidelines for the new coronavirus infected pneumonia. [cited 2020 Mar 4]. Available from: http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml

18. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-8.

19. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al; Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 infection in children. N Engl J Med. 2020;382(17):1663-5.

20. Aruru M, Truong HA, Clark S. Pharmacy Emergency Preparedness and Response (PEPR): a proposed framework for expanding pharmacy professionals' roles and contributions to emergency preparedness and response during the COVID-19 pandemic and beyond. Res Social Adm Pharm. 2020;S1551-7411(20)30323-5.

21. Liu S, Luo P, Tang M, Hu Q, Polidoro JP, Sun S, et al. Providing pharmacy services during the coronavirus pandemic. Int J Clin Pharm. 2020;42(2):299-304.

22. South China Morning Post. Chinese hospital pharmacist, 28, dies after 10 straight days helping fight coronavirus. [cited 2020 Apr 2]. Available from: https://www.scmp.com/news/china/society/article/3049381/chinesehospital-pharmacist-28-dies-after-10-straight-days

23. Xiang YT, Yang Y, Li W, Zhang L, Zhang Q, Cheung T, et al. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. Lancet Psychiatry. 2020;7(3):228-9.

24. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020;9(1):51-60.

COVID-19 and acute myocarditis: current literature review and diagnostic challenges

Tufan Çınar[1]
Mert İlker Hayıroğlu[2]
Vedat Çiçek[1]
Mehmet Uzun[1]
Ahmet Lütfullah Orhan[1]

1. Department of Cardiology, Haydarpasa Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey.
2. Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey.

http://dx.doi.org/10.1590/1806-9282.66.S2.48

SUMMARY

INTRODUCTION: *In the current literature, there has been an upsurge of cases of COVID-19-induced acute myocarditis. In this case-based review, we aimed to describe the clinical characteristics, imaging findings, and in-hospital course of acute myocarditis. In addition, the limitations of the myocarditis diagnosis were discussed since only fulminant myocarditis cases have been mentioned in the current literature.*

METHODS: *We performed a review of the literature of all patients who were diagnosed with COVID-19-induced acute myocarditis using the databases of PubMed, Embase, and the Cochrane.*

RESULTS: *16 case reports were found to be related to COVID-19-induced acute myocarditis. We observed that the ECG findings in most of the COVID-19 patients were non-specific, including diffuse ST-segment elevation, non-specific intraventricular conduction delay, sinus tachycardia, and inverted T-waves in anterior leads. Echocardiographic findings of COVID-19-induced acute myocarditis patients ranged from preserved left ventricular ejection fraction (LVEF) without segmental abnormalities to reduced LVEF with global hypokinesia. Interestingly, a few patients with COVID-19-induced acute fulminant myocarditis were steroid-responsive and had an amelioration with glucocorticoid and immunoglobulin therapy.*

CONCLUSION: *Despite the COVID-19 pandemic worldwide, a limited number of cases has been shared in the current literature. There are a lot of difficulties in the differential diagnosis of acute myocarditis in the context of COVID-19.*

KEYWORDS: *Coronavirus Infections. Betacoronavirus. Myocarditis. Cardiomyopathies.*

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new variant form of coronavirus that is responsible for the coronavirus disease 2019 (COVID-19). On March 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic after the confirmation of cases in five continents[1]. Although the virus mainly infects the lung epithelial cells causing respiratory signs and symptoms, there has been an upsurge of cases that presented COVID-19-induced acute myocarditis. Currently, several mechanisms have been proposed to explain the underlying pathophysiology of COVID-19-related acute myocarditis[2]. It has been suggested that direct viral contact through angiotensin-converting enzyme 2 (ACE-2)

DATE OF SUBMISSION: 23-Jun-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Tufan Çınar
Department of Cardiology, Haydarpasa Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey
Tel: +90 216 542-2010 / Fax: +90 216 542-2020
E-mail: drtufancinar@gmail.com

signaling pathways might have a role in the myocardial injury[3]. In addition, cytokine release syndrome has been proposed to be the main pathophysiology of COVID-19-induced acute fulminant myocarditis[3]. In this case-based review, we aimed to describe the clinical characteristics, imaging findings, and in-hospital course of acute myocarditis as well as the limitations in regard to myocarditis diagnosis. In addition, we tried to identify the possible underlying mechanisms of COVID-19-related acute myocarditis, whether it is caused by direct viral damage or an inadequate host immune response.

METHODS

We performed a review of the literature of all patients who were reported to have COVID-19-induced acute myocarditis using the databases of PubMed, Embase, and the Cochrane. All databases were searched in June 2020 using the following keywords: ''COVID-19, acute myocarditis' and 'COVID-19, acute myopericarditis'. In total, 16 case reports were found to be related to COVID-19-induced acute myocarditis. Despite the fact that neither endomyocardial biopsy (EMB) nor cardiac magnetic rezones imaging (CMR) have been performed in several reports, the cases reported under the title of acute myocarditis were included in order to provide the current circumstance in terms of acute myocarditis in the COVID-19 era.

Baseline clinical characteristics

Tables 1 and 2 summarize the clinical characteristics of COVID-19-induced acute myocarditis patients[4-17]. The majority of the cases were male, and hypertension is the most commonly observed risk factor. In all patients, chest pain and dyspnea were the most common symptoms even though one case presented with atypical symptoms such as neck pain and diarrhea[4-8]. Fever is the most commonly observed sign in COVID-19 patients with acute myocarditis. Patients with lower systolic blood pressure developed cardiogenic shock following admission[4].

Lab findings

It is recommended to screen for cardiac injury in patients hospitalized for COVID-19 infection because an early diagnosis has an ultimate role in changing management. Therefore, the measurement of cardiac biomarkers, including troponin and brain natriuretic peptide (BNP), should be performed on admission. We noted that most cases had elevated troponin and BNP levels on admission. Lymphopenia was present in patients with COVID-19-related acute myocarditis, as expected in a usual viral infection.

Imaging features

In patients who are suspected of having COVID-19-related acute myocarditis, baseline electrocardiography (ECG) should be carried out on admission. In this review, we observed that ECG findings in most of the COVID-19 patients were non-specific, including diffuse ST-segment elevation, non-specific intraventricular conduction delay, sinus tachycardia, and inverted T-waves in anterior leads[4-8,10,14,17]. Despite frequent changes in ECG, no specific changes were detected in some cases[9,16]. Because there is the possibility of using a point-of-care ultrasound, it is recommended that echocardiography (ECHO) should be performed if there is a suspicion of COVID-19-related acute myocarditis. In this case-based review, the ECHO findings of patients with COVID-19-induced acute myocarditis ranged from preserved left ventricular ejection fraction (LVEF) without segmental abnormalities to reduced LVEF with global hypokinesia[4,10,14-17]. Those with a severe and depressed LV function developed cardiogenic shock, thereby having a worse prognosis[4,6]. Although CMR was not performed in all cases because of prolonged acquisition time and the fact that COVID-19 infection is highly contagious, it showed myocardial edema and sub-epicardial late gadolinium enhancement in some parts of the LV[7-12,16]. Interestingly, no EMB was performed to confirm the diagnosis in all patients even though it is considered a gold standard. Hemodynamic instability, a contagious risk due to prolonged acquisition time, and coagulopathy were the main reasons for not performing EMB.

In-hospital treatment

There is no consensus for the prescription of the standard heart failure treatment in addition to the antiviral therapy to patients hospitalized with COVID-19-induced acute fulminant myocarditis. Interestingly, intravenous (IV) inotrope treatment and circulatory support have been used in selected cases. Moreover, IV glucocorticoid and immunoglobulin therapy have been implemented in patients with complicated acute myocarditis[4,6,10,15,17]. Most patients received heart failure therapy, antiviral, and antibiotic treatment according to the current literature. A few patients with COVID-19-induced acute fulminant myocarditis showed an

TABLE 1. BASELINE CHARACTERISTICS OF ALL COVID-19 ACUTE MYOCARDITIS PATIENTS

Case, author	Age, sex	Risk factors	Presenting symptoms	Admission findings	ECG findings	Lab findings
Case 1, Inciardi et al.[4]	53, F	-	Fatigue, chest pain and dyspnea	Fever: 36.6 °C HR:100 beats SBP: 90 mm Hg DBP:50 mm Hg Spo_2:98	Minimal diffuse ST-segment elevation (more prominent in the inferior and lateral leads), and an ST-segment depression with T-wave inversion in lead V1 and aVR	WBC: 8.0×10^3/μL Lymphocyte: 1.4×10^3/μL CRP: 25 mg/dl D-dimer: 500 U/F Troponin: 300 ng/L BNP: -
Case 2, Kim et al.[5]	21, F	-	Coughing, sputum, diarrhea, and shortness of breath	-	Nonspecific intraventricular conduction delay and multiple premature ventricular complexes	WBC: - Lymphocyte: - CRP: - D-dimer: Troponin: 1.26 ng/L BNP: 1929 pg/mL
Case 3, Zeng et al.[6]	63, M	-	Shortness of breath and chest tightness after activity	Fever: 39.3 °C HR: - SBP: - DBP: - Spo_2: 91	Sinus tachycardia and no ST-segment elevation	WBC: - Lymphocyte: - CRP: - D-dimer: - Troponin: 11.37 g/L BNP: 22.600 pg/ mL
Case 4, Doyen et al.[7]	69, M	Hypertension	Cough, fever, dyspnea	Fever: 39.1 °C HR: - SBP: - DBP: - Spo_2: 91	Inverted T waves in anterior leads	WBC: 15.400 g/L Lymphocyte: 141.9×10^9 per L CRP: - D-dimer: - Troponin: 9002 ng/L BNP: 22.600 pg/ mL
Case 5, Trogen et al.[8]	17, M	Obesity, asthma, spondylolysis	fever and neck pain, diarrhea	Fever 103 °F HR: 150 bpm SBP: 79 mm Hg DBP: 66 mm Hg Spo_2: 91	Sinus tachycardia and T-wave inversion particularly in the inferior leads	WBC: 15.4 g/dL Lymphocyte: 0.9×10^3/μL CRP: 167 mg/L D-dimer: 1218 ng/mL Troponin: 2.97 ng/ml BNP: 2124 pg/mL
Case 6, Sardari et al.[9]	31, M	-	Dyspnea on exertion and low-grade fever	Fever: 37.8 °C HR: 70 bpm SBP: 110 mm Hg DBP: 70 mm Hg Spo_2: 98	Normal findings	WBC: - Lymphocyte: - CRP: 105 mg/L D-dimer: - Troponin: 2.97 ng/ml BNP: -
Case 7, Coyle et al.[10]	57, M	Hypertension	Shortness of breath, fevers, cough, myalgia, decreased appetite, nausea and diarrhea	Fever: - HR: - SBP: - DBP: - Spo_2: -	Sinus tachycardia without ST/T wave changes	WBC: - Lymphocyte: Lymphopenia CRP: Elevated D-dimer: - Troponin: Rapid rise BNP: Rapid rise
Case 8, Beşler and Arslan[11]	20, M	-	Febrile sensation and chest pain	Fever: 39 °C HR: 111bpm SBP: 149 mm Hg DBP: 63 mm Hg Spo_2: 97	-	WBC: 6.74×10^9 per L Lymphocyte: Lymphopenia CRP: 0.0812 g/L D-dimer: - Troponin: 0.572 ng/mL BNP: 127 ng/L
Case 9, Yuan et al.[12]	33, M	Hypertension	Chest pain, fever, and muscle ache.	Fever: 37.3 °C HR: 121bpm SBP: 115mm Hg DBP: 79 mm Hg Spo_2: -	Ventricular tachycardia.	WBC: - Lymphocyte: - CRP: - D-dimer: - Troponin: - BNP: -
Case 10, Cizgici et al.[13]	78, M	-	Chest pain and shortness of breath.	Fever: 37.3 °C HR: 150 bpm SBP: 115 mm Hg DBP: 79 mm Hg Spo_2: -	Atrial fibrillation with 150 beats/minute and concave ST elevation except for aVR lead	WBC: Leukocytosis Lymphocyte: Lymphopenia CRP: 94.6 mg/L D-dimer: - Troponin: 998.1 ng/L BNP: 127 ng/L
Case 11, Asif and Ali[14]	64, M	Hypertension, hyperlipidemia	Dyspnea	Fever: - HR: 80 bpm SBP: 85 mm Hg DBP: 50 mm Hg Spo_2: 70	Non-specific T wave changes	WBC: Leukocytosis Lymphocyte: Lymphopenia CRP: 94.6 mg/L D-dimer: - Troponin: 0.17 ng/ml. BNP: -

TABLE 1. (CONCLUSION)

Case, author	Age, sex	Risk factors	Presenting symptoms	Admission findings	ECG findings	Lab findings
Case 12, Asif and Ali[14]	71, F	Multiple myeloma	Fever, cough, and dyspnea	Fever: - HR: 125 bpm SBP: 70 mm Hg DBP: 41 mm Hg Spo_2: 70	1 mm ST elevation in leads V2–V6 with associated Q waves in leads V4–V6	WBC: - Lymphocyte: - CRP: - D-dimer: - Troponin: 1.6 ng/ml BNP: -
Case 13, Juusela et al.[15]	45, F Pregnant (39 weeks)	Obesity, gestational diabetic	Contractions and emesis	Fever: 99.6 °F HR: 120 bpm SBP: 183 mm Hg DBP: 114 mm Hg Spo_2: 96	Nonspecific T-wave abnormalities	WBC: - Lymphocyte: - CRP: - D-dimer: - Troponin: 0.046 ng/mL BNP: 114 pg/mL
Case 14, Juusela et al.[15]	26, F Pregnant (33 weeks)	Obesity, polycystic ovary syndrome	Shortness of breath, dyspnea,	Fever: 99.6 °F HR: 130 bpm SBP: 110 mm Hg DBP: 70 mm Hg Spo_2: 95	Supraventricular tachycardia	WBC: - Lymphocyte: - CRP: 7.68 mg/dL D-dimer: - Troponin: 0.046 ng/mL, BNP: <10 pg/mL,
Case 15, Pavon et al.[16]	64, M	Pulmonary sarcoidosis and epilepsy	Chest pain and dyspnea.	Fever: 39.3°C HR: - SBP: - DBP: - SpO2: -	Unremarkable	WBC: 18.7 gr/L Lymphocyte: - CRP: - D-dimer: 1210 ng/ml Troponin: 1843 ng/L BNP: -
Case 16, Irabien-Ortiz et al.[17]	59, F	Hypertension, cervical degenerative arthropathy, chronic lumbar radiculopathy, erythema nodosum, migraine	Anginal chest pain in the absence of respiratory symptoms.	Fever: 39.3°C HR: - SBP: 75 mm Hg DBP: 53 mm Hg Spo_2: 96	Concave ST-segment elevation and PR-segment depression, as well as low voltages	WBC: 14.17x 10^9/L Lymphocyte: 2.59x10^9/L CRP: - D-dimer: 23.242 ng/mL Troponin: Elevated BNP: 4421 ng/L

Abbreviations: F; female, M; male, HR; heart rate, SBP; systolic blood pressure, DBP; diastolic blood pressure, WBC; white blood cell, CRP; c-reactive protein, BNP; brain natriuretic peptide.

TABLE 2. IMAGING FINDINGS, IN-HOSPITAL TREATMENT, AND COURSE OF ALL COVID-19 ACUTE MYOCARDITIS PATIENTS

Case, author	Echocardiographic findings	CMR imaging findings	EMB findings	In-hospital treatment	In-hospital course
Case 1, Inciardi et al.[4]	Diffuse hypokinesia, with an estimated left ventricle ejection fraction of 40%	Diffuse biventricular hypokinesia, especially in the apical segments, and severe LV dysfunction	-	Hydroxychloroquine (200 mg twice daily), lopinavir/ritonavir (2 tablets of 200/50 mg twice daily), and intravenous methylprednisolone (1 mg/kg daily for), 50 mg of kanrenone, 25 to 50 mg of furosemide, and 2.5 mg of bisoprolol	Cardiogenic shock, clinical follow-up
Case 2, Kim et al.[5]	Severe left ventricular systolic dysfunction	Diffuse high signal intensity in the left ventricle myocardium on T2 short inversion recovery image	-	-	Discharged
Case 3, Zeng et al.[6]	An enlarged left ventricle (61 mm), diffuse myocardial dyskinesia along with a low left ventricular ejection fraction of 32%	-	-	High-flow oxygen, lopinavir-ritonavir, interferon α-1b, methylprednisolone, immunoglobulin, piperacillin-tazobactam, and continuous renal replacement therapy	Cardiogenic shock, exitus
Case 4, Doyen et al.[7]	Mild left ventricle hypertrophy, the left ventricular ejection fraction and wall motion were within normal limits	Subepicardial late gadolinium enhancement of the apex and inferolateral wall—suggestive of myocarditis	-	Hydrocortisone, aspirin, fondaparinux	Acute respiratory distress syndrome, discharged

TABLE 2. (CONCLUSION)

Case, author	Echocardiographic findings	CMR imaging findings	EMB findings	In-hospital treatment	In-hospital course
Case 5, Trogen et al.[8]	Left ventricular ejection fraction qualitatively noted to be mildly depressed without obvious intracardiac clots or pericardial effusion	Normal size left ventricle (LV) with mildly decreased systolic function (40%) and normal right ventricular (RV) size with mildly diminished systolic function (RVEF of 39%). There was an area of mid-wall late gadolinium enhancement at the inferior LV–RV junction corresponding to an area of increased T2 signal, as well as an area of hypokinesia	-	Hydroxychloroquine, piperacillin/tazobactam, enoxaparin	Discharged
Case 6, Sardari et al.[9]	Mild left ventricular dysfunction	Normal left ventricular size with a mildly reduced ejection fraction of 50%. T2-weighted sequence with its post-analysis showed edema/inflammation in the mid inferoseptal and inferior wall. Late gadolinium enhancement showed subepicardial fibrosis in the mid inferior wall	-	Bisoprolol and lisinopril	Discharged
Case 7, Coyle et al.[10]	Moderate diffuse hypokinesia with relative apical sparing and a left ventricular ejection fraction of 35- 40%	Diffuse bi-ventricular and bi-atrial edema with a small area of late gadolinium enhancement	-	Hydroxychloroquine, azithromycin, ceftriaxone, methylprednisolone, colchicine	Discharged
Case 8, Beşler and Arslan[11]	-	Short tau inversion recovery (STIR) sequence revealed a subepicardial high signal intensity in the mid posterolateral wall of the left ventricle which suggests myocardial wall edema	-	Hydroxychloroquine, azithromycin, ceftriaxone, tigecycline, favipiravir, colchicine	Discharged
Case 9, Yuan et al.[12]	-	The signal of T2 weighted image in the apical region of the left ventricle was increased, which indicated the possibility of myocardial cell edema. Left ventricular systolic function was slightly decreased	-	-	-
Case 10, Cizgici et al.[13]	Not being able to perform echocardiography	Not being able to perform magnetic resonance imaging	-	Furosemide, beta-blocker, and angiotensin-converting enzyme inhibitor was added to his Covid-19 specific therapy.	-
Case 11, Asif and Ali[14]	Normal left ventricle ejection fraction of 70–75% with no regional wall motion abnormalities	-	-	Aspirin 81 mg, clopidogrel 75 mg, heparin, azithromycin, hydroxychloroquine, meropenem, tocilizumab, norepinephrine, phenylephrine, vasopressin, atracurium, propofol, fentanyl	Intubated
Case 12, Asif and Ali[14]	Normal left ventricle ejection fraction of 65–70% with no regional wall motion abnormalities	-		Aspirin 81 mg, clopidogrel 75 mg, heparin, azithromycin, cefepime, vancomycin, tocilizumab, norepinephrine, phenylephrine, midazolam, and fentanyl	Intubated
Case 13, Juusela et al.[15]	Moderately reduced left ventricular ejection fraction of 40% with global hypokinesia	-	-	IV methylprednisolone, hydroxychloroquine, tocilizumab .	Intubated, (a primary cesarean)
Case 14, Juusela et al.[15]	Moderately reduced left ventricular ejection fraction of 40-45% with global hypokinesia	-	-	Metoprolol	Cesarean
Case 15, Pavon et al.[16]	Moderately reduced left ventricular ejection fraction of 47%.	T2-mapping sequences showed myocardial edema and sub-epicardial late gadolinium enhancement in the anterior interventricular septum, in the inferior and inferolateral walls	-	Piperacillin/tazobactam	Discharged
Case 16, Irabien-Ortiz et al.[17]	Preserved left ventricular ejection fraction without segmental abnormalities, and moderate pericardial effusion with no clear signs of hemodynamic deterioration	-	-	Immunoglobulins (80 mg/d) methylprednisolone (500 mg/d), antiviral treatment consisting of interferon-B (0.25 mg/48 h) and ritonavir/lopinavir (400 mg/100 mg/12 h)	Cardiogenic shock

Abbreviations: CMR; cardiac magnetic resonance, EMB; endomyocardial biopsy

amelioration using IV glucocorticoid and immunoglobulin therapy. This finding appears as a clue highlighting the cytokine storm due to inadequate host immune response, which might be the main pathophysiology of COVID-19-induced acute fulminant myocarditis.

Limitations in the diagnosis of COVID-19-related acute myocarditis

Acute viral infections are one of the most common etiologic factors of acute myocarditis. Following the COVID-19 pandemic, several cases of acute myocarditis were reported worldwide, which were diagnosed with different modalities other than EMB. In our review, all of the published cases were mentioned in terms of clinical characteristics, imaging findings, and in-hospital course.

Troponin has been indicated as an independent predictor of mortality in hospitalized patients with COVID-19[18,19]. Since troponin has been defined as a noteworthy prognostic factor, the etiology of the higher levels of troponin gains clinical importance to regulate adequate medications. In COVID-19 patients who present with elevated troponin levels, it might be difficult to reach a definitive diagnosis of acute coronary syndrome (ACS) or acute myocarditis because there are similarities among them in regard to the elevation of troponin levels and ECG changes. It is reasonable not to perform CMR and MRI in most patients due to the contiguousness of COVID-19. On the other hand, underusing the aforementioned modalities in the differential diagnosis reveals a gap in the definite etiology of the myocardial injury. Thus, we may be underestimating the prevalence and importance of COVID-19-related acute myocarditis. Moreover, in severe patients, both ACS and acute myocarditis may present together because of the procoagulant and inflammatory nature of the COVID-19 infection.

CONCLUSION

Despite the COVID-19 pandemic worldwide, a limited number of cases has been shared in the current literature. There are a lot of difficulties for the differential diagnosis of acute myocarditis in the context of COVID-19, and information about COVID-19-related acute myocarditis remains unclear. Also, there is no consensus about the diagnostic and treatment algorithms in patients with COVID-19-induced acute myocarditis. Hence, further studies and case reports on COVID-19-associated acute myocarditis are needed to clarify an appropriate approach to these patients.

Conflict of interest

The authors have no conflicts of interest relevant for this article

Funding

The authors declare that this article has received no financial support.

Author's Contribution

Concept: T.Ç., M.İ.H.; Design: T.Ç., M.İ.H.; Supervision: M.U., A.L.O.; Funding: V.Ç.; Materials: T.Ç., M.İ.H., V.Ç.; Data collection: T.Ç., V.Ç.; Analysis: M.İ.H.; Literature review: T.Ç., M.İ.H., V.Ç.; Writing: T.Ç.; Critical review: M.U., A.L.O.

RESUMO

INTRODUÇÃO: *Na literatura atual, houve um aumento dos casos apresentados com doença coronavírus de 2019 (COVID-19) induzida por miocardite aguda. Nesta revisão baseada em casos, buscamos descrever as características clínicas, achados de imagem e curso hospitalar de miocardite aguda. Além disso, as limitações em relação ao diagnóstico de miocardite foram discutidas, uma vez que apenas casos de miocardite fulminante foram mencionados na literatura atual.*

MÉTODOS: *Fizemos uma revisão da literatura de todos os pacientes diagnosticados com miocardite aguda induzida por COVID-19 com a utilização das bases de dados PubMed, Embase e Cochrane.*

RESULTADO: *Dezesseis casos relatados estão relacionados com a miocardite aguda induzida pela COVID-19. Observamos que os achados de ECG na maioria dos pacientes com COVID-19 não eram específicos, incluindo elevação difusa do segmento ST, atraso não específico da condução intraventricular, taquicardia sinusal e ondas T invertidas em pistas anteriores. Os resultados ecocardiográficos de doentes com miocardite aguda COVID-19 variaram entre a fração de ejeção ventricular esquerda preservada (LVEF) sem anomalias segmentais e a LVEF reduzida com hipocinésia global. Curiosamente, alguns pacientes com COVID-19 induzidos à miocardite aguda fulminante eram sensíveis aos esteroides e tinham uma melhoria com glucocorticoides e terapia com imunoglobulina.*

CONCLUSÃO: *Apesar da pandemia de COVID-19 em todo o mundo, um número limitado de casos tem sido compartilhado na literatura atual. Há muitas dificuldades para o diagnóstico diferencial de miocardite aguda no contexto da COVID-19.*

PALAVRAS-CHAVE: *Infecções por coronavírus. Betacoronavírus. Miocardite. Cardiomiopatias.*

REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
2. Bavishi C, Bonow RO, Trivedi V, Abbott JD, Messerli FH, Bhatt DL. Acute myocardial injury in patients hospitalized with COVID-19 infection: a review. Prog Cardiovasc Dis. 2020;S0033-0620(20)30123-7.
3. Lang JP, Wang X, Moura FA, Siddiqi HK, Morrow DA, Bohula EA. A current review of COVID-19 for the cardiovascular specialist. Am Heart J. 2020;226:29-44.
4. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac ınvolvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):1-6.
5. Kim IC, Kim JY, Kim HA, Han S. COVID-19-related myocarditis in a 21-year-old female patient. Eur Heart J. 2020;41(19):1859.
6. Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, et al. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. Infection. 2020;1-5.
7. Doyen D, Moceri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. Lancet. 2020;395(10235):1516.
8. Trogen B, Gonzalez FJ, Shust GF. COVID-19-associated myocarditis in an adolescent. Pediatr Infect Dis J. 2020;39(8):e204-5.
9. Sardari A, Tabarsi P, Borhany H, Mohiaddin R, Houshmand G. Myocarditis detected after COVID-19 recovery. Eur Heart J Cardiovasc Imaging. 2020;jeaa166.
10. Coyle J, Igbinomwanhia E, Sanchez-Nadales A, Danciu S, Chu C, Shah N. A recovered case of COVID-19 myocarditis and ARDS treated with corticosteroids, tocilizumab, and experimental AT-001. JACC Case Rep. 2020;2(9):1331-6.
11. Beşler MS, Arslan H. Acute myocarditis associated with COVID-19 infection. Am J Emerg Med. 2020;S0735-6757(20)30463-0.
12. Yuan WF, Tang X, Zhao XX. An 'asymptomatic' driver with COVID-19: atypical suspected myocarditis by SARS-CoV-2. Cardiovasc Diagn Ther. 2020;10(2):242-3.
13. Cizgici AY, Zencirkiran Agus H, Yildiz M. COVID-19 myopericarditis: it should be kept in mind in today's conditions. Am J Emerg Med. 2020;38(7):1547.e5-1547.e6.
14. Asif T, Ali Z. Transient ST segment elevation in two patients with COVID-19 and a normal transthoracic echocardiogram. Eur J Case Rep Intern Med. 2020;7(5):001672.
15. Juusela A, Nazir M, Gimovsky M. Two cases of coronavirus 2019-related cardiomyopathy in pregnancy. Am J Obstet Gynecol MFM. 2020;2(2):100113.
16. Pavon AG, Meier D, Samim D, Rotzinger DC, Fournier S, Marquis P, et al. First documentation of persistent SARS-CoV-2 ınfection presenting with late acute severe myocarditis. Can J Cardiol. 2020;S0828-282X(20)30532-8.
17. Irabien-Ortiz A, Carreras-Mora J, Sionis A, Pàmies J, Montiel J, Tauron M. Fulminant myocarditis due to COVID-19. Rev Esp Cardiol (Engl Ed). 2020;73(6):503-4.
18. Nie SF, Yu M, Xie T, Yang F, Wang HB, Wang ZH, et al. Cardiac troponin I is an ındependent predictor for mortality in hospitalized patients with coronavirus disease 2019. Circulation. 2020. doi: 10.1161/CIRCULATIONAHA.120.048789.
19. Imazio M, Klingel K, Kindermann I, Brucato A, De Rosa FG, Adler Y, et al. COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? Heart. 2020;heartjnl-2020-317186. doi: 10.1136/heartjnl-2020-317186.

Ventilation mask adapted for endoscopy during the COVID-19 pandemic

José Luiz Paccos[1]
Ivandro Paulo de Lima[2]
Viviane Rissio Borba de Lima[2]
Natália Sayuri Mukai[1]

1. Médico do corpo clínico do Hospital Dr. Miguel Soeiro, Sorocaba, SP, Brasil.
2. Enfermeiro do corpo clínico do Hospital Dr. Miguel Soeiro, Sorocaba, SP, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.55

SUMMARY

In the context of the COVID-19 pandemic, endoscopy services must adopt preventive measures to maintain proper functioning due to a high risk of disease contagion. Triage protocols before and after the procedure, personal protective equipment, and environmental contamination control are some of the endoscopy society's recommendations. However, the risk of infection may remain high due to poor control over the source of contamination.

Using a combination of standardized supplies and accessories in a hospital, a ventilation mask adapted to be used in endoscopic procedures is proposed to reduce COVID-19 contamination.

KEYWORDS: *Endoscopy. Endoscopy, Digestive System. Personal protective equipment. Respiratory protective devices. Coronavirus infections.*

INTRODUCTION

During the period of the COVID-19 pandemic in Brasil, elective endoscopic examinations were suspended temporarily, being carried out only in cases of urgency and emergency[1]. Although this is not a commonly executed examination in COVID-19 cases, it is prudent to adopt precautionary measures for all patients, assuming that there are infected individuals who are asymptomatic, particularly in services that treat many cases of the disease[2].

The routes of Sars-Cov-2 transmission include contact from person to person and contact with secretions or aerosols[2]. Endoscopic procedures expose professionals who are involved in all these contamination routes[3]. The World Health Organization (WHO)[4] defines digestive endoscopy as a procedure with a potential to generate aerosols.

Several recommendations for endoscopy services suggest the control of infection transmission by preventing contact and cleaning up environments[3,5,6]. Thus, they propose, in addition to the screening of patients, the use of PPE and systematic disinfection of sites and surfaces. However, what happens during endoscopy is the protection of individuals present in the room, allowing the free dispersal of infectious material from the source (patient)[3,7]. Thus, there is some concern if we are really reducing the exposure of professionals and other patients at risk of contracting the infection. Studies show that viable virus particles

DATE OF SUBMISSION: 01-Jul-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: José Luiz Paccos
Hospital Dr. Miguel Soeiro, Rua Antônia Dias Petri, 135, Parque Santa Isabel, Sorocaba, SP, Brasil –18052-210
Tel: +55 15 3211-2325
E-mail: jlpaccos@gmail.com

may remain present in the air for up to three hours, and on surfaces, for up to three days[8]. Reducing the load of infective material that is released in the environment is, therefore, also a challenge.

METHODS

Assuming that any person can be infected, we propose a device to be used by the patient (blocking dispersing agents at the source). This device must, at the same time, act as a barrier, provide safe breathing, and allow the completion of the examination. We adapted an endoscopy mask that covers the airways of the patient, allowing them to breathe, coupled to a membrane filter that allows the passage of the endoscope through it (Figure 1). This set could be used for other procedures, such as transesophageal echocardiography and endoscopic retrograde cholangiopancreatography (ERCP).

FIGURE 1

DISCUSSION

In order to carry out the endoscopy, the patient's mask is removed to access the digestive tract. Similarly to what happens during orotracheal intubation, aerosols are released in the environment is, especially during the passage of the device through the cricopharynx, when the reactivity of the airways can occur and, consequently, cough[3]. At that moment, infectious particles can be released up to 2 or 3 meters away, reaching the space where doctors and assistants are positioned[3,9,10]. Another consideration is the direction of the spray of infectious particles towards the endoscopist due to the position of the patient, i.e., lateral decubitus with their face turned to the assistants. In addition, the mouthpiece and endoscopy device form a barrier to expiration; this increases the angle of aerosol dispersion and, similarly to what occurs in the presence of a tracheal tube and the hand of the doctor positioned opposite to the mouth of the patient, exhaled air spreads widely[2]. Thus, the use of masks and other barrier devices can reduce the distance of dispersion of infectious agents when worn by the patient[11]. A similar modified ventilation mask has already been proposed in another health service[12]. The great advantage of using this mask is that it requires existing and available material, in addition to its ease of use.

CONCLUSION

Although there are no scientific studies that confirm the effectiveness of this mask, we justify its use as a way to strengthen the protective barrier against COVID-19, in addition to other protective equipment already being used (impermeable aprons, goggles, among others).

Conflict of interest

The authors have no conflicts of interest (professional or financial and no direct or indirect benefits) that might influence or have influenced the research results or the content of the work.

Author's Contribution

All authors contributed equally to this work.

RESUMO

No contexto da pandemia de COVID-19, o serviço de endoscopia deve adotar ações preventivas para manter seu funcionamento devido ao grande risco de contágio da doença. Protocolos de triagem antes e após o procedimento, equipamentos de proteção individual e controle de contaminação do ambiente fazem parte das recomendações das sociedades de endoscopia. Entretanto, o risco de infecção pode permanecer alto devido ao pouco controle da fonte de disseminação de contaminantes. A partir da combinação de suprimentos e de acessórios padronizados em um hospital, uma máscara de ventilação adaptada para ser usada em procedimentos endoscópicos é proposta com a finalidade de reduzir a contaminação por COVID-19.

PALAVRAS-CHAVE: *Endoscopia. Endoscopia do sistema digestório. Equipamento de proteção individual. Dispositivos de proteção respiratória. Infecções por coronavírus.*

REFERENCES

1. Brasil. Gerência de Vigilância e Monitoramento em Serviços de Saúde, Gerência Geral de Tecnologia em Serviços de Saúde, Agência Nacional de Vigilância Sanitária. Nota técnica GVIMS/GGTES/ANVISA Nº 04/2020. Orientações para serviços de saúde: medidas de prevenção e controle que devem ser adotadas durante a assistência aos casos suspeitos ou confirmados de infecção pelo novo coronavírus (SARS-CoV-2). Brasília: Agência Nacional de Vigilância Sanitária; 2020. [cited 2020 May 8]. Available from: http://portal.anvisa.gov.br/documents/33852/271858/Nota+T%C3%A9cnica+n+04-2020+GVIMS-GGTES-ANVISA/ab598660-3de4-4f14-8e6f-b9341c196b28
2. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. 2020;323(14):1406-7.
3. Galloro G, Pisani G, Zagari RM, Lamazza A, Cengia G, Ciliberto E, et al. Safety in digestive endoscopy procedures in the COVID era recommendations in progres of the Italian Society of Digestive Endoscopy. Dig Liver Dis. 2020;52(8):800-7.
4. World Health Organization. Rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages. Geneva: World Health Organization; 2020. [cited 2020 May 8]. Available from: https://www.who.int/publications/i/item/rational-use-of-personal-protective-equipment-for-coronavirus-disease-(COVID-19)-and-considerations-during-severe-shortages
5. Sociedade Brasileira de Endoscopia Digestiva. Medidas de prevenção: casos suspeitos ou confirmados. São Paulo: Sociedade Brasileira de Endoscopia Digestiva; 2020. [cited 2020 Jun 4]. Available from: https://www.sobed.org.br/fileadmin/user_upload/sobed/2020/04/01/COVID_-_protecao.pdf
6. Soetikno R, Teoh AYB, Kaltenbach T, Lau JYW, Asokkumar R, Cabral-Prodigalidad P, et al. Considerations in performing endoscopy during the COVID-19 pandemic. Gatrointest Endosc. 2020;92(1):176-83.
7. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020;382(16):1564-7.
8. Knowlton SD, Boles CL, Perencevich EN, Diekema DJ, Nonnenmann MW; CDC Epicenters Program. Bioaerosol concentrations generated from toilet flushing in a hospital-based patient care setting. Antimicrob Resist Infect Control. 2018;7:16.
9. Kähler CJ, Hain R. Flow analyses to validate SARS-CoV-2 protective masks. Neubiberg: University of the Bundeswehr Munich; 2020. [cited 2020 Jun 2]. Available from: https://www.unibw.de/lrt7-en/report_mask-investigation_unibw_lrt7_06_04_2020.pdf
10. Bourouiba L, Dehandschoewercker E, Bush JW. Violent expiratory events: on coughing and sneezing. J Fluid Mech. 2014;745:537-63.
11. Viola IM, Peterson B, Pisetta G, Pavar G, Akhtar H, Menoloascina F, et al. Face coverings, aerosol dispersion and mitigation of virus transmission risk. Cornell University Medical Physics. [Online].; 2020. Available from: arXiv:2005.10720v1.
12. Marchese M, Capannolo A, Lombardi L, Di Carlo M, Marinangeli F, Fusco P. Use of a modified ventilation mask to avoid aerosolizing spread of droplets for short endoscopic procedures during coronavirus COVID-19 outbreak. Gastrointest Endosc. 2020;92(2):439-40.

ORIGINAL ARTICLE

The diagnostic process of covid-19 in the emergency department: laboratory and ımaging methods

Fatih Guneysu[1]
Yusuf Yurumez[2]
Ertugrul Guclu[3]
Mehmet Koroglu[4]
Alper Karacan[5]
Necip Gokhan Guner[1]
Yesim Durgun[1]

1. Sakarya University Training and Research Hospital, Clinic of Emergency Medicine, Sakarya, Turkey.
2. Sakarya University Faculty of Medicine, Department of Emergency Medicine, Sakarya, Turkey.
3. Sakarya University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Sakarya, Turkey.
4. Sakarya University Faculty of Medicine, Department of Clinic Microbiology, Sakarya, Turkey.
5. Sakarya University Faculty of Medicine, Department of Radiology, Sakarya, Turkey.

http://dx.doi.org/10.1590/1806-9282.66.S2.58

SUMMARY

OBJECTIVES: *The 2019 Novel coronavirus disease puts a serious burden on the health system. Therefore, the detection of particularly serious patients at an early stage is extremely important in terms of controlling the outbreak and improving the prognosis. We investigated the role of inflammatory markers studied in patients suspected of COVID-19 at an emergency department in predicting PCR and CT results.*

METHODS: *This retrospective study was carried out with 133 patients who were admitted between 13 March and 1st April 2020 with suspicion of COVID-19. The patients were divided into four groups according to CT and RT-PCR results and evaluated.*

RESULTS: *Considering all patients, no specific findings were found in the hematological and biochemical values of patients in the laboratory analyses. Although all of the results remained within the reference range, there was a significant difference in white blood cell, neutrophil, platelet, and lymphocyte values when the groups were compared [p = 0.000; p = 0.004; p = 0.022; p = 0.023].*

CONCLUSION: *Laboratory is not specific enough in the pre-diagnosis. In addition, this result does not alter with PCR or CT positivity. However, minimal changes observed in laboratory results may be partially guiding in patients in whom both PCR and CT are positive.*

KEYWORDS: *Coronavirus Infections/diagnosis. Laboratory Test. Diagnostic Imaging. Tomography, X-Ray Computed. Emergency Service, Hospital.*

INTRODUCTION

In early December 2019, the first patient of the 2019 novel coronavirus pneumonia emerged in the city of Wuhan, Hubei province, China[1]. The disease and the virus that causes it have been named as 2019 Novel coronavirus disease [COVID-19] and SARS-COV-2, respectively[2]. COVID-19 is transmitted by inhalation or contact with infected droplets and its incubation period ranges from 2 to 14 days[1].

DATE OF SUBMISSION: 02-Jun-2020
DATE OF ACCEPTANCE: 02-Jun-2020
CORRESPONDING AUTHOR: Fatih Güneysu
Sakarya University Training and Research Hospital, Clinic of Emergency Medicine, Sakarya, Turkey – 56000
E-mail: fatihguneysu55@hotmail.com

Similar to other viral respiratory pathogens, COVID-19 presents in the majority of cases with a rapidly progressive course of fever, cough, and dyspnea[3]. Despite the use of optimal supportive interventions, the fatality rate among hospitalized patients is over 10%[4].

Important distinguishing factors of the disease are leukopenia and the rapid progression to acute respiratory distress syndrome[ARDS][5]. Because of this, it is extremely important to detect the infected person at an early stage and immediately isolate them from the healthy population[6].

RealTime - Polymerase Chain Reaction [RT-PCR] is recommended to detect positive nucleic acid for SARS-CoV-2 in sputum, Oro-Nasopharyngeal Swab [ONS], and secretions of the lower respiratory tract samples for the diagnosis of patients with suspected infection; however, the low sensitivity of RT-PCR implies that many COVID-19 patients may not be identified and receive appropriate treatment in time[7]. Nevertheless, chest computed tomography [CT] is relatively easy to use as a routine imaging tool for the diagnosis of pneumonia and a rapid method 19 to diagnose COVID-19[6]. CT results are generally abnormal, even in those without symptoms[8]. In addition, biomarkers such as white blood cell [WBC], neutrophil [NEU], lymphocyte [LYM], platelet [PLT], neutrophil/lymphocyte ratio [NLR], platelet/lymphocyte ratio [PLR] and C-reactive protein [CRP] have been suggested as useful determinants for the prognosis of patients with viral pneumonia[9].

In this study, besides demonstrating the success of the laboratory and imaging methods in predicting the disease during the first application, we aimed to evaluate the diagnostic values of PCR and CT.

METHODS

This retrospective study was carried out among 133 patients who were admitted to the Sakarya University Education and Research Hospital between 13 March and 1st April 2020 with suspicion of COVID-19. The study protocol was approved by the local ethics committee of the Sakarya University School of Medicine [IRB No:71522473/050.01.04/21].

Patients and Study design

The data required for this retrospective study were obtained from the medical records of the patients in the information system of our hospital. Demographic characteristics, complaints, laboratory results [hematological, biochemical, and serological tests], RT-PCR assay of ONS swab samples, CT, and hospitalization requirements were recorded within the scope of the study.

The inclusion and exclusion criteria for the study are as follows.

- Inclusion criteria: Patients over 18 years old who underwent both chest CT imaging and RT-PCR test with ONS swab samples.
- Exclusion criteria: Patients under 18 years old and whose records could not be found were excluded from the study.

The patients were divided into four groups, based on the criteria described ahead, and examined.

- Group 1 [28 patients]: CT negative and RT-PCR negative;
- Group 2 [53 patients]: CT positive and RT-PCR negative;
- Group 3 [35 patients]: CT negative and RT-PCR positive;
- Group 4 [17 patients]: CT positive and RT-PCR positive.

In the study published by The Republic of Turkey Public Health Institution, patients over 50 were considered to be at high risk[10]. In our study, patients were examined in two groups, under 50 and over 50.

Chest CT protocol and image analysis

CT scans performed in the emergency room were included in this study and evaluated by our hospital's radiologists. All images were obtained using a CT system [Toshiba Alexion 16 Multi-Slice, Japan] with patients in the supine position. The radiologists reported the chest CT as COVID-19 positive or negative.

RT-PCR assay protocol

After the samples were brought to the microbiology laboratory, they were registered in the laboratory operating system, and the ONS sample from the same patient were sequentially analyzed with the same PCR set-up. The isolation of all samples was carried out in a negative-pressure room in a class 2-a biosafety cabinet.

RNA isolation from ONS samples was performed with the EZ1 [Qiagen, Germany] device. Elution of 60 µl of 400 µl sample was taken and used as a template in RT-PCR reaction.

For the RT-PCR study, a 10 µl master mix, 2 µl primer, and 8 µl RNA mixture were prepared per sample with genesis RT-PCR SARS-CoV-2 [Primer Design,

UK] kit. The reaction was carried out with a total reaction volume of 20 µl [Table-1].

At the end of the reaction, Cycle Threshold values were used as an approximate indicator of the number of copies of the SARS-CoV-2 RNA. A Cycle Threshold value of less than 45 was interpreted as positive for the SARS-CoV-2 RNA.

Statistical analysis

The SPSS software version 21.0 was used for statistical analyses. Mean values are specified for continuous variables that match the normal distribution, while median values are specified for continuous variables that do not conform to the normal distribution. Statistical analysis of non-parametric continuous variables used Mann Whitney U and Kruskal Wallis tests, as well as the student t-test and one-way ANOVA in the analysis of parametric continuous variables. Post hoc analyses were conducted according to Tamhane for non-parametric continuous variables that did not conform to the normal distribution, according to Tukey for parametric continuous variables that match the normal distribution. Percentage values are given in the sharing of Nominal Categorical data, and statistical analyzes were made by the X^2 test. All tests were done with a two-tailed significance of 5%. For each endpoint, the absolute and relative effects and their corresponding 95% CIs were calculated as recommended by Altman and colleagues.

RESULTS

The general characteristics of the 133 patients included in the study are shown in Table 2. 78 [58,6%] of the patients were male. Among these parameters, no specific findings were detected from the hematological and biochemical values of the patients. The CRP median value was found to be high as 16mg/dl. In contrast, 52 [39,1%] of the patients had positive RT-PCR results and 88 [66,2%] had pathological findings on CT. Most of the patients admitted to the emergency department were hospitalized and treated [n: 114, 85,7%].

The relationship between diagnostic parameters and age is shown in Table 3. We found that men are more affected than women, both under and over 50. A decrease in LYM and an increase in CRP values were observed in patients of 50 years, which was statistically significant [p=0.018, p=0.003]. There was no relationship between age and PCR results. On the other hand, a significant difference was found in patients under 50 and over 50 in terms of CT findings [p=0.002]. Hospitalization was statistically high in both groups [p=0.000].

The relationship between diagnostic parameters and gender is shown in Table 4. We observed that PLT and CRP levels were increased with statistical significance in men [respectively; p=0.024, p=0.016]. There was no significant difference in terms of hospitalization.

The relationship between laboratory parameters and the groups are shown in Table 5. When the groups were analyzed in terms of WBC, NEU, PLT, and LYM values, a significant difference was found between the groups [p=0.000; p=0.004; p=0.022; p=0.023, respectively]. It is also noteworthy that in Group 4, the median values of WBC, NEU, PLT, and LYM are lower than in the other groups and the CRP median value is higher. In the subgroup analysis, a

TABLE 1. TIME AND TEMPERATURE VALUES OF COVID-19 REAL-TIME PCR ASSAY.

Cycles		Temperature	Time
Reverse transcription		55 °C	10 minutes
Enzyme activation		95 °C	2 minutes
X50 cycles	Denaturation	95 °C	10 seconds
	Annealing and extension	60 °C	60 seconds

TABLE 2. GENERAL CHARACTERISTICS OF PATIENTS.

		n = 133
Age [Years; Mean [SD]]		49.50 [18.82]
Gender	Female [%]	55 [41.4]
	Male [%]	78 [58.6]
WBC[K/uL]		6.80 [5.2-8.4]
Neutrophil [K/uL]		4.30 [3.0-5.6]
Platelets [K/uL]		196.00 [160.00-246.50]
Lymphocytes [K/uL]		1.60 [1.10-2.15]
CRP[mg/L]		16.00 [5.00-46.00]
NLR		2.47 [1.71-3.54]
PLR		118.75 [83.86-162.67]
PCR	Positive [%]	52 [39.1]
	Negative [%]	81 [60.9]
CT	Positive [%]	88 [66.2]
	Negative [%]	45 [33.8]
Hospitalization	Discharge [%]	19 [14.3]
	Hospitalize [%]	114 [85.7]

Data are number [%] or a median, unless otherwise indicated. *The median values [25p-75p] were indicated because parameters did not fit the normal distribution.

WBC: White Blood Cell; CRP: C-Reaktive Protein; NLR: Neutrophil-Lymphocyte ratio; PLR: Platelet-Lymphocyte Ratio; PCR: Polymerase Chain Reaction; CT: Computed Tomography.

statistically significant difference in WBC values was found between Group 1 and Group 4 and between Group 2 and Group 4 [p=0.017; p=0.005, respectively]. When subgroup analysis was made in terms of NEU values, there was a statistically significant difference between Group 2 and Group 4 [p=0.004]. In the subgroup analysis of PLT values, a significant difference was found only between Group 3 and Group 4 [p=0.037]. When the median values of CRP were analyzed, they were found to be higher in Group 2 and Group 4 in patients with positive CT findings [Group 2, 19 mg/dl; Group 4, 18 mg/dl]. When evaluated in terms of Group 4, an increase in CRP and a decrease in other laboratory parameters were observed. The lowest median value in terms of CRP was seen in Group 3[5 mg/dl]. Despite all these results, we observed that all test values remained within the reference range.

TABLE 3. COMPARISON OF THE LABORATORY PARAMETERS, CT, PCR, AND HOSPITALIZATION BETWEEN PATIENTS UNDER 50 AND OVER 50 YEARS OLD.

		Age < 50[min-max]	Age ≥ 50[min-max]	p
Gender	Male n [%]	42 [31.6]	36 [27.1]	0.292
	Female n [%]	27 [20.3]	28 [21.1]	
WBC [K/uL]		7.09 [5.30-8.30]	6.65 [5.10-9.13]	0.864
Neutrophil [K/uL]		4.40 [3.00-5.50]	4.20 [2.96-6.58]	0.617
Platelets [K/uL]		196.00 [163.50-243.50]	195.00 [149.25-265.75]	0.836
Lymphocytes [K/uL]		1.70 [1.30-2.40]	1.50 [1.02-2.00]	0.018
CRP [mg/L]		10.00 [2.70-34.00]	19.50 [7.25-50.75]	0.003
NLR		2.30 [1.56-3.48]	2.70 [1.78-4.87]	0.617
PLR		118.75 [84.17-146.05]	117.20 [82.24-206.79]	0.836
CT	Positive n [%]	37 [27.8]	51 [38.3]	0.002
	Negative n [%]	32 [24.1]	13 [9.8]	
PCR	Positive n [%]	29 [21.8]	23 [17.3]	0.517
	Negative n [%]	40 [30.1]	41 [30.8]	
Hospitalization	Discharge n [%]	17 [12.8]	2 [1.5]	0.000
	Hospitalize n [%]	52 [39.1]	62 [46.6]	

Data shown are number [%] or a median, unless otherwise indicated. *The median values [25p-75p] were indicated because parameters did not fit the normal distribution.

WBC: White Blood Cell; CRP: C-Reaktive Protein; NLR: Neutrophil-Lymphocyte ratio; PLR: Platelet-Lymphocyte Ratio; PCR: Polymerase Chain Reaction; CT: Computed Tomography

TABLE 4. COMPARISON OF THE LABORATORY PARAMETERS, CT, PCR, AND HOSPITALIZATION BETWEEN MALE AND FEMALE PATIENTS.

		Male[min-max]	Female[min-max]	p
Age [Years]		50.29 [18.50]	48.05 [17.24]	0.481
WBC [K/uL]		7.10 [5.25-8.85]	6.60 [5.10-8.10]	0.317
Neutrophil [K/uL]		4.50 [3.19-6.20]	4.00 [2.70-5.30]	0.165
Platelets [K/uL]		185.00 [160.75-226.50]	212.00 [158.00-277.00]	0.024
Lymphocytes [K/uL]		1.50 [1.10-2.10]	1.70 [1.10-2.30]	0.257
CRP [mg/L]		21.00 [6.38-59.75]	8.00 [3.00-24.00]	0.016
NLR		2.79 [1.95-4.23]	2.25 [164-3.22]	0.062
PLR		118.61 [82.65-154.86]	120.56 [84.38-167.33]	0.569
PCR	Positive n [%]	31 [23.3]	21 [15.8]	0.856
	Negative n [%]	47 [35.3]	34 [25.6]	
CT	Positive n [%]	52 [39.1]	36 [27.1]	0.884
	Negative n [%]	26 [19.5]	19 [14.3]	
Hospitalization	Discharge n [%]	11 [8.3]	8 [6.0]	0.943
	Hospitalize n [%]	67 [50.4]	47[35.3]	

Data are number [%] or a median, unless otherwise indicated. *The median values [25p-75p] were indicated because parameters did not fit the normal distribution.

WBC: White Blood Cell; CRP: C-Reaktive Protein; NLR: Neutrophil-Lymphocyte ratio; PLR: Platelet-Lymphocyte Ratio; PCR: Polymerase Chain Reaction; CT: Computed Tomography.

TABLE 5. COMPARISON OF LABORATORY PARAMETERS BETWEEN THE GROUPS.

Groups n[%]	Group 1 [min-max]	Group 2 [min-max]	Group 3 [min-max]	Group 4 [min-max]	P
WBC [K/uL]	7.35 [6.17-9.17]	7.29 [5.45-9.1]	7.50 [5.5-8.45]	5.0 [4.4-6.7]	0.000
Neutrophil [K/uL]	4.70 [3.85-6.43]	5.07 [2.95-6.50]	4.70 [2.85-5.60]	3.30 [2.80-4.20]	0.004
Platelets [K/uL]	206.0 [190.0-266.5]	193.0 [158.0-266.5]	208.0 [195.0-260.5]	166.0 [144.0-212.0]	0.022
Lymphocytes [K/uL]	2.05 [1.45-2.57]	1.50 [1.10-2.10]	2.0 [1.15-2.65]	1.3 [1.01-1.80]	0.023
CRP [mg/L]	6.5 [2.0-29.75]	19.0 [8.0-71.5]	5.0 [1.0-18.5]	18.0 [6.0-49.0]	0.001
NLR	2.42 [1.53-4.32]	2.58 [1.96-4.84]	2.16 [1.31-3.34]	2.50 [1.69-3.46]	0.613
PLR	100.5 [82.50-134.1]	130.9 [85.9-205.7]	124.6[74.3-192.8]	120.6 [80.0-155.6]	0.430

Data are number [%] or a median, unless otherwise indicated. *The median values [25p-75p] were indicated because parameters did not fit the normal distribution

WBC: White Blood Cell; CRP: C-Reaktive Protein; NLR: Neutrophil-Lymphocyte ratio; PLR: Platelet-Lymphocyte Ratio.

DISCUSSION

COVID-19 is a pandemic that puts a serious burden on the health system. Therefore, the detection of particularly serious patients at an early stage is extremely important in terms of controlling the outbreak and improving prognosis[10]. COVID-19 can affect all age groups. However, it is believed that the group that is mostly affected is middle-aged and older adults, and that the clinical presentation is more severe in the elderly[5]. Looking at the literature on this issue, the average age of the affected individuals reported was 58 years in a Chinese-based publication, and 65.5 in a US-based study[11,12]. In our study, the average age was 49.5 years. This may be because the population of our country is younger than the population of China and the USA.

COVID-19 infection can affect both women and men. However, its incidence and severity in men are higher than in women. This was the same with MERS-COV and SARS-COV infections, which are of the same family. When the publications on exposure rate of males are examined, it is seen that this rate is 66%, 68%, and 75%[12-14] for MERS-COV and SARS-COV, respectively. It is believed that this is due to the X chromosome and sex hormones that exist in females, which play an important role in women's natural and adaptive immunity[15]. Indeed, our results support this data and the proportion of men in our study was 58.6%.

Laboratory markers for COVID-19 are not specific and their clinical benefit is limited. Doctors cannot rely on these laboratory markers to rule out or confirm the diagnosis while evaluating suspected cases. The most frequently reported laboratory abnormalities in the literature are lymphocytopenia and an increase in CRP values[14,16]. Indeed, these laboratory abnormalities were also observed in SARS and MERS patients[17-19]. In our study, only an increase in CRP levels was detected from laboratory results, and this result supports the idea that laboratory markers are not specific for COVID-19. However, a different situation emerges when results are interpreted considering age and gender. In our results, which are compatible with the literature, lymphocytopenia is seen in patients over the age of 50. On the other hand, when a comparison was made in terms of gender, it was observed that PLT, CRP, and NLR levels increased significantly in men. All these results suggest that age and gender should be taken into consideration when evaluating laboratory results.

A definitive diagnosis of COVID-19 is made by detecting SARS-CoV-2 RNA by RT-PCR[20]. However, the accuracy and predictivity of SARS-CoV-2 tests have not been systematically evaluated. The sensitivity of tests also depends on a precise RT-PCR assay, the type of specimen obtained, the quality of the specimen, and the duration of the illness at the time of testing[21]. In two different studies evaluating PCR, positivity rates were reported as 35% and 59%[6]. In our study, we found 39.1% of RT-PCR test positivity.

Compared to PCR, CT imaging may be a more reliable, practical, and fast method to diagnose and evaluate COVID-19, especially in epidemic regions, but availability, radiation, and cost cannot be ignored. In the literature, it is seen that nearly all COVID-19 patients have different ground-glass opacities, reticular interlobular septal thickening, multifocal pneumonia, and architectural distortion in a peripheral distribution[6]. Considering studies on CT positivity, in a meta-analysis of 2738 cases, the rate of COVID-19 compatible cases was 89.76%, while in another study involving 1014 patients, this rate was 88%[6,22]. In our

study, the rate of CT-positive patients was found to be 66,2%, similar to the literature. The reason for this may be that the number of patients in our study was less than other studies, and there were not enough PCR kits in our hospital at the beginning. Available data suggest that CT imaging plays a critical role in the initial diagnosis.

For COVID-19 infection, no specific consensus has been reached regarding patient hospitalization or discharge. Studies show that approximately 14% of those infected with COVID-19 have a serious illness, and 6% of them are critically ill, so 20% of all cases need to be hospitalized[13]. In our study, 85,7% of patients with suspected COVID-19 who attended the emergency service were hospitalized. COVID-19 guidelines were published by The Republic of Turkey Public Health Instutition[23]. In them, hospitalization is recommended for patients over the age of 50 and all age groups with positive CT findings. As a result, our hospitalization rate is high. Once COVID-19 is diagnosed, patients should be isolated from the community, so hospitalization may be increased to provide isolation.

In the absence of specific therapeutic drugs or vaccines for COVID-19, it is essential to detect the disease at an early stage, and immediately isolate the infected person from the healthy population[24]. Therefore, due to the low specificity of laboratory parameters and low positivity rates of RT-PCR tests, CT is needed regardless of the radiation load they create on patients. Indeed, in previous studies supporting this result, the relationship between CT and disease severity has been demonstrated[25]. Considering the comparison between groups in our study, it was revealed that CT was the diagnostic tool that contributed the most to diagnostic processes. In this study, the fact that inflammatory laboratory parameters, especially WBC, NEU, PLT, and LYM showed a significant correlation with the positivity of CT and PCR supports the idea that these should be used together.

CONCLUSIONS

Laboratory results are not specific enough in the pre-diagnosis. In addition, this result does not alter with PCR or CT positivity. However, minimal changes observed in laboratory results may be partially guiding in patients in whom both PCR and CT are positive.

All authors contributed equally to this study.

The authors declare that they have no conflict of interest. No financial support was received.

RESUMO

OBJETIVOS: *A nova doença de coronavírus de 2019 coloca um fardo sério para o sistema de saúde. Portanto, a detecção de pacientes especialmente graves em um estágio inicial é extremamente importante em termos de controle do surto e melhoria do prognóstico. Investigamos o papel dos marcadores inflamatórios estudados em pacientes suspeitos de COVID-19 no pronto-socorro na previsão de resultados de PCR e CT.*

MÉTODOS: *Este estudo retrospectivo foi realizado entre 133 pacientes que foram admitidos entre 13 de março e 1º de abril de 2020 com suspeita de COVID-19. Os pacientes foram divididos em quatro grupos de acordo com os resultados da TC e RT-PCR e avaliados.*

RESULTADOS: *Considerando todos os pacientes, não foram encontrados achados específicos nos valores hematológicos e bioquímicos dos pacientes em análises laboratoriais. Embora todos os resultados tenham permanecido dentro do intervalo de referência, houve uma diferença significativa nos valores de glóbulos brancos, neutrófilos, plaquetas e linfócitos quando os grupos foram comparados [p = 0,000; p = 0,004; p = 0,022; p = 0,023].*

CONCLUSÃO: *O laboratório não é suficientemente específico no pré-diagnóstico. Além disso, este resultado não se altera com a positividade para PCR ou CT. No entanto, alterações mínimas observadas nos resultados laboratoriais podem ser parcialmente norteadoras em pacientes com PCR e CT positivos.*

PALAVRAS-CHAVE: *Infecções por Coronavirus/diagnóstico. Testes Laboratoriais. Diagnóstico por Imagem. Tomografia Computadorizada por Raios X. Serviço Hospitalar de Emergência.*

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
2. World Health Organization. Coronavirus disease (COVID-2019) situation reports [Internet]. Situation report - 91. Geneva: World Health Organization; 2020. [cited 2020 April 20]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
3. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
4. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al; Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19). Electronic address: https://www.lancovid.org. Clinical, laboratory and ımaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.
5. Sah R, Rodriguez-Morales AJ, Jha R, Chu DKW, Gu H, Peiris M, et al. Complete genome sequence of a 2019 novel coronavirus (SARS-CoV-2) strain ısolated in Nepal. Microbiol Resour Announc. 2020;9(11):e00169-20.
6. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020;200642.
7. Adhikari SP, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty. 2020;9(1):29. doi: 10.1186/s40249-020-00646-x.
8. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020;87(4):281-6.
9. Zhang G, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. Respir Res. 2020;21(1):74.
10. COVID-19 Guide to Public Health in Turkey [Internet]. [cited 2020 April 14]. Available from: https://COVID-19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf
11. Li G, Clercq ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020;19(3):149-50.
12. Wu Z, McGoogan JM. Characteristics of and ımportant lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020. doi: 10.1001/jama.2020.2648.
13. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): early report from the United States. Diagnosis (Berl). 2020;7(2):91-6.
14. Nikpouraghdam M, Jalali Farahani A, Alishiri G, Heydari S, Ebrahimnia M, Samadinia H, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in Iran: a single center study. J Clin Virol. 2020;127:104378.
15. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.
16. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol. 2019;56(3):308-21.
17. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical ındexes from 2019-nCoV ınfected patients linked to viral loads and lung ınjury. Sci China Life Sci. 2020;63(3):364-74.
18. Leung WK, To KF, Chan PKS, Chan HLY, Wu AKL, Lee N, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus ınfection. Gastroenterology. 2003;125(4):1011-7.
19. Peiris JSM, Chu CM, Cheng VCC, Chan KS, Hung IFN, Poon LLM, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet. 2003;361(9371):1767-72.
20. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DAT, et al; KSA MERS-CoV Investigation Team. Hospital outbreak of middle east respiratory syndrome coronavirus. N Engl J Med. 2013;369(5):407-16.
21. Patel A, Jernigan DB, 2019-nCoV CDC Response Team. Initial public health response and ınterim clinical guidance for the 2019 novel coronavirus outbreak — United States, December 31, 2019–February 4, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(5):140-6.
22. Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-Ncov): a study of 63 patients in Wuhan, China. Eur Radiol. 2020;30(6):3306-9.
23. Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus disease 2019 (COVID-19) CT findings: a systematic review and meta-analysis. J Am Coll Radiol. 2020;17(6):701-9.
24. Sjödin H, Wilder-Smith A, Osman S, Farooq Z, Rocklöv J. Only strict quarantine measures can curb the coronavirus disease (COVID-19) outbreak in Italy, 2020. Euro Surveill. 2020;25(13):2000280.
25. Liu KC, Xu P, Lv WF, Qiu XH, Yao JL, Gu JF, et al. CT manifestations of coronavirus disease-2019: a retrospective analysis of 73 cases by disease severity. Eur J Radiol. 2020;126:108941.

ORIGINAL ARTICLE

The effects of favipiravir on hematological parameters of covid-19 patients

Selçuk Yaylaci[1]
Hamad Dheir[1]
Didar Şenocak[1]
Ahmed Bilal Genc[1]
Havva Kocayigit[2]
Deniz Çekiç[1]
Ceyhun Varım[1]
Abdülkadir Aydın[3]
Mehmet Koroglu[4]
Oğuz Karabay[5]

1. Sakarya University Faculty of Medicine, Department of Internal Medicine, Sakarya,Turkey
2. Sakarya University Education and Research Hospital, Department of Intensive Care, Sakarya,Turkey
3. Sakarya University Education and Research Hospital, Department of Family Medicine, Sakarya,Turkey
4. Sakarya University Faculty of Medicine Department Medical Microbiology, Sakarya,Turkey
5. Sakarya University Faculty of Medicine Department of Infectious Diseases, Sakarya,Turkey

http://dx.doi.org/10.1590/1806-9282.66.S2.65

SUMMARY

INTRODUCTION: *This study aims to evaluate changes in hematological parameters after the follow-up of patients who received treatment with favipiravir due to COVID-19 infections.*

METHODS: *Sixty-two cases receiving favipiravir treatment for at least five days due to COVID-19 infection were evaluated retrospectively. Parameters including age, gender, nasopharyngeal swab positivity, and chronic diseases were analyzed. Hematologic parameters were analyzed before and after the treatment.*

RESULTS: *The mean age of the patients receiving treatment with favipiravir was 63.7±12.3 years. Nasopharyngeal swab positivity was detected in 67.7%. The most common comorbid conditions detected in patients were hypertension in 25 cases (40.3%) and diabetes in 16 cases (25.8%). In the statistical analysis of the hematological parameters before and after treatment with favipiravir, WBC, PT-PTT-INR levels were found to be unaffected; the mean RBC was found to have decreased from 4.33 ± 0.58 M/uL to 4.16 ± 0.54 M/uL (p:0.003); the median hemoglobin level was found to have decreased from 12.3 g/dl to 11.9 g/dl (p:0.041); the hematocrit level decreased from 38.1% ± 4.8 to 36.9% ± 4.2 (p:0.026); the median neutrophil count decreased from 4.57 K/uL to 3.85 K/uL (p:0.001); the mean lymphocyte count increased from 1.22 ± 0.53 K/uL to 1.84 ± 1.19 K/uL (p:0.000); and the mean platelet count increased from 244.1 ± 85.1 K/uL to 281.9 ± 103.3 K/uL (p:0.005).*

CONCLUSION: *We concluded that the pathological effect of treatment with favipiravir on the hematologic system was the suppression in the erythrocyte series, and there were no adverse effects in other hematologic parameters.*

KEYWORDS: *Coronavirus Infections. Antiviral Agents. Blood. Blood Cells. Favipiravir.*

DATE OF SUBMISSION: 03-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Selcuk Yaylacı
Sakarya University Faculty of Medicine Department of Internal Medicine
Email: yaylacis@hotmail.com

INTRODUCTION

Sars-Corona Virus 2, (COVID-19) is a coronavirus that first appeared in China in December 2019, causing severe acute respiratory failure[1,2]. It has infected more than five million people as of May 2020. Worldwide, hydroxychloroquine, favipiravir, lopinavir, remidesivir, tocilizumab, and anakinra are the main drugs used for the treatment of COVID-19. Favipiravir is an antiviral drug developed against many RNA viruses (influenza, West Nile, yellow fever, flaviviruses, arenaviruses, bunyaviruses, and alphaviruses), acting by inhibiting RNA-dependent RNA polymerase[3,4]. Yet, in 2020, China reported that Favipiravir is effective against COVID-19[5].

Drugs can cause abnormalities in the hematopoietic system by affecting the leukocyte series, erythrocyte series, platelets, and the entire clotting system through various mechanisms[6]. We have relatively little clinical experience with favipiravir in this regard. Physicians should be aware of the potential hematologic complications due to the drugs used during the pandemic period. In animal studies related to treatment with favipiravir, its effect on various hematological parameters was studied[7-9]. In the literature, there was no study published in English about the effect of favipiravir on the hematological system in humans.

In this study, we aimed to retrospectively investigate the hematological parameters of patients receiving Favipiravir therapy, before and after the treatment.

METHODS

Sixty-two cases receiving favipiravir treatment for at least five days between March 25, 2020, and May 5, 2020, due to COVID-19 infections were evaluated retrospectively. Age, gender, nasopharyngeal swab positivity, findings from computerized tomography (CT) of the thorax, chronic diseases, intensive care unit or service admission, and other demographic parameters of the patients were analyzed. Patients with hematological coagulation and hematologic parameters, such as white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Htc), neutrophil, lymphocyte, platelet, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) before and after treatment, and those with an oncological disease, with a history of chemotherapy, receiving warfarin therapy or receiving medications simultaneously to favipiravir, or known to have hematologic side effects were excluded from the study.

Hemogram measurement

Hematologic analysis of the patients was performed by taking 24 parameters from the Cell Dyn 3700 brand hemogram device (Abbott, USA). Two-ml blood samples were taken from each patient via venipuncture and delivered to the laboratory for study within 2 hours.

Sample collection and Nükleic Acid Isolation And Reverse Transcription Polymerase Chain Reaction (RT-PCR) Study

Bio-Speedy® Viral Nucleic Acid Isolation Kit (Bioeksen, Turkey) was used for total nucleic acid isolation from the specimens. 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.

Ethics: An ethics committee approval from Sakarya University Medical Faculty was provided for this study.

Statistical Analysis: Quantitative data were expressed as mean values ± SD, medians, and ranges. Qualitative data were expressed as numbers and percentages. The assumption of normality was tested by the Kolmogorov-Smirnov test. Paired Samples T-test and Wilcoxon Signed Rank tests were used when appropriate. A p-value of less than 0.05 was considered statistically significant. Analyses were performed by using Statistical Package for the Social Sciences version 20.0 (IBM SPSS Statistics; Armonk, NY, USA).

RESULTS

The mean age of the patients receiving favipiravir due to COVID-19 infections was 63.7±12.3 years, and 36 (58.1%) were male. Forty-five (72.6%) patients with mild or moderate illness were followed-up in the ward, while 17 (27.4%) patients with severe illness were followed-up in the intensive care unit. COVID-19 RNA test was positive in a nasopharyngeal swab test in 42 (67.7%) patients. The most common comorbid conditions found in patients were hypertension in 25 (40.3%), diabetes mellitus in 16 (25.8%), and smoking history in 8 (12.9%) patients. Thorax CT findings were detected in 58 patients as bilateral and in 4 as unilateral involvement (Table 1, Figure 1).

In the statistical analysis of hematological

parameters before and after favipiravir, WBC, prothrombin time, activated partial thromboplastin time, and international normalized ratio (PT-PTT-INR) levels were found to be unaffected (p=0.141, 0.503, 0.111, 0.245, respectively); while the mean RBC was found to be decreased from 4.33 ± 0.58 M/uL to 4.16 ± 0.54 M/uL (p=0.003); the median Hb level was found to be decreased from 12.3 g/dl to 11.9 g/dl (p=0.041); Htc level was decreased from 38.1% ± 4.8 to 36.9% ± 4.2 (p=0.026); the median neutrophil count was decreased from 4.57 K/uL to 3.85 K/uL (p=0.001); the mean lymphocyte count was found to be increased from 1.22 ± 0.53 K/uL to 1.84 ± 1.19 K/uL (p=0.000); the mean platelet count was found to be increased from 244.1 ± 85.1 K/uL to 281.9 ± 103.3 K/uL (p=0.005) statistically (Table 2, Figure 2).

TABLE 1. THE BASELINE CHARACTERISTICS OF PATIENTS WHO USED FAVIPIRAVIR

Parameters	Value
Age (Years) mean values ± SD (min.-med.-max.)	63.7±12.3 (37.0 – 64.0 – 89.0)
Sex (F/M) (%)	26/36 (41.9/58.1)
Nasopharyngeal swab positivity (-/+) (%)	20/42 (32.3/67.7)
Number of intensive care unit patients	17 (%27.4)
Thorax CT Findings (bilateral-unilateral infiltration)	58 (%93.5)/ 4 (%6.5)
Comorbid Condition Smoking Hypertension Diabetes Mellitus Heart disease COPD Asthma	Frequency (%) 8 (12.9) 25 (40.3) 16 (25.8) 4 (6.5) 2 (3.2) 4 (6.5)

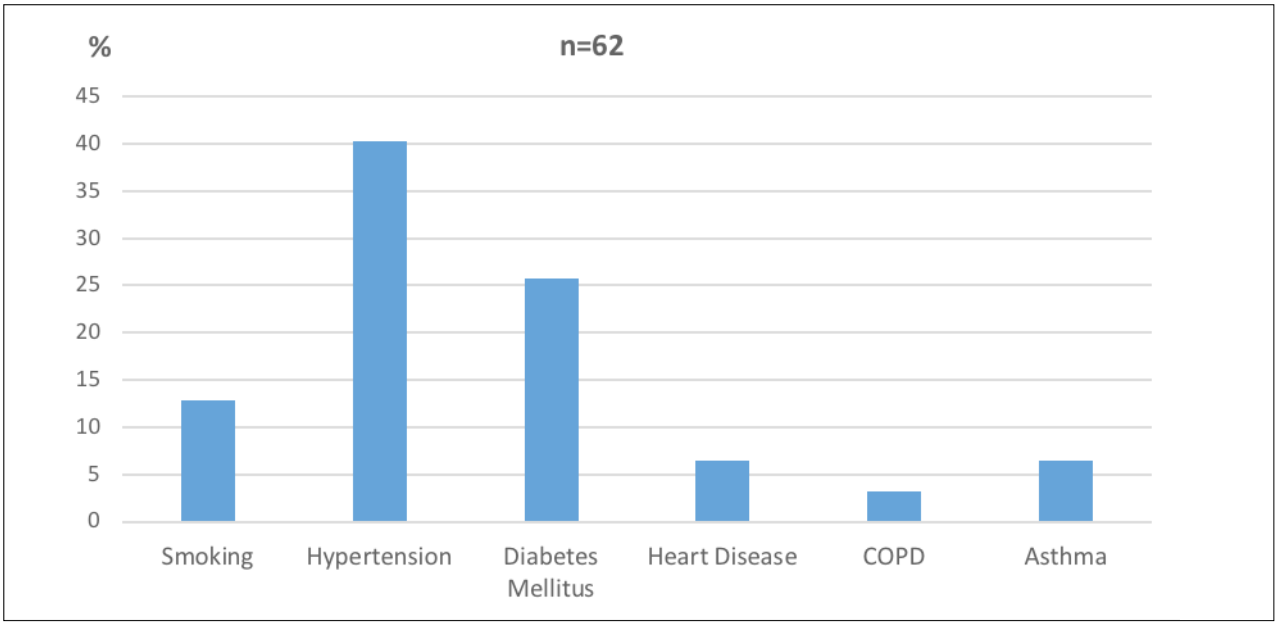
COPD: Chronic obstructive pulmonary disease

TABLE 2. COMPARISON OF THE HEMATOLOGICAL PARAMETERS OF PATIENTS BEFORE AND AFTER FAVIPIRAVIR TREATMENT

Parameters	Before favipiravir treatment mean ± SD(min.-med.-max.)	After favipiravir treatment mean ± SD (min.-med.-max.)	p
WBC (K/uL)	7.13 ± 3.27 (1.97 – 6.58 – 20.50)	6.59 ± 2.52 (0.67 – 6.58 – 20.50)	0.141*
RBC (M/uL)	4.33 ± 0.58 (3.01 – 4.34 – 5.48)	4.16 ± 0.54 (3.24 – 4.12 – 5.82)	0.003*
Hb (g/dl)	12.1 ± 1.6 (9.0 – 12.3 – 15.6)	11.8 ± 1.3 (9.2 – 11.9 – 14.5)	0.041**
Htc (%)	38.1 ± 4.8 (28.1 – 38.3 – 48.3)	36.9 ± 4.2 (28.1 – 37.0 – 46.1)	0.026*
Leu (K/uL)	1.22 ± 0.53 (0.35 – 1.23 – 3.05)	1.84 ± 1.19 (0.26 – 1.62 – 8.20)	0.000*
Neu (K/uL)	5.28 ± 2.98 (1.10 – 4.57 – 17.70)	4.21 ± 1.85 (1.62 – 3.85 – 10.10)	0.001**
Plt (K/uL)	244.1 ± 85.1 (81.0 – 230.0 – 460.0)	281.9 ± 103.3 (41.9 – 276.0 – 580.0)	0.005*
PT (sekond)	12.9 ± 1.3 (10.1 – 12.8 – 17.3)	12.9 ± 2.2 (10.3 – 12.5 – 25.8)	0.503**
PTT (sekond)	24.9 ± 2.7 (20.8 – 24.5 – 33.5)	25.9 ± 3.8 (18.7 – 25.3 – 41.6)	0.111*
INR	1.16 ± 0.15 (0.50 – 1.17 – 1.59)	1.15 ± 0.14 (0.70 – 1.14 – 1.61)	0.245**

* Paired Samples T-Test was used.** Wilcoxon Signed Rank Test was used.
White Cell Count (WBC): NV: 4.6-10.2 (K/uL), Lymphocyte Count (Leu): NV: 0.6-3.4 (K/uL), Platelet Count (Plt): NV: 142-424 (K/uL), Neutrophil Count (Neu): 2-6.9 (K/uL), Red Blood Cell ount (RBC): NV: 4-6.1 (M/uL), Hemoglobin (Hb): NV: 12.2-18.1 (g/dl), Hematocrit (Htc): NV: 37.7-53.7 (%), Prothrombin time (PT): NV: 7-12.9 (sekond), Activated Partial Thromboplastin Time (aPTT): NV: 18.5-33.5 (sekond), International Normalized Ratio (INR): NV: 0.8-1.3

FIGURE 1. COMORBID CONDITIONS OF PATIENTS WHO USED FAVIPIRAVIR



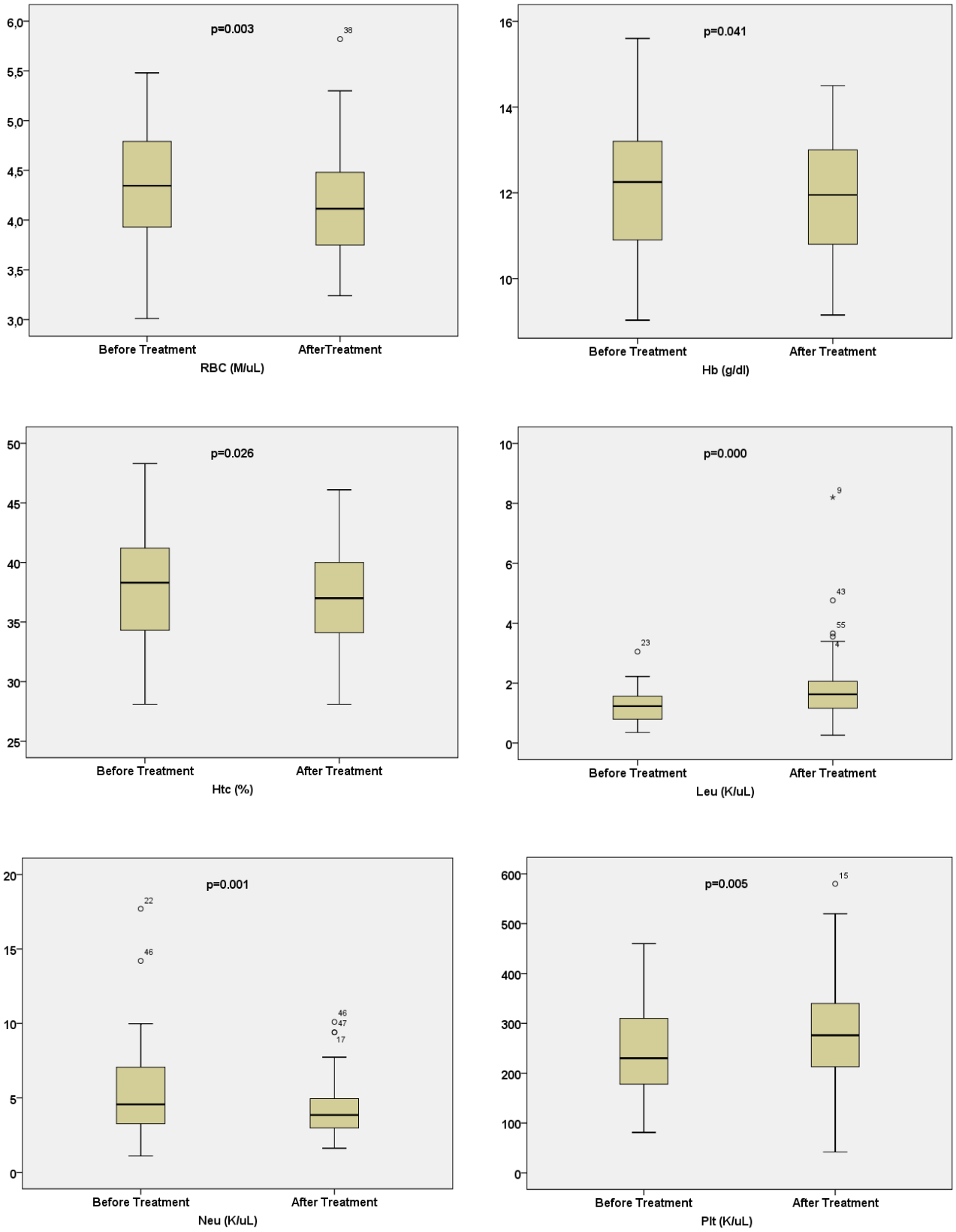


FIGURE 2. COMPARISON OF THE STATISTICALLY SIGNIFICANT HEMATOLOGICAL PARAMETERS OF THE PATIENTS BEFORE AND AFTER FAVIPIRAVIR TREATMENT

DISCUSSION

COVID-19 has caused a significant outbreak throughout the world and has challenged health care systems. Many pharmacological agents are used in its treatment, one of which is favipiravir[5]. Favipiravir was originally developed for influenza treatment, acting as a chain terminator at the point of binding of the viral RNA and reducing the viral load[4]. In addition to influenza, favipiravir has a wide spectrum of in-vitro anti-RNA virus activity and activities in deadly RNA viruses[4,5,10].

Hematologic system side effects associated with various antivirals have been reported in the literature[6]. For instance, one study found that anemia was significantly reduced after antiretroviral treatment, without any significant changes in other elements of the series[11]. In a different article, ribavirin, which is used together with peginterferon for the treatment of hepatitis C, was associated with anemia[12]. In another work, pure red cell aplasia was reported due to lamivudine used for human immunodeficiency virus (HIV) treatment and ribavirin used for hepatitis C treatment[13,14]. Another case report discusses thrombocytopenia development due to antiviral treatments for hepatitis C (daclatasvir and asunaprevir)[15].

Adverse effects on hematopoietic tissues such as elongation in PT, decreased myelopoiesis, decrease in erythrocyte series (RBC, Hb, Htc), and decrease in lymphocytes have been reported in toxicity studies conducted with animal experiments after oral favipiravir administration[16]. In another study, thrombocytopenia and coagulation parameters were found to be increased, although not significantly, as hematologic side effects[7,9]. In one mice study, there were no significant statistical differences in favipiravir hemogram parameters compared to the control group; but a decrease in the lymphocyte count and an increase in the neutrophil count were found in infected mice, compared to non-infected ones[8]. In another study, favipiravir was shown to prevent leukopenia and thrombocytopenia developed due to severe infection[17].

There were no studies in the literature investigating hematological parameters related to favipiravir treatment in humans. According to the literature data, lymphocyte and platelet levels in severe COVID-19 infections are lower than in mild COVID-19 infections and are indicated as a severity criterion for the disease[18,19]. Also, thrombocytopenia was shown to be associated with mortality in COVID-19 patients[20]. The results of our study showed that WBC, PT, PTT, and INR levels were unchanged after favipiravir use, RBC, Hb, htc, and neutrophil levels were decreased significantly ($P<0.05$), while lymphocyte and platelet levels were increased significantly ($P<0.05$). Considering the tendency of increase of platelet and lymphocyte levels after favipiravir treatment, as detected in our results, and since those parameters were shown to be severity criteria and mortality indicators in the literature, it can be stated that treatment with favipiravir has a positive effect on the hematologic parameters in COVID-19 patients.

According to our findings, suppression of the erythrocyte series was observed in the bone marrow with the use of favipiravir. Therefore, regular hemogram follow-up is required in patients using this medication. However, the positive effect of favipiravir on lymphocytes, neutrophils, and platelets should not be ignored.

LIMITATIONS: The low number of cases included in the study, its single-centered nature, and the short follow-up period can be considered limitations.

CONCLUSION

Favipiravir therapy used in the treatment of COVID-19 showed suppression of the erythrocyte series and a tendency to increase platelets. A therapeutic effect was observed on thrombocytopenia and lymphopenia, which are considered severity criteria and mortality predictor factors for this disease. Also, due to the limited information about treatment with favipiravir in COVID-19 patients, we believe that our findings will contribute significantly to the literature.

Author's Contribution

The authors contributed equally to the work.

RESUMO

INTRODUÇÃO: *Este estudo tem como objetivo avaliar as alterações nos parâmetros hematológicos após o acompanhamento de pacientes que receberam tratamento com favipiravir devido à infecção por Covid-19.*

MÉTODOS: *Sessenta e dois casos em tratamento com favipiravir por pelo menos cinco dias devido à infecção por Covid-19 foram avaliados retrospectivamente. Parâmetros como idade, sexo, positividade do swab nasofaríngeo e doenças crônicas foram analisados. Os parâmetros hematológicos foram analisados antes e após o tratamento.*

RESULTADOS: *A idade média dos pacientes que receberam tratamento com favipiravir foi de 63,7±12,3 anos. A positividade do swab nasofaríngeo foi detectada em 67,7%. As condições comórbidas mais comuns detectadas nos pacientes foram hipertensão em 25 casos (40,3%) e diabetes em 16 casos (25,8%). Na análise estatística dos parâmetros hematológicos antes e após o tratamento com favipiravir, os níveis de leucócitos, PT-PTT-INR não foram afetados. Verificou-se que o RBC médio diminuiu de 4,33±0,58 M/uL para 4,16±0,54 M/uL (p=0,003); o nível médio de hemoglobina foi reduzido de 12,3 g/dl para 11,9 g/dl (p=0,041); o nível de hematócrito diminuiu de 38,1%±4,8 para 36,9%±4,2 (p=0,026); a contagem mediana de neutrófilos diminuiu de 4,57 K/uL para 3,85 K/uL (p=0,001); a contagem média de linfócitos aumentou de 1,22±0,53 K/uL para 1,84±1,19 K/uL (p=0,000); a contagem média de plaquetas aumentou de 244,1±85,1 K/uL para 281,9±103,3 K/uL (p=0,005).*

CONCLUSÃO: *Concluiu-se que o efeito patológico do tratamento com favipiravir no sistema hematológico foi a supressão na série eritrocitária e que não houve efeitos adversos em outros parâmetros hematológicos.*

PALAVRAS-CHAVE: *Infecções por coronavírus. Antivirais. Sangue. Células sanguíneas. Favipiravir.*

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
3. Furuta Y, Takahashi K, Shiraki K, Sakamoto K, Smee DF, Barnard DL, et al. T-705 (Favipiravir) and related compounds: novel broad-spectrum inhibitors of RNA viral infections. Antiviral Res. 2009;82(3):95-102.
4. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther. 2020;209:107512.
5. Wu R, Wang L, Kuo H-CD, Shannar A, Peter R, Chou PJ, et al. An update on current therapeutic drugs treating COVID-19. Curr Pharmacol Rep. 2020;1-15.
6. Mintzer DM, Billet SN, Chmielewski L. Drug-induced hematologic syndromes. Adv Hematol. 2009;2009:495863.
7. Bixler SL, Bocan TM, Wells J, Wetzel KS, Van Tongeren SA, Dong L, et al. Efficacy of Favipiravir (T-705) in nonhuman primates infected with Ebola virus or Marburg virus. Antiviral Research. 2018;151:97-104.
8. Zhu W, Zhang Z, He S, Wong G, Banadyga L, Qiu X. Successful treatment of Marburg virus with orally administrated T-705 (Favipiravir) in a mouse model. Antiviral Res. 2018;151:39-49.
9. Rosenke K, Feldmann H, Westover JB, Hanley PW, Martellaro C, Feldmann F, et al. Use of Favipiravir to treat lassa virus infection in macaques. Emerg Infect Dis. 2018;24(9):1696-9.
10. Pilkington V, Pepperrell T, Hill A. A review of the safety of Favipiravir: a potential treatment in the COVID-19 pandemic? J Virus Erad. 2020;6(2):45-51.
11. Geletaw T, Tadesse MZ, Demisse AG. Hematologic abnormalities and associated factors among HIV infected children pre- and post-antiretroviral treatment, North West Ethiopia. J Blood Med. 2017;8:99-105.
12. McHutchison JG, Manns MP, Brown RS Jr, Reddy KR, Shiffman ML, Wong JB. Strategies for managing anemia in hepatitis C patients undergoing antiviral therapy. Am J Gastroenterol. 2007;102(4):880-9.
13. John MA, Rhemtula YA, Menezes CN, Grobusch MP. Lamivudine-induced red cell aplasia. J Med Microbiol. 2008;57(Pt 8):1032-5.
14. Tanaka N, Ishida F, Tanaka E. Ribavirin-induced pure red-cell aplasia during treatment of chronic hepatitis C. N Engl J Med. 2004;350(12):1264-5.
15. Arai K, Kuramitsu K, Fukumoto T, Kido M, Takebe A, Tanaka M, et al. A case report of drug-induced thrombocytopenia after living donor liver transplantation. Kobe J Med Sci. 2016;62(1):E9-12.
16. Japan. Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare. Report on the deliberation results. [cited 2020 May 19]. Available from: https://www.pmda.go.jp/files/000210319.pdf
17. Gowen BB, Juelich TL, Sefing EJ, Brasel T, Smith JK, Zhang L, et al. Favipiravir (T-705) inhibits Junin virus infection and reduces mortality in a guinea pig model of Argentine hemorrhagic fever. PLoS Negl Trop Dis. 2013;7(12):e2614.
18. Yang X, Yu Y, Xu J, Shu H, Xia J'an, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.
19. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19: a systematic review. Life Sci. 2020;254:117788.
20. Liu Y, Sun W, Guo Y, Chen L, Zhang L, Zhao S, et al. Association between platelet parameters and mortality in coronavirus disease 2019: retrospective cohort study. Platelets. 2020;31(4):490-6.

ORIGINAL ARTICLE

Impact of antihypertensive agents on clinical course and in-hospital mortality: analysis of 169 hypertensive patients hospitalized for COVID-19

Ibrahim Kocayigit[1]
Havva Kocayigit[2]
Selcuk Yaylaci[3]
Yusuf Can[4]
Ali Fuat Erdem[5]
Oguz Karabay[6]

1. Assistant Professor, University of Sakarya, Department of Cardiology, Sakarya, Turkey.
2. Sakarya University Education and Research Hospital, Department of Anesthesiology, Sakarya, Turkey.
3. Associate Professor, University of Sakarya, Department of Internal Medicine, Sakarya, Turkey.
4. University of Sakarya, Department of Cardiology, Sakarya, Turkey.
5. Professor, University of Sakarya, Department of Anesthesiology, Sakarya, Turkey.
6. Professor, University of Sakarya, Department of Infectious Diseases, Sakarya, Turkey.

http://dx.doi.org/10.1590/1806-9282.66.S2.71

SUMMARY

OBJECTIVE: *Coronavirus disease 2019 (COVID-19) is an emerging health threat caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Previous studies have noted hypertension is associated with increased mortality due to COVID-19; however, it is not clear whether the increased risk is due to hypertension itself or antihypertensive agents. We aimed to evaluate the impact of antihypertensive agents on the clinical outcomes of hypertensive patients with COVID-19.*

METHODS: *Our study included 169 consecutive hypertensive patients hospitalized due to COVID-19 between March 20 and April 10, 2020. The demographic characteristics, clinical data, and type of antihypertensive agents being used were reviewed.*

RESULTS: *The mean age of patients was 65.8±11.7 years.30 patients(17.7%) died during hospitalization. A total of 142 patients(84%) were using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), 91 (53.8%) were using diuretics, 69 (40.8%) were using calcium channel blockers (CCBs), 66 (39.1%) were using beta-blockers, 12 (7.1%) were using alpha-blockers, and 5 (2.9%) were using mineralocorticoid receptor antagonists (MRAs). There was no significant difference between survivors and non-survivors based on the type of antihypertensive agents being used. Binary logistic regression analysis showed that the type of the antihypertensive agent being used had no effect on mortality [OR=0.527 (0.130-2.138), p=0.370 for ACEIs/ARBs; OR=0.731 (0.296-1.808), p=0.498 for CCBs; OR=0.673 (0.254-1.782), p=0.425 for diuretics; OR=1.846 (0.688-4.950), p=0.223 for beta-blockers; OR=0.389 (0.089-1.695), p=0.208 for alpha-blockers; and OR=1.372 (0.107-17.639), p=0.808 for MRAs].*

CONCLUSION: *The type of antihypertensive agent being used had no effect on the clinical course and mortality in hypertensive patients with COVID-19. The use of these agents should be maintained for the treatment of hypertension during hospitalization.*

KEYWORDS: *Coronavirus Infections. Antihypertensive Agents. Hypertension. Hospital Mortality.*

DATE OF SUBMISSION: 02-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Ibrahim Kocayigit
Sakarya Education and Research Hospital, Department of Cardiology, Adnan Menderes Caddesi Saglik Sokak, Sakarya, Turkey – 54100
E-mail: ikocayigit@gmail.com

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging health threat caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Previous studies have noted that hypertension is associated with an increased risk of mortality due to COVID-19; however, it is not clear whether the increased risk is due to hypertension itself or the antihypertensive agents being used[1]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are the most important and widely used antihypertensive agents, they act by inhibiting the renin-angiotensin-aldosteron system (RAAS). It is known that coronavirus binds to the angiotensin-converting enzyme-2 (ACE-2) receptor, and there are controversial results in terms of the effects of ACEIs on the course of the disease[2-4]. However, the effect of other types of antihypertensive agents on this disease has not been elucidated yet. In our study, we aimed to investigate the association of antihypertensive agents and clinical outcomes of patients with hypertension and COVID-19.

METHODS

Our present study included 169 consecutive patients with a history of hypertension whose laboratory results confirmed COVID-19 and who were hospitalized in the Sakarya Education and Research Hospital between March 20 and April 10, 2020. All patients were diagnosed with COVID-19 according to World Health Organization interim guidance[5]. The demographic characteristics, clinical data, and type of antihypertensive agents used were recorded. We excluded patients under 18 years old and hypertensive patients without any medication. The ethics approval was obtained from the local ethics committee. Only cases confirmed by laboratory tests were considered positive based on a real-time reverse transcriptase-polymerase chain reaction assay of a specimen obtained from a naso- or oropharyngeal swab and were included in this study. To identify SARS-COV-2 infection, swab specimens were collected from all patients at admission and during hospitalization. The antihypertensive agents used by patients were continued during hospitalization unless contraindicated. Patients with respiratory distress (>30 breaths/min), oxygen saturation <90 at rest, under nasal oxygenation with 5-6 liters/min, arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) <300 mmHg were admitted to intensive care unit (ICU).

Statistical analysis

Descriptive analyses of the variables were expressed as mean±SD in normal distributions, and parameters with abnormal distribution were expressed as medians of the 25th–75th percentile. Categorical data were expressed as proportions. The chi-square and the Student's t-test were used for categorical and continuous variables, respectively. Fisher's exact test was applied to analyze small samples. For continuous variables, differences between the two groups were evaluated using the Student's t-test when data were normally distributed and the Mann–Whitney U test when the assumption of normality was not met. Binary logistic regression analysis was performed to determine independent factors associated with mortality. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using statistical software (SPSS 20.0, Chicago, IL, USA).

RESULTS

535 adult patients were hospitalized in the Sakarya University Education and Research Hospital with COVID-19 between March 20 and April 10, 2020. From these, we included 169 patients with a history of hypertension. The mean age of the patients was 65.8±11.7 years (range 37-96), and 90 of the patients were female (53.3%). 30 patients (17.7%) died during hospitalization and 45 (26.6%) required ICU intervention. 139 patients were discharged from hospital uneventfully. 59 of the patients (34.9%) had coexisting diabetes mellitus, 28 (16.6%) had hyperlipidemia, 25 (14.8%) had coronary artery disease, 18 (10.7%) had chronic obstructive pulmonary disease, 9 (5.3%) had cerebrovascular disease, 8 (4.7%) had chronic renal disease, 6 (3.6%) had congestive heart failure, 5 (2.9%) had malignities and 2 (1.2%) had peripheral artery disease. 142 of the patients (84%) were using ACEIs or ARBs, 91 (53.8%) were using diuretics, 69 (40.8%) were using calcium channel blockers (CCBs), 66 (39.1%) were using beta-blockers, 12 (7.1%) were using alpha-blockers and 5 (2.9%) were using mineralocorticoid receptor antagonists (MRAs) for the treatment of hypertension. The majority of the patients (131 [77.5%]) were using a combination of two or more antihypertensive agents (table 1). When we compared the type of antihypertensive agents being used between surviving

and non-surviving patients, there was no difference between the groups (Table 1). We also compared the type of antihypertensive agents between the patients with or without ICU requirement, there was no significant difference between the groups (Table 2). Binary logistic regression analysis was performed to identify independent factors associated with mortality due to COVID-19 in hypertensive patients. Age, gender, diabetes mellitus, coronary artery disease, chronic pulmonary disease, hyperlipidemia, and the type of antihypertensive agents being used were included in the equation. Age was found to be the only predictor for mortality (odds ratio=1.089, 95% confidence interval=1.038-1.142, p<0.001). The type of antihypertensive agent used had no effect on mortality [OR=0.527 (0.130-2.138), p=0.370 for ACEIs/ARBs; OR=0.731 (0.296-1.808), p=0.498 for CCBs; OR=0.673 (0.254-1.782), p=0.425 for diuretics; OR=1.846 (0.688-4.950), p=0.223 for beta-blockers; OR=0.389 (0.089-1.695), p=0.208 for alpha-blockers; and OR=1.372 (0.107-17.639), p=0.808 for MRAs] (Table 3).

DISCUSSION

Hypertension is one of the most frequent comorbidities among patients hospitalized for COVID-19[6,7]. Several vascular abnormalities including widespread microthrombotic and macrothrombotic events were frequently observed in critically ill patients with COVID-19. Potential microvascular complications caused by chronic hypertension may predispose these vascular events and worsen the prognosis and outcomes of the disease. Recent studies have claimed that hypertension is a clinically important risk factor for severe illness and mortality in COVID-19, but it is difficult to state that[1,6]. It is not clear whether the increased risk is due to hypertension itself or antihypertensive agents used. Although there are conflicting results with ACEIs and ARBs, other antihypertensive agents have not been fully evaluated for the treatment of hypertensive patients with COVID-19[8-10].

The prevalence of hypertension in Turkey is approximately 27.5%[11]. In our study, the incidence of hypertension was 29.9% in hospitalized patients due to COVID-19. Recent reports showed that hypertension is associated with poor outcomes in patients with COVID-19; however, it was also reported that hypertension was not more common in those than in the general population[7,12]. These reports do not reveal the mechanism of this increased risk, i.e., whether it is due to hypertension itself or the antihypertensive agent used. SARS-COV-2 binds to their target cells through ACE-2, which is expressed by epithelial cells of the lung, kidney, intestine, and vessels[13].

TABLE 1. DEMOGRAPHIC AND CLINICAL FEATURES OF HYPERTENSIVE PATIENTS WITH COVID-19.

Study population	All patients (n=169)	Non-survivors (n=30)	Survivors (n=139)	p
Age (mean±SD)	65.8±11.7	73.2±10.5	64.2±11.4	<0.001
Female gender (n, %)	90 (53.3)	15 (50)	75 (54)	0.694
Comorbidities				
Diabetes mellitus (n, %)	59 (34.9)	13 (43.3)	46 (33.1)	0.286
Hyperlipidemia (n, %)	28 (16.6)	7 (23.3)	21 (15.1)	0.272
Coronary artery disease (n, %)	25 (14.8)	8 (26.7)	17 (12.2)	0.043
Chronic pulmonary disease (n, %)	18 (10.7)	4 (13.3)	14 (10.1)	0.599
Cerebrovascular disease (n, %)	9 (5.3)	3 (10)	6 (4.3)	0.209
Chronic renal disease (n, %)	8 (4.7)	3 (10)	5 (3.6)	0.151
Congestive heart failure (n, %)	6 (3.6)	2 (6.7)	4 (2.9)	0.309
Malignities (n, %)	5 (2.9)	3 (10)	2 (1.4)	0.040
Peripheral artery disease (n, %)	2 (1.2)	2 (6.7)	0 (0)	0.031
Antihypertensive agents				
ACEIs/ARBs (n, %)	142 (84)	26 (86.7)	116 (83.5)	0.663
CCBs (n, %)	69 (40.8)	14 (46.7)	55 (39.6)	0.473
Diuretics (n, %)	91 (53.8)	19 (63.3)	72 (51.8)	0.250
Beta blockers (n, %)	66 (39.1)	9 (30)	57 (41)	0.262
Alpha blockers (n, %)	12 (7.1)	4 (13.3)	8 (5.8)	0.143
MRAs (n, %)	5 (2.9)	1 (3.3)	4 (2.9)	0.894
Combination therapy (n, %)	131 (77.5)	26 (86.7)	105 (75.5)	0.186

ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, CCBs: calcium channel blockers, MRAs: mineralocorticoid receptor antagonists.

TABLE 2. TYPE OF ANTIHYPERTENSIVE AGENTS USED IN PATIENTS WITH OR WITHOUT INTENSIVE CARE INTERVENTION.

	With ICU intervention (n=45)	No ICU intervention (n=124)	P
ACEIs/ARBs (n,%)	38 (84.4)	104 (83.9)	0.928
CCBs (n,%)	17 (37.8)	52 (41.9)	0.627
Diuretics (n,%)	26 (57.8)	65 (52.4)	0.537
Beta blockers (n,%)	15 (33.3)	51 (41.1)	0.359
Alpha blockers (n,%)	5 (11.1)	7 (5.6)	0.221
MRAs (n,%)	1 (2.2)	4 (3.2)	0.598
Combination therapy (n,%)	34 (75.6)	97 (78.2)	0.713

ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, CCBs: calcium channel blockers, MRAs: mineralocorticoid receptor antagonists.

TABLE 3. INDEPENDENT FACTORS ASSOCIATED WITH IN-HOSPITAL MORTALITY USING BINARY LOGISTIC REGRESSION ANALYSIS.

Variables	Exp (B) Odds ratio	95% confidence interval	P
Age, years	1.089	1.038-1.142	<0.001
Female gender	0.834	0.334-2.085	0.698
Diabetes mellitus	0.622	0.242-1.599	0.324
Coronary artery disease	0.581	0.173-1.954	0.380
Chronic pulmonary disease	1.045	0.274-3.990	0.948
Hyperlipidemia	0.525	0.154-1.785	0.302
ACEIs/ARBs	0.527	0.130-2.138	0.370
CCBs	0.731	0.296-1.808	0.498
Diuretics	0.673	0.254-1.782	0.425
Beta blockers	1.846	0.688-4.950	0.223
Alpha blockers	0.389	0.089-1.695	0.208
MRAs	1.372	0.107-17.639	0.808

ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, CCBs: calcium channel blockers, MRAs: mineralocorticoid receptor antagonists.

The expression of ACE-2 is substantially increased in patients treated with ACEIs and ARBs. The increased expression of ACE-2 may facilitate infection by COVID-19, therefore, it is hypothesized that hypertension treatment with ACE-2-stimulating drugs increases the risk of developing severe and fatal COVID-19[14]. On the contrary, Zhang et al.[4] showed that inpatient use of ACEIs orARBs was associated with a lower risk of all-cause mortality compared with ACEI or ARBs non-users among hospitalized COVID-19 patients with hypertension. It has been hypothesized that excessive activation of RAAS might contribute to the progression of acute respiratory distress syndrome (ARDS) in patients with COVID-19 by promoting increased inflammatory response and cytokine storm[15]. RAAS inhibition could mitigate this effect by interfering with the negative effects of angiotensin II on ACE-2 down-regulation in infected patients. RAAS inhibitors such as ACEIs or ARBs could have a favourable impact on clinical outcomes.

Solaimanzadeh[16] reported that dihydropyridine CCBs such as nifedipine and amlodipine is associated with significantly improved mortality in elderly patients hospitalized for COVID-19. They also revealed that CCBs are associated with a significantly decreased risk for intubation and mechanical ventilation[16]. Previous studies revealed that nifedipine and amlodipine were found to increase pulmonary vasodilatation without decreasing arterial oxygenation in the treatment of pulmonary hypertension[17,18]. Amlodipine was also found to be an effective pulmonary vasodilator agent in pulmonary hypertension secondary to chronic obstructive pulmonary disease[19]. Nifedipine was shown to reduce pulmonary vascular resistance and increase oxygen delivery both at rest and during exercise even in patients with normal pulmonary artery pressures[20]. Based on these results, they suggested that CCBs may be used as a first-line treatment in hospitalized patients with COVID-19.

Since all research on COVID-19 and antihypertensive treatment is especially focused on ACEIs and ARBs, there are not enough publications in the literature about other widely used antihypertensive agents such as beta-blockers, alpha-blockers, MRAs, and diuretics. In our study, we did not observe any effect of these antihypertensive agents on the clinical outcomes and in-hospital mortality.

Several reports revealed that ARDS in COVID-19 was associated with a strong interaction between SARS-CoV-2 and the ACE-2 receptor[21,22]. Therefore, an increase in expression of ACE-2 receptors attached to the lung endothelium could facilitate the entrance of SARS-CoV-2 into pulmonary cells and the progression of ARDS. Although attached ACE-2 may allow SARS-CoV-2 to enter cells, its free circulating forms may inactivate SARS-CoV-2 by stopping coupling to membrane ACE-2 receptors. Spironolactone, which is the main representative of mineralocorticoid receptor antagonists, has been reported to increase ACE-2 expression in plasma[23]. In contrast, it has been shown that ACEIs or ARBs have no effect on the plasma ACE-2 activity[24]. Additionally, spironolactone does not act in pulmonary RAAS, so it could reduce ACE-2 expression on lung-cell surfaces.

In conclusion, based on the results of this current study, the type of antihypertensive agent used had no effect on the clinical course and mortality of hypertensive patients with COVID-19. The use of these agents

should be maintained for the treatment of hypertension during hospitalization. Further larger studies are needed to examine the role of these agents and their influence on the course of COVID-19.

Our study has some limitations. Firstly, this study was conducted in a single center, the study sample-size was modest and included 169 hypertensive patients. Secondly, due to the retrospective nature of this study, some parameters were not available in all patients, such as smoking habits.

Author's Contribution

Ibrahim Kocayigit: Conceptualization, data curation, methodology, visualization, original draft, review & editing; Havva Kocayigit: Conceptualization, supervision, original draft, review & editing; Selcuk Yaylaci: Methodology, resources, visualization; Yusuf Can: Conceptualization, data curation, formal analysis; Ali Fuat Erdem: Visualization, original draft, review & editing; Oguz Karabay: Data curation, original draft, review & editing.

RESUMO

OBJETIVO: *A doença de coronavírus 2019 (COVID-19) é uma ameaça emergente à saúde causada por um novo coronavírus denominado síndrome respiratória aguda grave coronavírus 2 (Sars-COV-2). Estudos anteriores observaram que a hipertensão está associada a um aumento da mortalidade devido ao COVID-19, no entanto, não está claro se o aumento do risco pertence à própria hipertensão ou a agentes anti-hipertensivos. Nosso objetivo foi avaliar o impacto de agentes anti-hipertensivos nos resultados clínicos em pacientes hipertensos com COVID-19.*

MÉTODOS: *Nosso estudo incluiu 169 hipertensos consecutivos internados por COVID-19 entre 20 de março e 10 de abril de 2020. As características demográficas, dados clínicos e o tipo de anti-hipertensivos em uso foram revistos.*

RESULTADOS: *A idade média dos pacientes foi de 65,8±11,7 anos. Trinta pacientes (17,7%) faleceram durante a internação. Cento e quarenta e dois pacientes (84%) usavam inibidores da enzima de conversão da angiotensina (ACEIs) ou bloqueadores dos receptores da angiotensina II (ARBs), 91 (53,8%) usavam diuréticos, 69 (40,8%) usavam bloqueadores dos canais de cálcio (CCBs), 66 (39,1%) usavam betabloqueadores, 12 (7,1%) usavam bloqueadores alpha e cinco (2,9%) usavam antagonistas dos receptores de mineralocorticoides (MRAs). Não houve diferença significativa entre sobreviventes e não sobreviventes com base no tipo de agentes anti-hipertensivos em uso. A análise de regressão logística binária mostrou que o tipo de agente anti-hipertensivo utilizado não teve efeito na mortalidade (OR=0,527 (0,130-2,138), p=0,370 para ACEIs/ARB; OR=0,731 (0,296-1,808), p=0,498 para CCBs; OR=0,673 (0,254-1,782), p=0,425 para diuréticos; OR=1,846 (0,688-4,950), p=0,223 para bloqueadores beta; OR=0,389 (0,089-1,695), p=0,208 para bloqueadores alpha e OR=1,372 (0,107-17,639), p=0,808 para MRAs).*

CONCLUSÃO: *O tipo de agente anti-hipertensivo utilizado não teve efeito no curso clínico e na mortalidade em pacientes hipertensos com COVID-19. O uso desses agentes deve ser mantido no tratamento da hipertensão durante a hospitalização.*

PALAVRAS-CHAVE: *Infecções por coronavírus. Anti-hipertensivos. Hipertensão. Mortalidade hospitalar.*

REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
2. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol. 2020;e201624.
3. Meng J, Xiao G, Zhang J, He X, Ou M, Bi j, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect. 2020;9(1):757-60.
4. Zhang P, Zhu L, Cai J, Lei F, Quin JJ, Xie J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. 2020;126(12):1671-81.
5. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. Geneva: World Health Organization; 2020. [cited 2020 May 8]. Available from: https://apps.who.int/iris/handle/10665/330893
6. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.
7. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al; China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
8. Hanff TC, Harhay MO, Brown TS, Cohen JB, Mohareb AM. Is there an association between COVID-19 mortality and the renin-angiotensin system: a call for epidemiologic investigations. Clin Infect Dis. 2020;ciaa329.
9. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? JAMA. 2020. doi: 10.1001/jama.2020.4812
10. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin angiotensin-aldosterone system inhibitors in patients with COVID-19. N Engl J Med. 2020;382(17):1653-9.
11. Kılıçkap M, Barçın C, Göksülük H, Karaaslan D, Özer N, Kayıkçıoğu M, et al. Data on prevalence of hypertension and blood pressure in Turkey: systematic review, meta-analysis and meta-regression of epidemiological studies on cardiovascular risk factors. Turk Kardiyol Dern Ars. 2018;46(7):525-45.
12. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-5.

13. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94(7):e00127-20.

14. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8(4):e21.

15. Rodriguez-Iturbe B, Pons H, Johnson RJ. Role of the immune system in hypertension. Physiol Rev. 2017;97(3):1127-64.

16. Solaimanzadeh I. Nifedipine and amlodipine are associated with improved mortality and decreased risk for intubation and mechanical ventilation in elderly patients hospitalized for COVID-19. Cureus. 2020;12(5):e8069.

17. Muramoto A, Caldwell J, Albert RK, Lakschminarayan S, Butler J. Nifedipine dilates the pulmonary vasculature without producing symptomatic systemic hypotension in upright resting and exercising patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease. Am Rev Respir Dis. 1986;132(5):963-6.

18. Woodmansey PA, O'Toole L, Channer KS, Morice AH. Acute pulmonary vasodilatory properties of amlodipine in humans with pulmonary hypertension. Heart. 1996;75(2):171-3.

19. Sajkov D, Wang T, Frith PA, Bune AJ, Alpers JA, McEvoy RD, et al. A comparison of two long-acting vasoselective calcium antagonists in pulmonary hypertension secondary to COPD. Chest. 1997;111(6):1622-30.

20. Kennedy TP, Michael JR, Huang CK, Kallman CH, Zahka K, Schlott W, et al. Nifedipine inhibits hypoxic pulmonary vasoconstriction during rest and exercise in patients with chronic obstructive pulmonary disease: a controlled double-blind study. Am Rev Respir Dis. 1984;129(4):544-51.

21. Hoffmann M, Kleine-Wever H, Kruger N, Müller M, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry in target cells. BioRxiv. 2020; 01.31.929042. doi.org/10.1101/2020.01.31.929042.

22. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-74.

23. Keidar S, Gamliel-Lazarovich A, Kaplan M, Pavlotzky E, Hamoud S, Hayek T, et al. Mineralocorticoid receptor blocker increases angiotensin-converting enzyme 2 activity in congestive heart failure patients. Circ Res. 2005;97(9):946-53.

24. Wysocki J, Ye M, Rodriguez E, Gonzalez-Pacheco FR, Barrios C, Evora K, et al. Targeting the degradation of angiotensin II with recombinant angiotensin-converting enzyme 2: prevention of angiotensin II-dependent hypertension. Hypertension. 2010;55(1):90-8.

ORIGINAL ARTICLE

Neutrophil count to albumin ratio as a new predictor of mortality in patients with COVID-19 ınfection

Ceyhun Varim[1]
Selcuk Yaylaci[1]
Taner Demirci[1]
Tezcan Kaya[1]
Ahmet Nalbant[1]
Hamad Dheir[2]
Didar Senocak[1]
Rumeysa Kurt[3]
Hasret Cengiz[4]
Cengiz Karacaer[4]

1. Associate Professor, Department of Internal Medicine, Sakarya University Medicine Faculty, Sakarya, Turkey.
2. Associate Professor, Department of Internal Medicine Division of Nephrology, Sakarya University Medicine Faculty, Sakarya, Turkey.
3. Medical Doctor, Department of Internal Medicine, Sakarya University Medicine Faculty, Sakarya, Turkey.
4. Hasret Cengiz, Medical Doctor, Department of Endocrinology, Sakarya University Medicine Faculty, Sakarya, Turkey.

http://dx.doi.org/10.1590/1806-9282.66.S2.77

SUMMARY

BACKGROUND: *Coronavirus Disease 2019 is an acute inflammatory respiratory disease. It causes many changes in hemogram parameters. Low albumin levels are associated with mortality risk in hospitalized patients. The aim of the present study is to reveal the place of neutrophil count to albumin ratio in predicting mortality in patients with COVID-19.*

METHODS: *144 patients, 65 females and 79 males, were included in the study. Patients were divided into 2 groups. Group 1 was the non-severe group (n:85), and Group 2 was severe (n:59). Demographic data, neutrophil, lymphocyte and platelet counts, albumin and C-reactive protein (CRP) levels were recorded. Neutrophil count to albumin ratio (NAR) was calculated by dividing the absolute neutrophil counts by the albumin levels. The NAR and levels of the two groups were then compared.*

RESULTS: *There were no significant differences in gender and platelet count (201 vs. 211 K/mL) between the groups (p>0,05). Ages (62.0 ± 14.3 vs 68.6 ± 12.2 years), albumin (33.1 vs 29.9 gr/L), CRP (33 vs 113 mg/l), neutrophil count (4 vs 7.24 K/mL), WBC counts (6.70 vs 8.50 K/mL), NAR values (113.5 vs 267.2) and number of Death (5 vs 33) were found to be statistically higher (p <0.001) in Group 2 than in Group 1. The NAR value of 201.5 showed mortality in all patients with COVID-19 to have 71.1% sensitivity and 71.7% specificity (AUC:0.736, 95% CI: 0.641-0.832, p<0.001)*

CONCLUSION: *The present study showed that NAR levels can be a cheap and simple marker for predicting mortality in patients with COVID-19.*

KEYWORDS: *Neutrophils. Albumins. Coronavirus Infections. Mortality.*

DATE OF SUBMISSION: 05-Jul-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Ceyhun Varım
Adnan Menderes caddesi, Sağlık Sokak, n.195, Adapazarı, Sakarya, Turkey – 54000
Tel: +90 264 255-2106 / Fax: +90 264 255-2105
E-mail: ceyhunvarim@sakaryaedu.tr

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19), as named by the World Health Organization, was caused by the severe acute respiratory syndrome coronavirus (SARS-CoV)-2. This novel virus is a member of the coronavirus family, like SARS-CoV and Middle East respiratory syndrome coronavirus. Coronaviruses (CoVs) are single chain, enveloped RNA viruses with positive polarity. Coronaviruses are animal-derived viruses (zoonotic). They can cause infection in humans and various animals, including mammals, birds, camels, cats, and bats. As a result of detailed research, it has been revealed that SARS-CoV is transmitted from musk cats and MERS-CoV is transmitted from single-humped camels to humans. The source of the SARS-CoV-2 infection has not become clear yet. The options available indicate that wild animals used illegally in the Huanan Chinese Seafood Wholesale Market could have been responsible for it[1-4].

Neutrophils drive the early inflammatory response following an acute infection, and high neutrophil count was demonstrated as an important marker for systemic infection[5]. Albumin is a negative acute-phase reactant and decreases in acute infection. Low albumin levels are associated with mortality risk in hospitalized patients[6]. Neutrophil/albumin ratio (NAR) is a new marker indicating systemic inflammation and mortality which can be calculated using hemogram parameters. This is a cheap and easy method to predict mortality in patients with COVID-19.

In this study, we aim to reveal the place of neutrophil count to albumin ratio in predicting mortality in patients with COVID-19.

Methods

A total of 144 patients (65 women, 79 men) who had been hospitalized at the clinic of internal medicine of the Sakarya University Medicine Faculty between 01 April 2020 and 31 May 2020 and tested for COVID-19 with real-time reverse transcription-polymerase chain reaction (RRT-PCR) were enrolled in the study. Nasal and pharyngeal swabs of all patients were obtained. The isolated patient samples that were obtained with VNAT viral transport and brought to the molecular virology laboratory were examined using the Biospedy (Bioeksen, Turkey) RRT-PCR kit provided by the Ministry of Health of Turkey. The patients whose RRT-PCR results were positive were regarded as COVID-19 (+). Hospital records (demographic, clinical, and laboratory data) of the cases above 18 years old were analyzed retrospectively. The patients were divided into two groups based on the severity of the disease. Thus, there was a non-critical group (consisting of 85 patients) and a critical group (consisting of 59 patients). critical illnesses include patients with respiratory failure, shock, or multiorgan dysfunction. The white blood cell (WBC) count, neutrophil, lymphocyte count, platelet, and albumin values of all patients were recorded, and the NAR (neutrophil count/albumin) values were calculated.

Hemogram results and biochemical results at the time of diagnosis were measured. Hematological parameters were analyzed using a hematology analyzer (Abbott CELL DYN 3700 System, Ramsey, Minnesota 55303, USA) within 30 minutes. The reports from the thoracic computed tomographies were obtained from a data management system. Serum urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin were analyzed using the kinetic alkaline picrate method with the Architect C 16000 (Abbott) device at the biochemistry laboratory of the hospital.

This study was approved by the local ethics committee and performed in accordance with the Helsinki Declaration (18.04.2019-71522473/050.01.04/55).

Statistical Analysis

Data analysis was performed by using SPSS-22 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z). The variables were investigated using visual (histograms, probability plot) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. We performed analyses to describe and summarize the distributions of variables. The continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution. Categorical variables were interpreted by frequency tables. The Mann–Whitney U test was used to compare the variables that were not normally distributed. On the other hand, the Student's t-test was used to compare the variables with a normal distribution. Categorical features and relationships between groups were assessed using an appropriate chi-square test. Logistic regression was conducted to assess whether the predictor variables such as laboratory rates significantly predict mortality. The capacities of the neutrophil percentage to albumin ratio and neutrophil count to albumin ratio parameters to predict mortality

were analyzed by the "Receiver Operating Properties (ROC)" curve analysis. In the presence of significant limit values, the sensitivity and specificity values of these limits were calculated. While evaluating the area under the curve, a 5% type-1 error level was used to accept a statistically significant predictive value of the test variables. The statistically significant two-tailed p-value was considered as <0.05.

RESULTS

A total of 144 patients were included in this retrospective study. The groups (Group 1 of non-critical patients, Group 2 of critical patients) were determined to be homogenous in terms of gender. There were no significant gender differences between the two groups. The average age was 62.0 ± 14.3 years in Group 1 and 68.6 ± 12.2 years in Group 2 at p<0.004. (Table 1).

The white Blood Cell (WBC), platelet, neutrophil counts, albumin, D-dimer, ferritin, and C-reactive protein (CRP), and NAR levels of Group 1 and Group 2 are shown in Table 2.

TABLE 1. DEMOGRAPHIC CHARACTERISTICS

Parameters	Non-critical patients	Critical patients	P-values
Patients (n)	85	59	
Male/Female (n)	48/37	19/208	0.641
Age (years)	62.0 ± 14.3	68.6 ± 12.2	0.004

TABLE 2. COMPARISON OF CLINICAL AND LABORATORY RESULTS

Parameters	Non-critical patients (n:85)	Critical Patients (n:59)	P-values
D-Dimer (ng/mL)	657.0 (319 - 1470)	1680 (844 - 3690)	<0.001
Ferritin (ng/mL)	348.0 (165.5 – 637.5)	776.0 (411.0 – 1545.0)	<0.001
CRP (mg/L)	33.0 (10.95 – 72.20)	113.0 (37.2 – 169.0)	<0.001
WBC (K/mL)	6.70 (4.75 – 8.00)	8.50 (5.80 – 14.90)	<0.001
PLT (K/mL)	201 (163.5 – 270.5)	211 (149-277)	0.858
NEU (K/mL)	4.00 (3.00 - 5.77)	7.24 (3.90 - 12.40)	<0.001
Albumin (gr/L)	33.10 (29.85 – 37.05)	29.90 (26.60 – 33.00)	<0.001
NAR	113.5 (81.5 - 201.8)	267.2 (128.9 – 409.2)	<0.001
Death n(%)	5 (5,9)	33 (55)	<0.001

NAR: Neutrophil Count to Albumin Ratio; WBC: White Blood Cell; CRP: C-reactive protein.

WBC counts were 6.70 10^3/mm^3 (4.75 – 8.00) in Group 1 and 8.50 10^3/mm^3 (5.80 – 14.90) in Group 2 at p<0.001. The platelet counts were 201 K/mL (163.5 – 270.5) in Group 1 and 211 K/mL (149-277) in Group 2, at p=0.858. The neutrophil counts were 4.0 K/mL (3.00 - 5.77) in Group 1 and 7.24 K/mL (3.90 - 12.40) in Group 2, at p <0.001. Albumin levels were 33.10 gr/L (29.85 – 37.05) in Group 1 and 29.90 (26.60 – 33.00) in Group 2, at p<0.001, and the D-dimer levels were 657.0 ng/mL (319 - 1470) in Group 1 and 1680 ng/mL (844 - 3690) in Group 2, at p<0.001. The ferritin levels were 348.0 ng/mL (165.5 – 637.5) in Group 1 and 776.0 ng/mL (411.0 – 1545.0) in Group 2, at p<0.001. The CRP levels were 33.0 mg/L (10.95 – 72.20) in Group 1 and 113.0 mg/L (37.2 – 169.0) in Group 2, at p<0.001. The mean NAR values were 113.5 (81.5 - 201.8) in Group 1 and 267.2 (128.9 – 409.2) in Group 2 at p<0.001. The number of deaths was 5 in Group 1 and 33 in Group 2, at p<0.001 (re-1) (Table 2).

The ROC analysis was performed to determine the cut off values of NAR to predict mortality in patients with a COVID-19 infection. The ROC curve is shown in Figure 1. NAR was predictive at 201.5, with 71.1% sensitivity and 71.7% specificity (AUC:0.736, 95% CI: 0.641-0.832, p<0.001) (Figure 2).

DISCUSSION

We found higher WBC, neutrophil, D-dimer, CRP, ferritin, and NAR values and lower lymphocyte and albumin values in the critical patients than in the non-critical patients in our study. Higher WBC,

FIGURE 1. THE RESULTS OF "NEUTROPHIL COUNT TO ALBUMIN RATIO" WERE SCHEMATIZED ACCORDING TO WHETHER THE DISEASE WAS CRITICAL OR NOT.

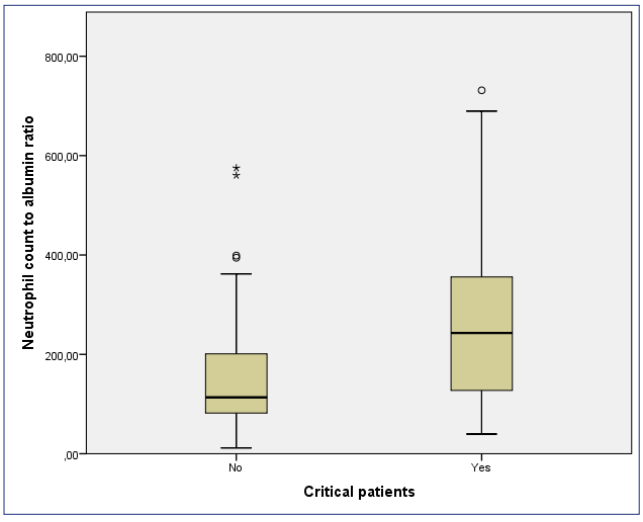
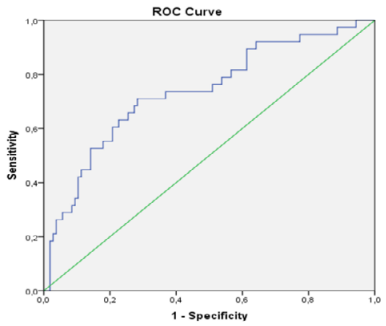


FIGURE 2. RECEIVER OPERATING CHARACTERISTIC (ROC) CURVE OF NEUTROPHIL COUNT TO ALBUMIN RATIO IN PREDICTING MORTALITY.



Area Under the Curve

Test Result Variable(s): Neutrophil_count_to_Albumin_Ratio

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
,736	,049	,000	,641	,832

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

neutrophil, D-dimer, CRP, ferritin, and NAR values and lower lymphocyte and albumin values are associated with poor prognosis.

We performed a ROC analysis for NAR values, and basal NAR greater than 201.5 had 71.1% sensitivity and 71.7% specificity in predicting the mortality of patients with a COVID-19 infection.

Neutrophils and lymphocytes are important components of the immune system. Neutrophils are cells that release chemokines and cytokines. These released cytokines and chemokines stimulate angiogenesis, cytogenesis, antiviral defense, and help regulate the immune response[7]. In severe viral infections, the number of neutrophils in the peripheral blood increases significantly; increased neutrophil counts induce a cytokine-chemokine storm and, ultimately, lead to lung injury and acute respiratory distress syndrome[8].

When the literature is examined, there are many studies on neutrophil count and neutrophil/lymphocyte ratio (NLR) in COVID-19 patients. The relationship between neutrophil counts, NLR, and mortality has been examined in COVID-19 patients in some of these studies, as has the prognosis of COVID-19 in other studies[8-11]. We found a positive relationship between neutrophil counts and poor prognosis and mortality. Our findings are consistent with the literature.

Albumin is the biggest and most abundant protein in plasma. Albumin is found in high concentrations in the intestine, muscle, skin, and all body fluids. Albumin interacts with many endogenous and exogenous molecules. There is a complex relationship between intracellular and extracellular albumin levels. Intracellular albumin intake increases and serum albumin levels decrease due to stress and inflammation. Albumin is also known as a negative acute phase reactant with low blood levels in acute inflammation and inversely associated with the magnitude of systemic inflammatory response. Low albumin levels are associated with mortality risk in hospitalized patients[6,12-14].

We found low albumin levels in our study. Low albumin levels are associated with poor prognosis and mortality. Our findings are consistent with the literature. Aziz et al.[15] made a meta-analysis of 11 studies that examined serum albumin levels in patients with COVID-19. In ten of these eleven studies, an inverse proportion was found between low serum albumin levels and the severity of the disease. In one, this relationship was not observed. In another study, serum albumin levels were found to be significantly lower in patients with COVID-19 than in healthy individuals[16]. In a study by Mishra et al.[17], serum albumin-mediated strategies were shown to be useful in the treatment of patients with COVID-19.

We developed and tested a simple index of the neutrophil count to albumin ratio (NAR) for predicting mortality of COVID-19 and found 71.1% sensitivity and 71.7% specificity. This simple index can be used instead of the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, fibrinogen/albumin ratio, and lymphocyte/C-reactive protein ratio.

High admission NAR was identified as an independent predictor in patients with COVID-19. Our results suggest that COVID-19 patients with high NAR values should be carefully monitored and considered for intensive care because of the close association with early mortality. Further studies are still required to confirm and illuminate the clinical implications of these findings.

Conflict of Interest

All authors declare that there is no potential conflict of interest relevant to this article.

Author's Contribution

Concept: Ceyhun Varım; Design: Selçuk Yaylacı; Literature search: Cengiz Karacaer; Clinical studies: Ahmet Nalbant; Data acquisition: Hamad Dheir; Data analysis: Hasret Cengiz; Statistical analysis: Taner Demirci; Manuscript preparation: Tezcan Kaya; Manuscript editing: Didar Senocak; Manuscript review: Rumeysa Kurt.

RESUMO

ANTECEDENTES: *A doença de coronavírus 2019 é uma doença respiratória inflamatória aguda. Causa muitas alterações nos parâmetros do hemograma. Baixos níveis de albumina estão associados ao risco de mortalidade em pacientes hospitalizados. O objetivo do presente estudo é revelar o local da razão entre contagem de neutrófilos e albumina na predição de mortalidade em pacientes com COVID-19.*

MÉTODOS: *Cento e quarenta e quatro pacientes do sexo feminino e 79 do sexo masculino foram incluídos no estudo. Os pacientes foram divididos em dois grupos: Grupo 1 não grave (n: 85), Grupo 2 grave (n: 59). Dados demográficos, contagem de neutrófilos, linfócitos e plaquetas, níveis de albumina e proteína C reativa (PCR) foram registrados. A razão de contagem de neutrófilos para albumina (NAR) foi calculada dividindo-se as contagens absolutas de neutrófilos pelos níveis de albumina. O NAR e os níveis dos dois grupos foram comparados.*

RESULTADOS: *Não houve diferenças significativas no sexo e na contagem de plaquetas (201 vs 211 K/mL) entre os grupos (p>0,05). Idade (62,0±14,3 vs 68,6±12,2 anos), albumina (33,1 vs 29,9 gr/L), PCR (33 vs 113 mg/l), contagem de neutrófilos (4 vs 7,24 K/mL), contagem de leucócitos (6,70 vs 8,50 K/mL), valores de NAR (113,5 vs 267,2) e número de óbitos (5 vs 33) foram estatisticamente maiores (p<0,001) no Grupo 2 que no Grupo 1. O valor NAR de 201,5 mostrou mortalidade em todos os pacientes com COVID-19 com sensibilidade de 71,1% e especificidade de 71,7% (AUC: 0,736, IC 95%: 0,641-0,832, p<0,001).*

CONCLUSÃO: *O presente estudo mostrou que os níveis de NAR podem ser um marcador barato e simples para predizer mortalidade em pacientes com COVID-19.*

PALAVRAS-CHAVE: *Neutrófilos. Albuminas. Infecções por coronavírus. Mortalidade.*

REFERENCES

1. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. Severe acute respiratory syndrome-related coronavirus: the species and its viruses - a statement of the Coronavirus Study Group. bioRxiv. 2020. doi: https://doi.org/10.1101/2020.02.07.937862.
2. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418-23.
3. Hui DS. Epidemic and emerging coronaviruses (severe acute respiratory syndrome and middle east respiratory syndrome). Clin Chest Med. 2017;38(1):71-86.
4. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet. 2020;395(10225):689-97.
5. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81(1):e6-e12.
6. Akirov A, Masri-Iraqi H, Atamna A, Shimon I. Low albumin levels are associated with mortality risk in hospitalized patients. Am J Med. 2017;130(12):1465. e11-1465.e19.
7. Tecchio C, Micheletti A, Cassatella MA, Neutrophil-derived cytokines: facts beyond expression. Front Immunol. 2014;5:508.
8. Wang H, Zhang Y, Mo P, Liu J, Wang H, Wang F, et al. Neutrophil to CD4+ lymphocyte ratio as a potential biomarker in predicting virus negative conversion time in COVID-19. Int Immunopharmacol. 2020;85:106683.
9. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. 2020;92(7):797-806.
10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
11. Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: a retrospective cross-sectional study. J Med Virol. 2020;10.1002/jmv.26061.
12. Mishra PM, Uversky VN, Nandi CK. Serum albumin-mediated strategy for the effective targeting of SARS-CoV-2. Med Hypotheses. 2020;140:109790.
13. Chojkier M. Inhibition of albumin synthesis in chronic diseases: molecular mechanisms. J Clin Gastroenterol. 2005;39(4 Suppl 2):S143-6.
14. Koh YW, Lee HW. Prognostic impact of C-reactive protein/albumin ratio on the overall survival of patients with advanced nonsmall cell lung cancers receiving palliative chemotherapy. Medicine (Baltimore). 2017;96(19):e6848.
15. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care. 2020;24(1):255.
16. Mardani R, Vasmehjani AA, Zali F, Gholami A, Mousavi Nasab SD, Kaghazian H, et al. Laboratory parameters in detection of COVID-19 patients with positive RT-PCR: a diagnostic accuracy study. Arch Acad Emerg Med. 2020;8(1):e43.
17. Mishra PM, Uversky VN, Nandi CK. Serum albumin-mediated strategy for the effective targeting of SARS-CoV-2. Med Hypotheses. 2020;140:109790.

ORIGINAL ARTICLE

Demographic characteristics and neurological comorbidity of patients with COVID-19

Türkan Acar[1]
Bilgehan Atılgan Acar[1]
Yeşim Güzey Aras[1]
Turan Doğan[1]
Sena Boncuk[1]
Halil Alper Eryılmaz[1]
Nimet Can[1]
Yusuf Can[1]

1. Sakarya University Training and Research Hospital, Sakarya, Turkey.

http://dx.doi.org/10.1590/1806-9282.66.S2.82

SUMMARY

ABSTRACT: *The COVID-19 infection that started in the Wuhan Province of the People's Republic of China and has now spread throughout the world is not limited to the respiratory system, but also causes other systemic symptoms through viremia. Recent data show that the central and peripheral nervous system involvement is particularly substantial. Thus, the present study aims to investigate the current neurological comorbidities and symptoms of patients with COVID-19 who were followed up by our clinic physicians.*

KEYWORDS: *Coronavirus Infections. Comorbidity. Neurologic Manifestations.*

INTRODUCTION

The disease, named "new coronavirus disease" (COVID-19), which first appeared in December 2019, has rapidly spread from the Wuhan province of the People's Republic of China to other provinces and then all over the world[1]. Coronaviruses are single-stranded, positive polarity, enveloped RNA viruses with rod-shaped protrusions on their surfaces in a roughly spherical and pleomorphic form, which is about 125 nm in diameter[2]. It is known that these virus infections are highly contagious, transmitted from person to person, and from contaminated surfaces[3]. The effects of the COVID-19 infection are not only limited to the lungs but can cause other symptoms through viremia after the virus enters the body. In COVID-19 patients, fever, dry cough, and fatigue are the primary symptoms; in some patients, sore throat, chest tightness, sputum, loss of appetite, abdominal pain, diarrhea, vomiting, and conjunctivitis are also observed. It can be difficult to differentiate COVID-19 from other respiratory diseases[4]. In some groups of patients, neurological symptoms are observed without any respiratory system symptoms[5-7]. Researchers have detected the coronavirus nucleic acid component in patients' CSF analyses[8]. Neurological involvements

DATE OF SUBMISSION: 02-Jun-2020
DATE OF ACCEPTANCE: 03-Jul-2020
CORRESPONDING AUTHOR: Türkan Acar
Sakarya University Training and Research Hospital, Neurology's Department, Sakarya, Turkey
Tel: +90 505 794-8815
E-mail: tdeniz38@hotmail.com

have also been supported by case reports in the literature. Several neurological symptoms, including central nervous system (CNS) involvement, peripheral nervous system (PNS) involvement, and skeletal muscle damage, were reported in more than a third of patients[6]. In this study, the demographic data of the COVID-19 patients followed-up in our clinic and their neurological comorbidities were investigated in detail.

METHODS

The patients with COVID-19 followed-up at the Sakarya University Training and Research Hospital Neurology Clinic in April 2020 were retrospectively investigated. Patients in the 18-100 age group with a COVID-19 diagnosis, who presented any symptoms, were included in the study. All the neurological and non-neurological symptoms of the patients were classified.

Ethics Committee Approval

Approval was received from the Ethics Committee of the Faculty of Medicine of the Sakarya University.

RESULTS

The study was conducted with a total of 30 patients, of which 13 (43.3%) were male and 17 (56.7%) were female, followed by the diagnosis of COVID-19. The age range of the patients was 26-91 (average of 51.6 years). Of the patients, 28 (93.3%) were hospitalized for treatment (Table 1).

In the examination of the neurological and non-neurological comorbidity information from the patients' histories followed by COVID-19 diagnosis, 8 (26.7%) patients had hypertension (HT), 6 (20%) had diabetes mellitus (DM), 3 (10%) had coronary artery disease (CAD), 1 (3.3%) had chronic renal failure (CRF), 1 (3.3%) had Parkinson's disease, 1 (3.3%) had restless leg syndrome (RLS), 3 (10%) had cerebrovascular disease (CVD), 1 (3.3%) had renal transplantation, and 1 (3.3%) patient had polyneuropathy (Table 2).

According to the neurological and non-neurological presentation of symptoms, distribution by gender, and the average age of the patients followed-up after the COVID-19 diagnosis, fever was present in a total of 23 patients, of which 10 were male, and the average age was 48.7. Cough was present in 11 patients in total, of which 5 were male, and the average age was 54.6. Shortness of breath was found in 10 patients, of which 6 were male, and the average age was 52.6. Myalgia was found in 15 patients, of which 5 were male, and the average age was 52.7. Headache was found in 10 patients in total, of which 5 were male, and the average age was 42.4. Dizziness was only present in 3 female patients, and the average age was 40. Diarrhea was only present in 3 female patients, and the average age was 44.6. Nausea and vomiting were found in 2 female patients, and their average age was 48. CVD comorbidity was detected in 2 female patients with COVID-19, and their age average was 58. Fatigue was present in 11 patients in total, of which 4 were male, and the average age was 51.1. Anosmia was present in 10 patients, of which 5 were male, and the average age was 44.9. Syncope was found in 1 male patient, and his age was 38. Delirium was present in 4 patients, of which 3 were male, and the average age was 78.2 (Table 3).

The time between the onset of symptoms and hospital admission was in the range of 1-10 days, and the average was 3.4 days. The time from the start of the treatment to discharge was in the range of 3-28 days, and the average was 8.5 days (Table 3). During the treatment, 2 patients died.

For the treatment, all the patients received hydroxychloroquine, 60% received oseltamivir, 80%

TABLE 1. DEMOGRAPHIC DATA OF PATIENTS FOLLOWED UP DUE TO COVID-19 DIAGNOSIS

Demographic data	n (%)
Total	30
Age (age range, average)	26-91 (51.6)
Gender	
Male	13 (43.3)
Female	17 (56.7)
Inpatient treatment	28 (93.3)

TABLE 2. COMORBIDITY INFORMATION OF PATIENTS FOLLOWED-UP DUE TO COVID-19 DIAGNOSIS

Comorbidity	n (%)
HT	8 (26.7)
DM	6 (20)
CAD	3 (10)
CRF	1 (3.3)
Parkinson's disease	1 (3.3)
RLS	1 (3.3)
CVD	3 (10)
RENAL TRANSPLANTATION	1 (3.3)
PNP	1 (3.3)

HT: Hypertension; DM: Diabetes Mellitus; CAD: Coronary Artery Disease; CRF: Chronic Renal Failure; RLS: Restless Leg Syndrome; CVD: Cerebrovascular Disease; PNP: Polyneuropathy.

received azithromycin, 20% received favipiravir, and 60% received enoxaparin (Table 4).

DISCUSSION

The SARS-CoV-2 virus is a member of the Betacoronavirus genus, known for its neurological invasive potential. The virus is able to enter the cell by binding to the Angiotensin-converting enzyme 2 (ACE2), which acts as a receptor. It is present in many tissues in the human body, including the ACE2 nervous system and skeleton muscle. The expression of ACE2 in the nervous system and skeletal muscles may explain some of the neurological features that have been reported so far[9-11]. A cytokine storm, a well-known immune reaction to this viral infection, can lead to the inflammation of the central nervous system (CNS)[12].

TABLE 3. NEUROLOGICAL AND NON-NEUROLOGICAL PRESENTATION OF SYMPTOMS, DISTRIBUTION BY GENDER, AND THE AVERAGE AGE RANGE IN PATIENTS FOLLOWED-UP DUE TO COVID-19 DIAGNOSIS

Symptom	(n) (male n)	(%)	Average age
Fever	23 (10)	(76.6)	48.7
Cough	11 (5)	(36.7)	54.6
Shortness of breath	10 (6)	(33.3)	52.6
Myalgia	15 (5)	(50)	52.7
Headache	10 (5)	(33.3)	42.4
Dizziness	3 (0)	(10)	40
Diarrhea	3 (0)	(10)	44.6
Nausea-Vomiting	2 (0)	(6.7)	48
CVD	2 (0)	(6.7)	58
Fatigue	11 (4)	(36.7)	51.1
Anosmia	10 (5)	(33.3)	44.9
Syncope	1 (1)	(3.3)	38
Delirium	4 (3)	(13.3)	78.2
The period from the onset of the symptom to admission	Min-max		Avg:
	1-10		3.4
Time of discharge after treatment	3-28		8.5

TABLE 4. TREATMENT OPTIONS FOR PATIENTS FOLLOWED-UP DUE TO COVID-19 DIAGNOSIS

Treatment option	n (male n)	(%)	Average age
Oseltamivir	18 (7)	(60)	47.7
Hydroxychloroquine	30 (13)	(100)	51.6
Azithromycin	24 (10)	(80)	53.1
Favipiravir	6 (3)	(20)	50.8
LMWH	18 (5)	(60)	58.8

LMWH: Low-molecular-weight heparin

The process of neurological involvement in COVID-19 can be analyzed in three parts; 1) neurological characteristics of the viral infection; 2) neurological complications after infection; 3) infection in patients with neurological comorbidities[13]. In our study, current neurological symptoms and neurological comorbidity in patients were investigated in the active period of the virus. The neurologic symptoms that we could detect in patients of our clinic were headache, dizziness, anosmia, myalgia, CVD, and delirium. One of the most important details that drew attention in our results was that neurologic symptoms, including headaches, dizziness, and anosmia were more common in patients under the average age of 45. In particular, the occurrence of headaches in younger COVID-19 patients has a similarity with the mechanisms that explain frequent primary headaches in young people, which could be a separate research topic. Another important issue is that CVD, delirium, and the deterioration of the overall condition was more common in patients over the age of 55 in both groups. This may be due to the increased risk factors in patients of this age group.

In a retrospective study conducted by Mao et al.[14], the most frequent causes of neurological presentation were dizziness, headache, and anosmia. In our cases, the incidence of headache and anosmia was found to be 33.3%, whereas the incidence of dizziness was 10%.

In another study by Chen et al.[15], the rate of loss of consciousness among patients who died was 22%, while this rate was 1% among the survivors. Among our patients, the number of patients with delirium and linked deterioration of the overall condition was 13.3, and one of these patients died on the 11th day, under treatment.

Common microvascular thromboses develop as a result of prothrombotic activation along with cytokine increase in COVID-19 infection, and D-dimer levels are high in these patients. In the new guidelines by the AHA/ASA[16], it is emphasized that stroke is observed in 5.9% of the patients, 10 days after the onset of the symptoms in COVID-19. In addition, the first observations are that cerebrovascular diseases are often seen in the group of COVID-19 patients with poor prognosis[17]. Indeed, in our study, 2 patients had acute CVD, and one patient died on the 5th day of treatment.

Fever, cough, shortness of breath, and myalgia are among the most common of COVID-19 symptoms. In a comparative analysis of the coronavirus family, the incidence of myalgia secondary to COVID-19 was

found as 14.8%, and myalgia incidence was found to be 50% in our study[18].

Worldwide, medical practices are carried out in extraordinary conditions during the pandemic. In Turkey, providing the most suitable treatments for our conditions should be our main goal[19]. All the inpatients who were treated received a full dose of hydroxychloroquine. Other treatment options, such as oseltamivir, azithromycin, or favipiravir, were administered as a combined therapy for appropriate patients with additional comorbidity.

CONCLUSION

Although the COVID-19 pandemic is currently starting to lose its momentum, the risk of a new potential increase is likely to remain on our agenda for a long time. Given the current studies and meta-analyses, it is observed that the rates of neurological involvement in COVID-19 are significant, in addition to the respiratory system involvement. So we presented the data that we think might be particularly useful to neurologists in this study. We believe that the additional data will help with the fact that neurological involvement is substantial and more diverse.

There is no conflict of interest or financial support in the article.

Author's Contribution

Türkan Acar - Main concept, data collection, writing of the article; Bilgehan Atılgan Acar - Main concept, data collection; Yeşim Güzey Aras, Turan Doğan - Data collection, analysis of the findings; Sena Boncuk, Yusuf Can - Analysis of the findings, resource access; Halil Alper Eryılmaz, Nimet Can - Writing of the article, resource access.

RESUMO

RESUMO: *A infecção de COVID-19 que começou na província de Wuhan, na República Popular da China, e já se espalhou por todo o mundo não se limita ao sistema respiratório, mas também causa outros sintomas sistêmicos através de viremia. Dados recentes mostram que seus efeitos no sistema nervoso central e periférico são particularmente significativos. Assim, o presente estudo tem como objetivo investigar as atuais comorbidades e sintomas neurológicos de pacientes com COVID-19 que foram acompanhados pelos médicos da nossa clínica.*

PALAVRAS-CHAVE: *Infecções por Coronavirus. Comorbidade. Manifestações Neurológicas.*

REFERENCES

1. Çalişmasi BK. COVID-19 (SARS-CoV-2 Enfeksiyonu) Rehberi. Ankara: TC Sağlık Bakanlığı; 2020.
2. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1-23.
3. Pascarella G, Strumia A, Piliego C, Bruno F, Buono RD, Costa F, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med. 2020;10.1111/joim.13091.
4. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect. 2020;9(1):687-90.
5. Ozturk S. COVID-19 and neurology. Turk J Neurol. 2020. DOI:10.4274/tnd.galenos.2020.73384
6. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. medRxiv 2020. doi: https://doi.org/10.1101/2020.02.22.20026500.
7. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
8. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis. 2004;10(2):342-4.
9. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses. 2020;12(4):372.
10. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
11. Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: properties and future directions. J Neurochem. 2008;107(6):1482-94.
12. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv. 2020. doi: https://doi.org/10.1101/2020.02.10.20021832.
13. Lahiri D, Ardila A. COVID-19 pandemic: a neurological perspective. Cureus. 2020;12(4):e7889.
14. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):1-9.
15. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.
16. AHA/ASA Stroke Council Leadership. Temporary emergency guidance to US stroke centers during the COVID-19 pandemic: On Behalf of the American Heart Association/American Stroke Association Stroke Council Leadership. Stroke. 2020;51(6):1910-2.
17. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.
18. Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: a comparative overview. Infez Med. 2020;28(2):174-84.
19. Acar T, Demirel EA, Afşar N, Akçalı A, Demir GA, Alagöz AN, et al. Nörolojik bakış açısından COVID-19. Turk J Neurol. 2020;26:56-106.

ORIGINAL ARTICLE

The effect of abo and rh blood group antigens on admission to intensive care unit and mortality in patients with COVID-19 infection

Selçuk Yaylacı[1]
Hamad Dheir[1]
Kubilay İşsever[1]
Ahmed Bilal Genc[1]
Didar Şenocak[1]
Havva Kocayigit[2]
Ertugrul Guclu[3]
Kezban Suner[2]
Hasan Ekerbicer[4]
Mehmet Koroglu[5]

1. Sakarya University Faculty of Medicine, Department of Internal Medicine.
2. Sakarya University Education and Research Hospital, Department of Intensive Care.
3. Sakarya University Faculty of Medicine Department of Infectious Diseases.
4. Sakarya University Faculty of Medicine Department of Public Health.
5. Sakarya University Faculty of Medicine Department Medical Microbiology.

http://dx.doi.org/10.1590/1806-9282.66.S2.86

SUMMARY

AIM: *The aim of this study is to analyze the prognostic significance of ABO and Rh blood group antigens along with various parameters in patients followed-up with the diagnosis of COVID-19.*

METHODS: *We evaluated 397 patients who were follow-up and treated due to COVID-19 infections. The ages, genders, chronic diseases, ABO and Rh blood group antigens, admission rates to Intensive Care Units (ICU), and mortality rates of the patients were analyzed.*

FINDINGS: *The mean age of the 397 patients with COVID-19 was 47±17 years. In the blood group analysis of the patients, A Rh-positive (A +) was the most frequently seen blood type (176 patients, 44.3%) followed by O Rh-positive (0 +) (109 patients, 27,5%); 38 patients were Rh negative (Rh -) (9,6%). 53 of the patients (13,4%) were followed in ICU and 29 patients died (7,3%). Neither mortality nor admission to ICU was seen for Rh – group. The comparison of Rh groups concerning the need for ICU admission revealed a significantly high rate of ICU admission in the Rh + group (p=0,011), while no significant relationship was found between mortality and Rh antigen (p=0,069).*

CONCLUSION: *The most frequently seen blood type among COVID-19 patients was A +. The Rh + blood group was found in all cases who were admitted to ICU and had a death outcome. The Rh + blood group was found in a significantly high number of patients who were admitted to ICU, while no significant relationship was found between mortality and Rh blood group.*

KEYWORDS: *Coronavirus Infections. ABO Blood-Group System. Rh-Hr Blood-Group System. Intensive care units. Mortality.*

INTRODUCTION

Health care systems, diagnosis, and treatment processes have been struggling with difficulties concerning the pandemic caused by the novel coronavirus SARS-CoV-2 all over the world. This new

DATE OF SUBMISSION: 05-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Selcuk Yaylacı
Sakarya University Faculty of Medicine Department of Internal Medicine
E-mail: yaylacis@hotmail.com

coronavirus caused 309.827 deaths and 4.664569 confirmed cases as of 16 May 2020, spreading rapidly worldwide[1]. Thus, there is a need to identify who is at more risk and, according to this, provide protective measures as soon as possible.

Advanced age, chronic diseases, gender, and abnormalities in some laboratory parameters are known risk factors for morbidity and mortality in the course of COVID-19 infections[2-4]. The relationship between SARS-CoV-1 and ABO blood groups was defined firstly in 2005[5]. Although another study revealed a relationship between COVID-19 and ABO blood groups, there is not enough evidence in this respect[6]. Yet, the relationship between ABO and Rh blood types and mortality is not clear.

In our study, we aimed to analyze ABO and Rh blood group antigens and the effect of these blood group parameters on mortality and ICU admission in patients with COVID-19.

METHODS

A descriptive cross-sectional study was conducted among 397 COVID-19 patients between 19 March and 19 April 2020. Data such as age, gender, chronic diseases (diabetes mellitus, hypertension, chronic pulmonary diseases, malignant diseases, cardiovascular diseases, chronic renal failure, etc.), ABO and Rh blood type, ICU admission, and mortality of patients were recorded. The mean age, gender, and number of chronic diseases of the patients were analyzed. The distribution of COVID-19 patients according to blood groups was assessed. ICU admission and mortality rates according to ABO and Rh blood group of the patients were analyzed.

An ethics committee approval from Sakarya University Medical Faculty was provided for this study (approval number: 71522473/050.01.04/).180

Statistical analysis

Quantitative data were expressed as mean values ± SD, medians, and ranges. Qualitative data were expressed as numbers and percentages. After performing the Kolmogorov-Smirnov test to assess the normality of distribution, a nonparametric Mann-Whitney test was used to compare the ages of patients between Rh + and Rh - groups. The Chi-square or Fisher's exact test was used for categorical variables. P values < 0.05 were considered statistically significant. Analyses were performed using Statistical Package for the Social Sciences version 20.0 (IBM SPSS Statistics; Armonk, NY, USA).

RESULTS

The mean age of the 397 patients with COVID-19 was 47±17.5 years (min-max: 17-92). Out of these, 176 of the patients were male (44.3 %) and 221 were female (55.7 %). In the blood group analysis of the patients, A Rh-positive (A +) was the most common blood type (176 patients, 44.3%), followed by O Rh-positive (O +) (109 patients, 27.5%); 53 patients were B + (13.4%), 25 patients were A – (6.3%), 21 patients were AB + (5.3%), 11 patients were 0 – (2.8%), 2 patients were B – (0.5%) and no patients were AB -. A total of 38 patients were Rh - (9.6%), while 359 patients were Rh + (90.4%). Of all patients, 53 (13.4%) were followed in ICU. In the blood group analysis of the 53 ICU patients, we found that 17 were 0 + (15.6%), 8 were B + (15.1%), 26 were A + (14.8%), 2 were AB + (9.5%). The lowest ratio of ICU admission among Rh + blood group patients was found for the AB + group (9.5%). In the analysis of mortality ratios according to blood types (29 dead patients, 7.3%), it was found that 5 of B + patients (9.4%), 15 of A + patients (8.5%), 8 of O + patients (7.3%), 1 of AB + patients (4.8%) died in ICU. Neither mortality nor admission to ICU was seen for the Rh – group (Table 1). The variables of age, gender, and having at least one chronic disease were statistically similar for Rh + and Rh - patients (Table 2). In the comparative analysis of Rh groups regarding ICU admission, a statistically significant relationship was found between having Rh + blood group and the ICU admission rate (p=0.011). Nevertheless, in the comparison analysis of Rh groups regarding mortality rates, no significant relationship was found between Rh factor and mortality rates (p=0.069). The lowest mortality

TABLE 1. DISTRIBUTION OF ABO AND RH BLOOD GROUPS, MORTALITY AND ICU ADMISSION RATES OF COVID-19 PATIENTS

BLOOD GROUP	n	%	ICU (n-%)		Mortality	
O Rh -	11	2,8	0	0	0	0
O Rh +	109	27,5	17	15,6	8	7,3
A Rh -	25	6,3	0	0	0	0
A Rh +	176	44,3	26	14,8	15	8,5
AB Rh +	21	5,3	2	9.5	1	4,8
AB Rh -	0	0	0	0	0	0
B Rh -	2	,5	0	0	0	0
B Rh +	53	13,4	8	15,1	5	5,9
Total	397	100	53	13,4	29	7,3

ratio was found in AB + patients among the Rh + blood group (4.8%, Table 3). None of the comparative analyses of O, A, B, and AB groups with other blood groups revealed a significant relationship with ICU admission and mortality (Table 4).

DISCUSSION

Advanced age, comorbid diseases, male gender, and high levels of lactate dehydrogenase (LDH), neutrophil/lymphocyte ratio, and D-dimer are known as poor prognostic factors for COVID-19 infection[3,4,7]. The pathogenesis and prognostic indicators of COVID-19 disease are still not fully known. İn this study, we investigated whether there is an association between COVID-19 disease progression and blood groups. The surface of red blood cells is covered with antigens (sugars and proteins) which are integrated with membrane proteins and lipids. ABO and Rh blood type systems are crucial for safe blood and organ transplantation processes. Blood group antigens exist on the surface of each erythrocyte. If there is only antigen A on the erythrocyte, it becomes group A, and if there is only antigen B on the erythrocyte, it becomes group B. If antigen A and B exist at the same time on the surface of the erythrocyte, it becomes group AB; while if there is no antigen on the surface of that erythrocyte, it becomes group O. On the other hand, reciprocal antibodies exist in the plasma of human body. Group B antibody is present in the plasma of the A blood group while A antibody is present in the plasma of the B blood group. A and B antibody exist at the same time in the plasma of the O blood group. Rh antigens are also located on the membrane of erythrocytes and consist of three pairs, i.e., Dd, Cc, and Ee. Besides these, there are many other antigens such as Duffy,

TABLE 2. COMPARISON OF AGES, GENDERS, AND HAVING AT LEAST ONE CHRONIC DISEASE, ACCORDING TO THE PATIENT'S RH FACTORS (N=397)

Patient Characteristics	Rh+. n: 359 (90.4 %)	Rh-. n: 38 (9.6 %)	p
Mean age±SD (min.-med.-max)	49.6±17.5 (17.0-47.0-92.0)	44.4±15.9 (19.0-43.0-85.0)	0.099*
Sex (M/F)	176/221 (45.7 %/54.3 %)	12/26 (31.6 %/68.4 %)	0.136**
At least one chronic disease (yes/no)	132/226 (36.9 %/63.1 %)	13/25 (34.2 %/65.8 %)	**0.883

* Mann-Whitney test was used.** Chi Square test was used.

TABLE 3. ANALYSIS OF ICU ADMISSION AND MORTALITY RATES ACCORDING TO PATIENTS' RH FACTORS

Rh	ICU admission		p	Mortality		p
	No n (%)	Yes n (%)		No n (%)	Yes n (%)	
Rh -	38 (100.0 %)	0 (0.0 %)	0.011	38 (100.0 %)	0 (0.0 %)	0.069
Rh +	306 (85.2 %)	53 (14.8 %)		330 (91.9 %)	29 (8.1 %)	
Total	344 (86.6 %)	53 (13.4 %)		368 (92.7 %)	29 (7.3 %)	

* Chi-Square test was used.

TABLE 4. COMPARISON OF EACH BLOOD GROUP WITH OTHER BLOOD GROUPS RELATING TO ICU ADMISSION AND MORTALITY RATES

Blood groups	ICU Admission		p	Mortality		p
	No n (%)	Yes n (%)		No n (%)	Yes n (%)	
Group O	103 (85,8 %)	17 (14.2 %)	0.877*	112 (93.3 %)	8 (6.7 %)	0.911*
Other	241 (87.0 %)	36 (13.0 %)		256 (92.4 %)	21 (7.6 %)	
Group A	175 (87.1 %)	26 (12.9 %)	0.922*	186 (92.5 %)	15 (7.5 %)	0.903*
Other	169 (86.2 %)	27 (13.8 %)		182 (92.9 %)	14 (7.1 %)	
Group B	47 (85,5 %)	8 (14.5 %)	0.946*	50 (90.9 %)	5 (9.1 %)	0.577**
Other	297 (86.8%)	45 (13.2 %)		318 (93.0 %)	24 (7.0 %)	
Group AB	19 (90.5 %)	2 (9.5 %)	1.000**	20 (95.2 %)	1 (4.8 %)	1.000**
Other	325 (86.4 %)	51 (13.6 %)		348 (92.6 %)	28 (7.4 %)	
Total	344 (86.6 %)	53 (13.4 %)		368 (92.7 %)	29 (7.3 %)	

* Chi-Square test was used.** Fisher's Exact Test was used.

Lewis, Kidd, MNS, and Kell[8]. Additionally, some red blood cell surface antigens have clinically important cellular functions, while some others are targets for immune system attacks in the course of infections[8].

For blood donors, the O blood group was evaluated as a higher risk in terms of HIV and Hepatitis B infection[9]. In another study, blood group O and Rh + were associated with a higher risk of Hepatitis B infection[10].

In our study, we tried to analyze the frequencies of ABO and Rh blood types in COVID-19 patients and the relationships of these frequencies with ICU admissions and mortality rates. To our knowledge, no study published in peer-reviewed journals related to this subject could be found in the literature. A few preprint or non-refereed studies have been published so far. Blood group A was reported to be associated with a higher risk of COVID-19, and blood group O was reported to be associated with a lower risk of COVID-19 in these studies[6,11,12]. People with O blood group were reported to be at lower risk for SARS coronavirus infection in a study published in 2005[5]. It is stated that the A-type antibody may provide protection by inhibiting the interaction between the virus and ACE2 receptor[13]. In a series of blood group analyses performed in our country, the frequencies of blood groups A, B, AB, and O were 40-45%, 15-19%, 5-14%, and 28-36%, respectively. The frequency of Rh positivity was reported as 84-92%, while the frequency of Rh negativity was reported as 8-16%[14]. In a study including 13116 cases from our local region, frequencies of blood groups were analyzed and frequencies of blood types A +, O +, and Rh – were found as 38.1%, 30.2%, and 15.2%, respectively[15]. A comparison of the data from these studies with our data reveals a quite similar distribution of blood groups, as well as a higher frequency of blood group A in COVID-19 patients. The detection of a high frequency of COVID-19 patients with blood group A may be caused by the deficiency of the A-type antibody protection, but it is not clear yet. The mechanism behind the susceptibility of blood group A to COVID-19 infection needs advanced analysis to be well understood.

In our study, no relationship was found between blood groups and mortality or ICU admission. The variables of age, gender, and having at least one chronic were similar in Rh + and Rh - patients. Regarding ICU admission, a statistically significant relationship was found between having Rh + factor and the ICU admission rate (p=0,011), and no significant relationship was found between Rh factor and mortality rates (p=0,069). Neither comparison analysis of O, A, B, and AB groups with other blood groups revealed a significant relationship with ICU admission and mortality.

According to these results, we can state that patients with A blood group might be at higher risk for COVID-19 infection and Rh + patients might show poor outcomes as they are at higher risk for ICU admission. More multicenter researches with a higher number of cases are needed to clarify the effects of ABO and Rh blood types on the prognosis.

CONCLUSION

A specific blood group might face more risk of COVID-19 infection. More need for ICU admission is seen in Rh + COVID-19 patients. Although statistically insignificant, all cases in which the outcome was death were found in the Rh + group.

Limitations

Our study has some limitations. It was conducted in a single center and has a relatively small number of patients.

Acknowledgments

We would like to thank our supervisors, Prof. Oguz Karabay, Prof. Yakup Tomak, and Prof. Ali Fuat Erdem. We thank all the medical, nursing, and technical staff from the Sakarya University Training and Application Hospital, for their dedicated care of patients during the COVID-19 pandemic.

Conflict of interest

The authors declare that they have no competing interests. Ethical standard: This study was conducted in accordance with the Declaration of Helsinki.

The study was approved by the Ethics Committee of Sakarya University Medical Faculty.

Author's Contribution

SY, HD: Data analysis and interpretation, drafting the article, critical revision of the article, final approval of the version; KI, ABG, DS, HK: Data collection, conception or design of the work, data analysis and interpretation, critical revision of the article, final approval of the version; EG, KS, HE, MK: Data analysis and interpretation, final approval of the version to be published.

RESUMO

OBJETIVO: *O objetivo deste estudo é analisar o significado prognóstico dos antígenos do grupo sanguíneo ABO e Rh, juntamente com vários parâmetros em pacientes acompanhados com o diagnóstico de COVID-19.*

MÉTODOS: *Foram avaliados 397 pacientes que foram acompanhados e tratados devido à infecção por COVID-19. Foram analisadas as idades, gêneros, doenças crônicas, antígenos do grupo sanguíneo ABO e Rh, taxas de internação em unidades de terapia intensiva (UTI) e taxas de mortalidade dos pacientes.*

A idade média de 397 pacientes com COVID foi de 47 ± 17 anos. Na análise do grupo sanguíneo dos pacientes, A Rh positivo (A +) foi o tipo sanguíneo mais frequentemente observado (176 dos pacientes, 44,3%), seguido pelo O Rh positivo (0 +) (109 dos pacientes, 27,5%) 38 dos pacientes eram Rh negativos (Rh -) (9,6%). 53 dos pacientes (13,4%) foram acompanhados em UTI e 29 faleceram (7,3%). Não houve mortalidade nem admissão na UTI para o grupo Rh. A comparação dos grupos Rh quanto à necessidade de admissão na UTI revelou uma taxa significativamente alta de admissão na UTI no grupo Rh + (p = 0,011), enquanto não foi encontrada relação significativa entre mortalidade e antígeno Rh (p = 0,069).

CONCLUSÃO: *O tipo sanguíneo mais frequentemente observado foi o A + entre os pacientes com COVID-19. O grupo sanguíneo Rh + foi encontrado em todos os casos admitidos na UTI e com evolução mortal. O grupo sanguíneo Rh + foi encontrado em um número significativamente alto de pacientes internados na UTI, enquanto nenhuma relação significativa foi encontrada entre a mortalidade e o grupo sanguíneo Rh.*

PALAVRAS-CHAVE: *Infecções por Coronavirus. Sistema ABO de Grupos Sanguíneos. Sistema do Grupo Sanguíneo Rh-Hr. Unidades de terapia intensive. Mortalidade.*

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-2019) situation reports 94. Geneva: World Health Organization; 2020. [cited 2020 May 30]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200423-sitrep-94-COVID-19.pdf?sfvrsn=b8304bf0_4
2. Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T, et al; Medical Treatment Expert Group for COVID-19. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest. 2020;S0012-3692(20)30710-8.
3. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504.
4. Li R, Tian J, Yang F, Lv L, Yu J, Sun G, et al. Clinical characteristics of 225 patients with COVID-19 in a tertiary hospital near Wuhan, China. J Clin Virol. 2020;127:104363.
5. Cheng Y, Cheng G, Chui CH, Lau FY, Chan PKS, Ng MHL, et al. ABO blood group and susceptibility to severe acute respiratory syndrome. JAMA. 2005;293(12):1450-1.
6. Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, et al. Relationship between the ABO blood group and the COVID-19 susceptibility. medRxiv preprint. doi: https://doi.org/10.1101/2020.03.11.20031096.
7. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;S0091-6749(20)30495-4.
8. Uhl L. Red blood cell antigens and antibodies. Uptodate. 2020. [cited 2020 May 30]. Available from: https://www.uptodate.com/contents/red-blood-cell-antigens-and-antibodies
9. Siransy LK, Nanga ZY, Zaba FS, Tufa NY, Dasse SR. ABO/Rh blood groups and risk of HIV infection and hepatitis B among blood donors of Abidjan, Côte D'ivoire. Eur J Microbiol Immunol. 2015;5(3):205-9.
10. Liu J, Zhang S, Liu M, Wang Q, Shen H, Zhang Y. Distribution of ABO/Rh blood groups and their association with hepatitis B virus infection in 3.8 million Chinese adults: a population-based cross-sectional study. J Viral Hepat. 2018;25(4):401-11.
11. Zeng X, Fan H, Lu D, Huang F, Meng X, Li Z, et al. Association between ABO blood groups and clinical outcome of coronavirus disease 2019: evidence from two cohorts. medRxiv preprint. doi: https://doi.org/10.1101/2020.04.15.20063107.
12. Fan H, Zhang L, Huang B, Zhu M, Zhou Y, Zhang H, et al. Retrospective analysis of clinical features in 101 death cases with COVID-19. medRxiv preprint. doi: https://doi.org/10.1101/2020.03.09.20033068.
13. Guillon P, Clément M, Sébille V, Rivain JG, Chou CF, Ruvoën-Clouet N, et al. Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology. 2008;18(12):1085-93.
14. Akın G, Dostbil N. Türkiye'de kan grubu araştırmaları. Ankara Üniversitesi Dil ve Tarih-Coğrafya Fakültesi Dergisi. 2005;45(2):1-15.
15. Cekdemir D, Ergenc H, Ucar A, Cekdemir YE, Gunduz M, Oren AC, et al. Blood groups distributions of donors/patients in a tertiary hospital. Sakarya Med J. 2018;8(4):753-8.

ORIGINAL ARTICLE

Investigation of the frequency of COVID-19 in patients treated with intravesical BCG

Oğuz Karabay[1]
Osman Köse[2]
Aysel Tocoglu[3]
Burak Uysal[2]
Hamad Dheir[3]
Selcuk Yaylaci[3]
Ertugrul Guclu[1]

1. Sakarya University Faculty of Medicine Department of Infectious Diseases, Sakarya, Turkey
2. Sakarya University Education and Research Hospital, Department of Urology, Sakarya, Turkey
3. Sakarya University Faculty of Medicine, Department of Internal Medicine, Sakarya, Turkey

http://dx.doi.org/10.1590/1806-9282.66.S2.91

SUMMARY

INTRODUCTION: *In this retrospective study, we aimed to investigate the frequency of COVID-19 in patients with and without BCG application due to bladder tumors.*

METHODS: *The presence of COVID-19 was investigated in 167 patients with BCG and 167 without bladder cancer. All patients were compatible with COVID-19 infection. Patients with RT-PCR positive for SARS-CoV-2 and/or Chest CT positive for viral pneumonia between March and May 2020 were included in the study.*

RESULTS: *A total of 334 patients were included in the study. The mean age of the 167 patients in the study group was 71.1±14.2 1 (min. 38.0– max. 98.0 years), 141 (84.4%) were male. The mean age of the 167 patients in the control group was 70.5±13.8 years (min. 41.0–max. 96.0 years), and 149 were male (p> 0.05). COVID-19 was detected in 5 patients in the BCG group and in 4 patients in the control group (P> 0.05).*

CONCLUSION: *Intravesical BCG administration does not decrease the frequency of COVID-19 infection.*

KEYWORDS: *COVID-19, Intravesical BCG*

INTRODUCTION

The COVID-19 outbreak from SARS-CoV-2, which started in China in 2019, caused a pandemic all over the world. In this disease, serious damage can occur in many organs, especially the lungs (Figure 1). Different treatment options continue to be investigated for COVID-19. This infection, which still has no effective treatment, spreads from country to country, infecting new people. Despite all efforts on vaccine production, an effective vaccine has not been found so far. Therefore, efforts to increase the immunity of individuals are considered important. Some information has been published recently showing that the Bacillus Calmette Guerin (BCG) vaccine can be used in the treatment of COVID-19[1].

DATE OF SUBMISSION: 13-Jun-2020
DATE OF ACCEPTANCE: 27-Jun-2020
CORRESPONDING AUTHOR: Selcuk Yaylacı
Sakarya University Faculty of Medicine Department of Internal Medicine
E-mail: yaylacis@hotmail.com

FIGURE: 1. COMPUTERIZED TOMOGRAPHY OF THE THORAX IN COVID-19 PATIENT

The BCG vaccine is a live bacterial vaccine from *Mycobacterium bovis*, which has been used to protect against tuberculosis for about a century. In the treatment of alternating bladder epithelial cell cancer, the BCG strain is administered into the bladder through a urethral catheter in high-risk patients to prevent relapse. BCG immunotherapy is applied in 6 doses for 6 weeks, for induction purposes, in non-muscle-invasive patients of high-risk (Figure 2). BCG therapy or any other immunoregulatory therapy is not used in patients with a tumor limited to the urothelium and classified as a low-risk[2]. After induction therapy, a maintenance treatment is given for 3 weeks, once a week with 6-month intervals for 3 years. The effect is non-specific stimulation, which takes a short time[3].

However, it has been reported that immunity enhanced by BCG may provide efficacy against COVID-19[3]. Although the epidemiological relationship between BCG and COVID-19 is striking, it has not been tested in well-designed clinical trials. Therefore, in the absence of evidence, the BCG vaccine cannot be recommended to prevent COVID-19. The results of ongoing RCTs will guide us further. However, what is the frequency of COVID-19 in those who still have BCG inside the bladder due to bladder cancer? According to our information, there is no study on this subject. With this study, for the first time, the frequency of COVID-19 was investigated in patients with bladder cancer.

METHODS

Center: This study was done in a tertiary hospital with a 1100- bed capacity. A total of > 2000 patients were followed-up in this hospital during the COVID-19 season.

The diagnosis of COVID-19 was based on the criteria of the Turkish National Health Commission. The COVID-19 data of all the patients included in the study were obtained from the hospital information system retrospectively. All the patients were compatible with COVID-19 infection. Patients with RT-PCR positive for SARS-CoV-2 and/or Chest CT positive for viral pneumonia between March and May 2020 were included in the study.

Patients: We included those with no additional disease affecting the immune system, followed up by the Sakarya University Urology clinic and diagnosed with non-muscle-invasive, altered epithelial cell bladder cancer. This descriptive retrospective cross-sectional study was conducted with patients with bladder cancer, between March 15, and May 20, 2020.

Patients were divided into two groups: those who received intravesical BCG due to bladder cancer (Study group) and those who did not receive BCG despite the diagnosis of bladder cancer (Control group).

Study group patients: In the urology service of our hospital, patients who received intra-cavitary BCG immunotherapy due to non-muscle-invasive

FIGURE 2. INTRAVESICAL BCG APPLICATION

exchange epithelial cell bladder cancer were selected retrospectively.

- Bladder cancer was diagnosed as a result of histopathological examination of the tumoral area, which was observed by transurethral resection, in cystoscopy performed on patients with suspected bladder cancer. Patients diagnosed with non-invasive bladder cancer as a result of histopathological examination were divided into low-, medium-, and high-risk groups based on the pathological stage, gradient, and clinical course of the tumor. Intracavitary BCG immunotherapy was given to patients who were in the high-risk group. Patients in the low- and medium-risk group were treated with different methods that did not include immunotherapy.
- BCG application in the study group: After transurethral resection, intravesical ONCOTICE (2-8 x 108 CFU [Colony-Forming Unit]) Bacillus Calmette-Guérin 81 mg Pasteur BCG was given to the non-muscle invasive group once a week for 6 weeks after transurethral resection. Afterward, intracavitary BCG administration was given as maintenance therapy to patients with 3-month intervals for 3 years, and once a week for 6 years intervals.

Control group patients: Patients registered in the urology service of our hospital, diagnosed with low-risk bladder cancer histopathologically, and living in the city of Sakarya during an epidemic without BCG or any other immune regulator treatment were selected retrospectively.

Statistical analysis

All analyses were performed in Epi-Info ver 6.0 (CDC-USA). Statistical analysis was performed using Independent Samples T-test and Yates correction chi-square test. A P value <0.05 was accepted as significant.

The study was carried out upon receiving the approval of the Ethics Committee of the Sakarya University Faculty of Medicine (No: 71522473 /050.01.04/248).

RESULTS

A total of 334 patients were included in the study. The mean age of the 167 patients in the study group was 71.1 ± 14.2 1 (min. 38.0– max. 98.0 years), and 141 (84.4%) were male. The mean age for the 167 patients in the control group was 70.5 ± 13.8 (min. 41.0 – max. 96.0 years), and 149 were male (p> 0.05) (Figure 3). COVID-19 was detected in 5 patients in

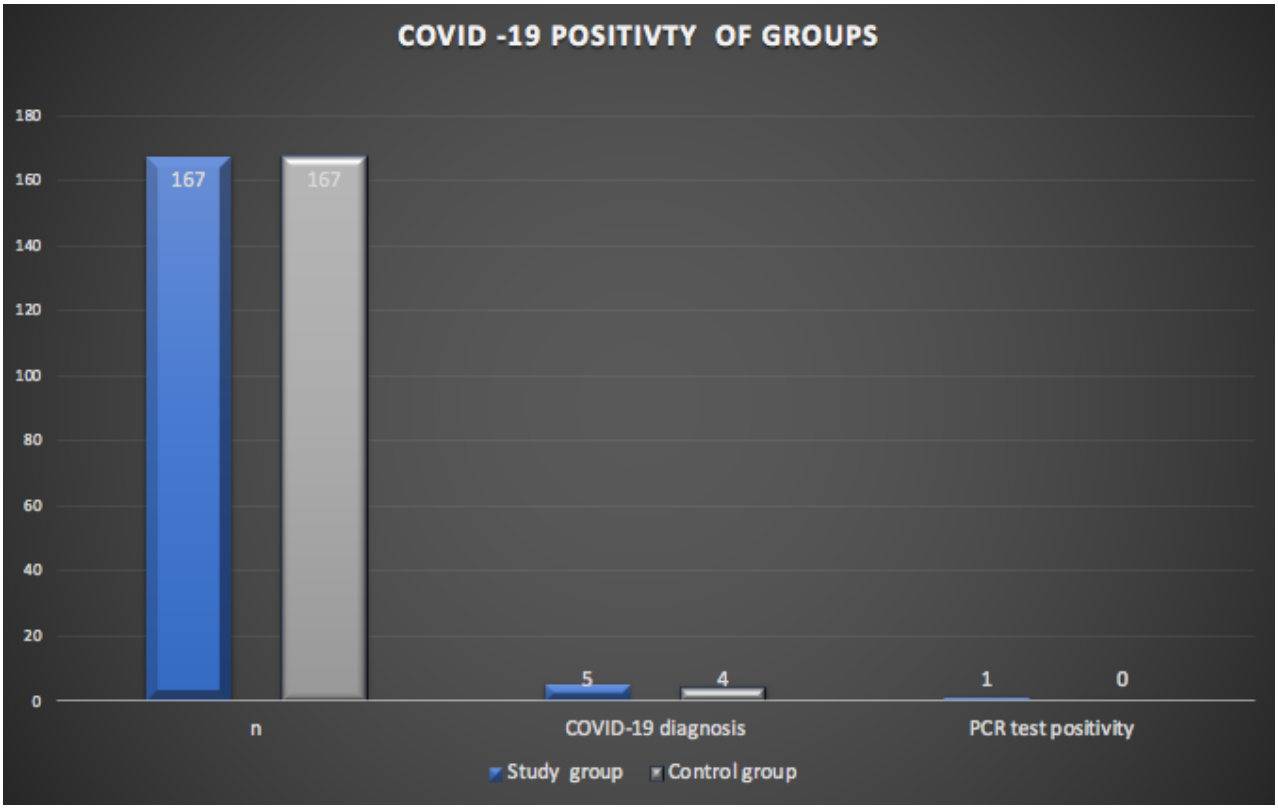


FIGURE 3. COVID-19 TEST POSITIVITY OF GROUPS

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

Parameter	Study group	Control group	P-value
n	167	167	NA
Male	141 (84.4%)	149 (89.2%)	>0.05
Female	26 (15.5%)	18 (10.8%)	>0.05
Mean age	71.1 ± 14.2 1	70.5 ± 13.8	>0.05
COVID-19 diagnosis	5 (2.9%)	4 (2.3%)	>0.05
PCR test positivity	1 (0,05%)	0	NA
Mean age of COVID-19 Positive patients	70.04	73.02	>0.05

NA: Not Applicable

the BCG group and in 4 patient in the control group (P> 0.05) (Table 1).

DISCUSSION

Numerous epidemiological, clinical, and immunological studies have shown that BCG vaccination affects immunity to infections, thereby reducing morbidity and mortality. BCG is reported to increase immunity to viral infections by inducing heterologous lymphocyte activation by increasing cytokine production, macrophage activity, T-cell responses, and antibody titers[4]. BCG has been used in intravesical immunotherapy of bladder cancers for nearly 40 years. It has been administered intravesically in recurrent superficial bladder cancers and has been reported to reduce cancer recurrence rates[5]. In a study, BCG vaccination has been shown to reduce the incidence of respiratory syncytial virus infection[6].

BCG stimulates congenital immunity, and this can be important to create a defense against viral respiratory infections. This is a different route of administration than the arm, which is the standard. While the BCG vaccine protects against the herpes simplex virus type 2 (HSV2), subcutaneous administration of muramyl dipeptide (MDP), a component of the mycobacterium cell wall, protected against the vaccine virus and HSV 2 infections in mice[7]. However, in this study, patients receiving BCG received it administered into the bladder. Therefore, our findings do not fully demonstrate the effectiveness of standard therapy[8].

BCG is a bacterial vaccine. It is not surprising that this vaccine does not sufficiently provide protection against a pervasive virus such as COVID-19. More importantly, the fact that our study group consisted of cancer patients is also important for limiting the effects of BCG on the immune system. However, the use of a cancer group and a control group also provides a comparison. After BCG vaccination, there was increased production of pro-inflammatory cytokines such as IL-1, tumor necrosis factor (TNF), and IL-6[9]. However, one of the most feared situations in COVID-19 patients who died is macrophage activation syndrome caused by the excessive increase of cytokines such as IL-1, IL-6, IL-8 in the blood. BCG vaccine, which is expected to be useful in this, may conversely harm this patient group[10].

However, despite all this information, there is no clear evidence that the intravesical BCG vaccination protects people against COVID-19. Indeed, in this study, we found that the frequency of COVID-19 in those who received intravesical BCG was not different from those who did not. According to our findings, we could not show the utility of intravesical BCG in the prevention of COVID-19. However, the data we obtained are based on the results of intravesical administration. The hypothesis that intra-dermal application can protect against COVID-19 needs to be tested in rigorous randomized clinical trials.

Author's Contribution

OK: Data analysis and interpretation, drafting the article, critical revision of the article, approval of the final version.

OK: Conception and design of the work, data analysis and interpretation, critical revision of the article, final of the final version.

AT; BU; HD; SY; EG: Data collection, data analysis and interpretation, critical revision of the article, approval of the final version to be published.

RESUMO

INTRODUÇÃO: *Neste estudo retrospectivo, objetivou-se investigar a frequência de COVID-19 em pacientes com e sem aplicação de BCG por tumor de bexiga.*

MÉTODOS: *A presença de COVID-19 foi investigada em 167 pacientes com BCG e 167 sem câncer de bexiga. Todos os pacientes compatíveis para infecção por COVID-19. Resumidamente, os pacientes foram incluídos no estudo com RT-PCR positivo para Sars-CoV-2 e/ou TC de tórax positivo para pneumonia viral entre março e maio de 2020.*

RESULTADOS: *Um total de 334 pacientes foi incluído no estudo. A idade média dos 167 pacientes no grupo de estudo foi de 71,1±14,2 1 (min. 38,0 - máx. 98,0 anos), 141 (84,4%) eram do sexo masculino; 167 pacientes do grupo controle tinham idade média de 70,5±13,8 (min. 41,0 - máx. 96,0 anos) e 149 eram do sexo masculino (p>0,05). A COVID-19 foi detectada em cinco pacientes no grupo BCG e em um no grupo controle (p>0,05).*

CONCLUSÃO: *A administração intravesical de BCG não diminui a frequência da infecção por COVID-19.*

PALAVRAS-CHAVE: *COVID-19. BCG intravesical.*

REFERENCES

1. Sharma M, Surani S. Searching an Effective Therapy for the Coronavirus Pandemic: Do We See Light at the End of the Tunnel? [Internet]. Cureus. 2020. Available from: http://dx.doi.org/10.7759/cureus.7415
2. Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol [Internet]. 2020 Apr 29; Available from: http://dx.doi.org/10.1016/j.eururo.2020.03.055
3. Kumar J, Meena J. Demystifying BCG Vaccine and COVID-19 Relationship. Indian Pediatr [Internet]. 2020 Apr 30; Available from: https://www.ncbi.nlm.nih.gov/pubmed/32358227
4. Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. Clin Microbiol Infect. 2019 Dec;25(12):1473–8.
5. Iori F, Di Seri M, De Nunzio C, Leonardo C, Franco G, Spalletta B, et al. Long-term maintenance bacille Calmette-Guérin therapy in high-grade superficial bladder cancer. Urology. 2002 Mar;59(3):414–8.
6. Stensballe LG, Nante E, Jensen IP, Kofoed P-E, Poulsen A, Jensen H, et al. Acute lower respiratory tract infections and respiratory syncytial virus in infants in Guinea-Bissau: a beneficial effect of BCG vaccination for girls community based case-control study. Vaccine. 2005 Jan 26;23(10):1251–7.
7. Ikeda S, Negishi T, Nishimura C. Enhancement of non-specific resistance to viral infection by muramyldipeptide and its analogs. Antiviral Res. 1985 Aug;5(4):207–15.
8. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? Nat Rev Immunol [Internet]. 2020 May 11; Available from: http://dx.doi.org/10.1038/s41577-020-0337-y
9. Kleinnijenhuis J, Quintin J, Preijers F, Joosten LAB, Ifrim DC, Saeed S, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. Proc Natl Acad Sci U S A. 2012 Oct 23;109(43):17537–42.
10. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033–4.

REVIEW ARTICLE

Impact of oral hygiene in patients undergoing mechanical ventilation in the COVID-19 pandemic

Dayane Helen Ferreira Silva[1]
Júlia Hinkelmann de Camargos[1]
Jefferson Guimarães Rodrigues[1]
Leilismara Sousa Nogueira[2]
Dênia Alves de Azevedo[3]
Maria das Graças Carvalho[4]
Melina de Barros Pinheiro[5]

1. Cirurgiã-dentista. Mestranda em Ciências da Saúde (UFSJ). Divinópolis, MG, Brasil
2. Cirurgião-dentista, aluno do curso de especialização em Prótese Dentária (SLMANDIC), Belo Horizonte, MG, Brasil.
3. Farmacêutica bioquímica. Doutora em Ciências da Saúde (UFSJ), Universidade Federal de São João del-Rei, Campus Centro-Oeste Dona Lindu, Divinópolis, MG, Brasil.
4. Médica pneumologista. Docente do Curso de Medicina na Universidade Federal de São João del-Rei (UFSJ), Divinópolis, MG, Brasil
5. Farmacêutica bioquímica. Doutora em Hematologia pela Universidade de Southampton. Docente titular do Curso de Farmácia na Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brasil.
6. Farmacêutica bioquímica. Doutora em Ciências Farmacêuticas (UFMG). Docente do Curso de Medicina na Universidade Federal de São João del-Rei (UFSJ), Campus Centro-Oeste Dona Lindu, Divinópolis, MG, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.96

SUMMARY

COVID-19, caused by SARS-CoV-2, can present respiratory complications that often lead patients to depend on mechanical ventilation (MV) for several days. It is known that Pneumonia Associated with Mechanical Ventilation (PAMV) is frequent in patients who use this equipment for a long time. As a consequence of COVID-19, its prolonged use can lead to a worse prognosis for the patients. For this reason, in addition to the insufficiency of devices for mechanical ventilation to meet the current demand, it is necessary to adopt measures aimed at preventing complications that may aggravate the patient's clinical condition and, consequently, increase the average hospital stay and the respective hospital care costs. Therefore, the objective of this study was to discuss, in a concise and practical way, and based on the available literature, the importance of adopting adequate oral hygiene protocols for patients on mechanical ventilation. Based on the data obtained, it was identified that the adoption of effective oral hygiene measures, especially under the supervision of dental professionals, can contribute to the reduction of morbidity and mortality associated with MV, resulting in greater availability of mechanical ventilation equipment. Since such equipment is in great demand during the COVID-19 pandemic, the knowledge and implementation of effective oral hygiene measures will undoubtedly have an impact on improving the quality of care offered to patients, therefore benefiting all those in critical health conditions and assisted in ICUs.

KEYWORDS: *Respiration, Artificial. Coronavirus Infections. Pneumonia, Ventilator-Associated. Oral hygiene. Severe Acute Respiratory Syndrome.*

INTRODUCTION

In December 2019, an outbreak of pneumonia caused by a new Coronavirus (CoV), later named severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2), began in the city of Wuhan, in the Hubei province, China, and rapidly spread to 24 other countries, receiving the name of Coronavirus Disease 2019 (COVID-19)[1-5]. In the last 20 years, the coronaviruses were responsible for two major epidemics, the Severe

DATE OF SUBMISSION: 04-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Melina de Barros Pinheiro
Universidade Federal de São João del-Rei (UFSJ), Campus Centro-Oeste Dona Lindu, Rua Sebastião Gonçalves Coelho, 400, Bloco D, sala 308.1, Bairro Chanadour, 35501-296 - Divinópolis, MG, Brasil.
E-mail: melinapinheiro@ufsj.edu.br

Acute Respiratory Syndrome (SARS), caused by the Severe Acute Respiratory Syndrome Coronavirus (Sars-Cov), in 2002; and the Middle East Respiratory Syndrome (Mers), caused by the Middle East Respiratory Syndrome Coronavirus (Mers-Cov), in 2012[6-8]. Considering that the Sars-CoV-2 is still spreading throughout the world, on 30 January 2020, the World Health Organization (WHO) declared a state of emergency in public health, and on 11 March 2020, declared the COVID-19 pandemic[9,10].

Due to its recent discovery, knowledge about COVID-19 is still limited. There is no specific antiviral treatment or vaccines currently available, scientists throughout the world test have been testing new drugs and approaches, but further studies are needed to obtain conclusive results[11].

On 13 March 2020, the WHO issued a document summarizing the guidelines and scientific evidence from the treatment of previous epidemics caused by CoV. Among the recommendations, they presented strategies to treat respiratory failure in severe cases; this included mechanical ventilation as an important ally in these cases[12].

Therapy for patients with severe cases of COVID-19 has been symptomatic, and oxygen therapy is the primary intervention. However, in cases in which respiratory failure is resistant to oxygen therapy, it is necessary to use mechanical ventilation, which brings with it not only the benefits for patients but also the risk of developing complications[13].

Pneumonia Associated with Mechanical Ventilation (PAMV) is one of the most common infections related to intubated patients, so it is necessary to adopt measures to reduce its occurrence[14]. In this context, oral hygiene, done correctly, is a beneficial modifier factor for the occurrence of this infection. Thus, this brief but concise and essentially practical review aims to emphasize the importance of effective oral hygiene in patients on mechanical ventilation and address its positive impacts on the outcome of patients affected by COVID-19.

USE OF MECHANICAL VENTILATORS

Mechanical ventilation (MV) is a support method for the treatment of patients with acute or exacerbated chronic respiratory failure. Its main objectives are: to maintain gas exchanges, relieve the strain on respiratory muscles, revert or prevent the fatigue of respiratory muscles, decrease the consumption of oxygen, and alleviate respiratory discomfort[15].

The Chinese Center for Disease Control and Prevention (CCDC) assessed the severity of COVID-19 cases by analyzing 72,314 records, including: 44,672 (61.8%) confirmed cases, 16,186 (22.4%) suspected cases, 10,567 (14.6%) clinically diagnosed cases, and 889 asymptomatic cases (1.2%). From this study, we can conclude that 80.9% of the total confirmed cases were "mild". However, it is alarming that serious cases accounted for 13.8% and critical cases, 4.7% of the cases confirmed, and that 5% of the total cases required an Intensive Care Unit (ICU) and 2.3% mechanical ventilation[16.17].

Lai et al.[18], after evaluating three [19-21] large-scale Chinese studies to understand the manifestations of COVID-19, concluded that out of the 278 patients with pneumonia caused by Sars-CoV-2, 72 (25.9%) were admitted to the ICU, 56 (20.1%) developed acute respiratory distress syndrome, and 23 (8.3%) needed mechanical ventilation.

In view of the high demand for this equipment throughout the world due to the COVID-19 pandemic, this item is already considered scarce in the market. According to data collected from the *Cadastro Nacional de Estabelecimentos de Saúde* (CNES)[22], Brasil had, in April 2020, 70,516 respirators in operation, considering both public and private healthcare institutions, which means 33 pieces of equipment for every 100,000 inhabitants[23]. However, even with the addition of 5,649 machines, in relation to January of 2020, their distribution throughout the Brazilian territory is uneven, since 51.4% of them are in the Southeastern region[22]. Therefore, it is important to devise strategies to reduce the damage caused by the lack of such equipment and to reduce the duration of its use, when possible.

Complications from the use of mechanical ventilators

It is known that Pneumonia Associated with Mechanical Ventilation (PAMV) is an important healthcare-related infection (HCRI) and causes an increase in mortality, days of ICU stay, and hospital costs[14]. In the context of the COVID-19 pandemic, these indicators may be even more worrying, considering the pathogenesis of Sars-CoV-2 and the complications already associated with this infection.

In 2011, approximately 157 thousand cases of healthcare-related pneumonia were reported in ICUs in the United States (USA), and 39% were considered

VAP. The incidence density of this infection remains approximately in the range of 4.4 cases/1,000 days of mechanical ventilation in American ICUs[24]. In Brasil, in a study carried out in the University Hospital of the North of Minas Gerais with 190 ICU patients, the incidence of VAP was 23.2% and there was a positive association between the occurrence of pneumonia, duration of hospital stay >15 days, duration of MV >10 days, and reintubation[25].

It has been proposed that PAMV occurs through four mechanisms, which are: (1) aspiration of secretions, (2) inhaling of contaminated aerosols, (3) dissemination of bacteria through the hematogenic route, and (4) translocation of bacteria from the gastrointestinal tract. Of these mechanisms, the aspiration of secretion from the oral cavity and oropharynx is the most relevant, and it is called aspiration pneumonia[26].

MEASURES TO REDUCE THE RISK OF PAMV

In intubated patients, the coughing reflex, which promotes airway clearance, does not occur or occurs precariously. Since the airways are frequently contaminated by microorganisms of the nasal, oral, and pharyngeal regions, the chances of contamination, without such mechanical clearing, greatly increase. Therefore, oral hygiene can reduce oral colonization, prevent infections, and maintain the integrity of the mucosa, in addition to providing some comfort for the patient[27].

In hospital environments, the oral hygiene of patients is performed by nursing technicians, under the supervision of nurses or physicians responsible for the patient. However, this task is not a priority in the everyday lives of these professionals, perhaps to a lack of knowledge about the importance of the procedure or because it is not part of the routine standard care in institutions[27]. In this sense, the curricula for professional nursing training should be reformulated so that nurses have sufficient theoretical support to guide the rest of the team on oral care.

The contribution of effective programs of oral hygiene is widely known for reducing the indices of PAMV28.29. However, when it comes to techniques, frequency, and products to be used in the process of oral hygiene of intubated patients, there is still no consensus on which are the most effective. Some studies recommend brushing the teeth twice a day[30]. Regarding the use of products, Wakiuchi et al.[31], after analyzing 17 studies on the topic, identified that four recommended the use of alcoholic chlorhexidine 0.12%. The Brazilian Health Regulatory Agency (Anvisa)[32] recommends, with a high level of evidence, using chlorhexidine for oral hygiene to prevent HCRI. A study that evaluated oral hygiene with 0.12% chlorhexidine every 12 hours, in 105 ICU patients, concluded that VAP occurred less frequently in the group that received the intervention (15.9%) than in the control group (16.2%), which was composed of 108 patients[33].

It is worth mentioning that, in patients hospitalized in the ICU, oral hygiene can become precarious by the association of some factors, such as: reduction of the natural cleaning of the mouth provided by chewing and the movement of the tongue and cheeks, and possible reduction in the salivary flow caused by some medications. In addition, when there is the presence of a tracheal tube, the access to the oral cavity becomes even more difficult and may increase the formation of biofilm[34].

An important contribution to improve the oral health care of patients in MV is including a dentistry team in patient care. A study conducted by Souza et al.[35] evaluated the inclusion of a dentistry team in a public hospital in the city of Belo Horizonte, MG, aiming to implement a new oral hygiene protocol using 0.12% chlorhexidine to prevent infections associated with the ICU environment. The *ventilation bundle,* a protocol of measures based on evidence and implemented together, was deployed by the medical and nursing team to reduce the incidence of PAMV. Pneumonia, which was the main pathological manifestation from ICU infections (33.3%), was no longer the most frequent event (3.5%) after the implementation of the oral hygiene protocol. The process of oral hygiene is not always included in *the bundle*; however, the inclusion of the procedure is recommended given its proven positive impact. Regarding the perception of professionals involved in the care of these patients on the inclusion of dentistry in the ICU, 100% were favorable to it, and 62% acknowledged the contribution of the oral hygiene protocol in reducing the number of VAP cases.

Franco et al.[36] suggest a oral hygiene protocol to be carried out by a dental surgeon along with the nursing team. It begins with basic principles, covering, for example, the positioning of the patient on the bed (dorsal decubitus at 30 to 45 degrees) and the observation of the patient's monitoring parameters, which must be maintained after the procedure. Oral

hygiene must be carried out using a swabbing device and chlorhexidine 0.12%, every 12 hours. The protocol includes the following steps: (1) Disinfect hands; (2) put on sterile gloves; (3) constantly aspire the oral cavity during the procedure; (4) carry out oral hygiene with a swab soaked in chlorhexidine 0.12% on tooth surfaces, mucosa, palate, dorsum of the tongue, and intubation tube; and (5) apply oral lubricant on the lips every 6 hours to minimize dryness (Figure 1). According to Santos et al.[37], the use of a tongue scraper leaner is also an effective mechanism to reduce biofilm in patients undergoing mechanical ventilation.

Dental surgeons are still not part of most hospital teams. The main obstacle to their inclusion is the lack of prioritization of dental care in the face of the many complications that patients already present[38]. However, it is worth mentioning that, when present, the dentistry work should focus on patient care, aiming to reduce the risk of aggravation and/or systemic complications as a result of their oral health, this includes a prior assessment of the patient, continuous monitoring during their hospital stay, and follow-up after the completion of the treatment[34.39]. Thus, the inclusion of hospital dentistry is important to promote integral patient care through a multidisciplinary team, and, consequently, improve the health condition[40].

FIGURE 1. ORAL HYGIENE PROTOCOL IN PATIENTS UNDERGOING MECHANICAL VENTILATION. ADAPTED FROM LAMBERTUCCI ET AL.[36]

Given the above, it is expected that dental support in severe cases, when the survival of the patient requires MV, can be widely recognized as a strategy that can effectively contribute to the reduction of comorbidities, provide more comfort, and improve the general conditions of the patient.

FINAL CONSIDERATIONS

Pneumonia Associated with Mechanical Ventilation (PAMV) is an important complication in patients in intensive care and undergoing mechanical ventilation, with a great impact on health indicators. Although there is no scientific consensus about techniques, frequency, and products to be used in the process of oral hygiene of intubated patients, chlorhexidine has been the most recommended, including by the Brazilian National Health Agency. Additional measures, such as the removal of the dental biofilm and orotracheal aspiration, may help to reduce the incidence, duration, and aggravation of PAMV cases. These measures are essential, particularly in the current pandemic scenario, in which the pathogenesis of Sars-CoV-2 and the complications from COVID-19 often lead to the use of MV. Considering the documented number of mechanical ventilators, which are insufficient to meet the many critical cases of COVID-19, measures that may reduce the need for MV are very welcome and should be widely disseminated among health professionals and the population in general.

Finally, it is worth reiterating that the inclusion of dentistry in hospital environments is also an important ally, both in the implementation of oral hygiene protocols and in conducting studies that might lead to conclusions about the procedures and products that are more effective in oral health care and, consequently, in reducing the morbidity and mortality of patients.

Therefore, it is recommended that public health authorities stimulate the joint participation, responsibility, and continuing education of all professionals involved in the oral hygiene of patients undergoing mechanical ventilation in ICUs, and, in particular in serious cases of COVID-19. By effectively deploying and implementing this strategy, there will be a

significant gain in the status of patients under treatment and hospitalized in ICUs due to the worsening of Sars-CoV-2 infections, as well as an optimization regarding the use of equipment intended for MV.

Acknowledgments

The present study was carried out with the support of the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (Capes) - Funding code 001.

Author's Contribution

1, 2, 3 - Project Concept, data curatorship, research, methodology, and drafting.

4, 5, 6 - Data analysis, methodology, and review of the draft and final text.

7 - Concept, data analysis, methodology, project management, supervision, review of the draft and final text.

RESUMO

A COVID-19, causada pelo Sars-CoV-2, pode apresentar complicações respiratórias que, muitas vezes, levam o paciente a depender da ventilação mecânica por vários dias. Sabe-se que a Pneumonia Associada à Ventilação Mecânica (PAVM) é frequente nos pacientes que utilizam esse equipamento por um longo período de tempo e que sua ocorrência, consequente à COVID-19, pode cursar com um pior prognóstico para o paciente. Por esse motivo, e somado à insuficiência de aparelhos para atendimento da demanda atual, faz-se necessária a adoção de medidas que visem à prevenção de complicações que possam agravar o quadro clínico do paciente e, consequentemente, aumentar o tempo médio de internação e os respectivos custos da assistência. Sendo assim, o objetivo deste estudo foi discorrer de forma concisa e prática, com base na literatura disponível, sobre a importância da adoção de protocolos adequados de higiene oral nos pacientes em ventilação mecânica. Com base nos dados obtidos, identificou-se que a adoção de medidas efetivas de higiene oral, principalmente sob a supervisão do profissional dentista, pode contribuir para a redução da morbimortalidade associada à PAVM, resultando em maior disponibilidade de equipamentos de ventilação mecânica. Desde que tais equipamentos estão sendo muito demandados durante a pandemia da COVID-19, o conhecimento e a implantação de medidas efetivas de higiene oral, indubitavelmente, repercutirão na melhoria da qualidade da assistência oferecida aos pacientes, portanto, beneficiando todos aqueles em situação crítica de saúde e assistidos em UTIs.

PALAVRAS-CHAVE: *Respiração artificial. Infecções por coronavírus. Pneumonia associada à ventilação mecânica. Higiene bucal. Síndrome respiratória aguda grave.*

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
2. Cossarizza A, De Biasi S, Guaraldi G, Girardis M, Mussini C; Modena COVID-19 Working Group (MoCo19)#. SARS-CoV-2, the virus that causes COVID-19: cytometry and the new challenge for global health. Cytometry A. 2020;97(4):340-3.
3. Gorbalenya A, Baker S, Baric R. Severe acute respiratory syndrome-related coronavirus: the species and its viruses - a statement of the Coronavirus Study Group. bioRxiv. 23 Feb 2020 2020:1-15.
4. Xu H, Zhong L, Deng J, Jiakuan Peng, Hongxia Dan, Xin Zeng, et al. High expression of ACE 2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12(1):8.
5. World Health Organization. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Geneva: World Health Organization; 2020. [cited 2020 May 23]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020.
6. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev. 2007;20(4):660-94.
7. Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin Microbiol Rev. 2015;28(2):465-522.
8. Peng X, Xu X, Li Y, Cheng L, Zhou X, Ren B. Transmission routes of 2019-nCoV and controls in dental practice. Int J Oral Sci. 2020;12(1):9.
9. Bouadma L, Lescure FX, Lucet JC, Yazdanpanah Y, Timsit JF. Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists. Intensive Care Med. 2020;46(4):579-82.
10. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Geneva: World Health Organization; 2020. [cited 2020 May 23]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-COVID-19---11-march-2020.
11. World Health Organization. There are currently no drugs licensed for the treatment or prevention of COVID-19. Geneva: World Health Organization; 2020. [cited 2020 May 18]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters
12. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance 2020. [cited 2020 May 18]. Available from: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf
13. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). In: StatPearls. Treasure Island: StatPearls Publishing; 2020.
14. CDC. Pneumonia (ventilator-associated [VAP] and non-ventilator-associated pneumonia [PNEU]) event. [cited 2020 May 18]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf
15. Carvalho CR, Toufen Jr C, Franca SA. Mechanical ventilation: principles, graphic analysis and ventilatory modalities. J Bras Pneumol. 2007;33(Suppl 2S):S54-70.
16. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(2):145-51.
17. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
18. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):105924.

19. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

20. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.

21. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.

22. Brasil. Ministério de Saúde. Cadastro Nacional de Estabelecimentos de Saúde (CNES). [cited 2020 May 18]. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?cnes/cnv/equipobr.def

23. Instituto Brasileiro de Geografia e Estatística. Projeção da população do Brasil e das Unidades da Federação. [cited 2020 May 18]. Available from: https://www.ibge.gov.br/apps/populacao/projecao/

24. Dudeck MA, Weiner LM, Allen-Bridson K, Malpiedi PJ, Peterson KD, Pollock DA, et al. National Healthcare Safety Network (NHSN) report, data summary for 2012, device-associated module. Am J Infect Control. 2013;41(12):1148-66.

25. Mota EC, Oliveira SP, Silveira BRM, Silva PLN, Oliveira AC. Incidência da pneumonia associada à ventilação mecânica em unidade de terapia intensiva. Medicina (Ribeirao Preto Online). 2017;50(1):39-46.

26. Lorente L, Blot S, Rello J. Evidence on measures for the prevention of ventilator-associated pneumonia. Eur Respir J. 2007;30(6):1193-207.

27. Orlandini GM, Lazzari CM. Conhecimento da equipe de enfermagem sobre higiene oral em pacientes criticamente enfermos. Rev Gaúcha Enferm. 2012;33(3):34-41.

28. Chlebicki MP, Safdar N. Topical chlorhexidine for prevention of ventilator-associated pneumonia: a meta-analysis. Crit Care Med. 2007;35(2):595-602.

29. Ames NJ, Sulima P, Yates JM, McCullagh L, Gollins SL, Soeken K, et al. Effects of systematic oral care in critically ill patients: a multicenter study. Am J Crit Care. 2011;20(5):e103-14.

30. Halm MA, Armola R. Effect of oral care on bacterial colonization and ventilator-associated pneumonia. Am J Crit Care. 2009;18(3):275-8.

31. Wakiuchi J, Fontes MCF, Papa MAF. Oral hygiene in patients under mechanical ventilation: an integrative review. Rev enferm UFPE on line. 2014;8(supl. 1):2479-86.

32. Brasil. Agência Nacional de Vigilância Sanitária. Medidas de prevenção de infecção relacionada à assistência à saúde. Brasília: Anvisa; 2017. p.29-31.

33. Vidal CFL. Impacto da higiene oral com clorexidina com e sem escovação dental na prevenção da pneumonia associada à ventilação mecânica: estudo randomizado [Tese de doutorado]. Recife: Centro de Ciências da Saúde, Universidade Federal de Pernambuco; 2014.

34. Silva IO, Amaral FR, Cruz PM, Sales TO. A importância do cirurgião-dentista em ambiente hospitalar. Rev Méd Minas Gerais. 2017;27:e-1888.

35. Souza AF, Guimarães AC, Ferreira EF. Avaliação da implementação de novo protocolo de higiene bucal em um centro de terapia intensiva para prevenção de pneumonia associada à ventilação mecânica. REME Rev Min Enferm. 2013;17(1):177-84.

36. Franco JB, Jales SMCP, Zambon CE, Fujarra FJC, Ortegosa MV, Guardieiro PFR, et al. Higiene bucal para pacientes entubados sob ventilação mecânica assistida na unidade de terapia intensiva: proposta de protocolo. Arq Med Hosp Fac Cienc Med Santa Casa São Paulo. 2014;59(3):126-31.

37. Santos PS, Mariano M, Kallas MS, Vilela MC. Impact of tongue biofilm removal on mechanically ventilated patients. Rev Bras Ter Intensiva. 2013;25(1):44-8.

38. Morais TMN, Silva A, Avi ALRO, Souza PHR, Knobel E, Camargo LFA. A importância da atuação odontológica em pacientes internados em unidade de terapia intensiva. Rev Bras Ter Intensiva. 2006;18(4):412-7.

39. Costa ACO, Rezende NPM, Martins FM, Santos PSS, Gallottini MHC, Ortega KL. A odontologia hospitalar no serviço público do estado de São Paulo. Rev Assoc Paul Cir Dent. 2013;67(4):224-8.

40. Silva EDA, Oliveira RLB, Azevedo LM, Felix VB. A importância da equipe odontológica no ambiente hospitalar. GEP News. 2017;1(4):14-8.

REVIEW ARTICLE

Chest tubes in COVID-19 times: a safe way to protect the team

Bruno José da Costa Medeiros[1]
Fernando Luíz Westphal[1]

1. Universidade Federal do Amazonas, Programa de Pós-Graduação em Cirurgia, Manaus, AM, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.102

SUMMARY

INTRODUCTION: *What has been published so far regarding safe methods to deal with chest tube insertion during COVID-19.*

METHODS: *A descriptive study of the literature available in the Medline/PubMed, Lilacs, Scopus databases and specialized books. The search was carried out using the terms "infectious diseases"; "COVID-19"; "Chest tubes".*

RESULTS: *This paper aggregates and consolidates some old concepts to new tactics to minimize the contamination of teams who deal with chest tubes, before, during, and after the procedure.*

CONCLUSIONS: *Health officials are under increasing pressure to control the spread of COVID-19, which is a very virulent disease. Our analysis brought together old rules against contamination along with new tactics for professionals who deal with chest drains in order to minimize the contamination of teams during the Pandemic.*

KEYWORDS: *Communicable Diseases. Coronavirus Infections. Chest tubes.*

INTRODUCTION

So far, 1,086,990 cases of the new coronavirus have been recorded in Brasil, with 50,659 deaths in the entire territory[1]. As in other parts of the world, there is great concern about the contamination of health professionals who are dealing daily with suspected and confirmed patients of this new disease.

In China, the initial epicenter of the disease, more than 3,300 cases were reported among health professionals and about 22 deaths[2].

Only among nursing professionals, 30 deaths were registered and another 4,000 had to be removed from work due to COVID-19, by April 2020 in Brasil[3].

The SARS COV-2 that leads to COVID-19 has already been shown to be viable in aerosols and transmitted through droplets[4].

Chest tube insertion is one of the most common procedures performed in trauma hospitals, Intensive Care Units, and elective surgery services, not only by surgeons but also by Clinicians and Emergency Doctors.

It is a procedure with great potential for generating aerosol during the procedure and the convalescence of the disease that generated the indication for drainage, especially in patients with continuous aerial escape[5].

The purpose of this document is to list some maneuvers and precautions that can minimize the contamination of the team during the management of chest drains in this Pandemic.

DATE OF SUBMISSION: 22-Jun-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Bruno José da Costa Medeiros
Jitauna street, n.85, Flores, Manaus, AM, Brasil – 69058-825
Tel: +55 54 99245-8756
E-mail: brunaojose@bol.com.br

METHODS

A descriptive study of the literature available in the Medline/PubMed, Lilacs, Scopus databases and specialized books. The search was carried out using the terms "infectious diseases"; "COVID-19"; "Chest tubes". Our study brings what is known about the coronavirus and ways to protect teams dealing with chest tubes. This can assist hospitals in the next steps that can be taken to protect health professionals. This is a review article that brings information collected from different articles published since the beginning of the 2019 novel coronavirus epidemic.

RESULTS

Before the procedure

All materials needed to perform the procedure must be prepared before surgery. Some authors suggest the preparation of a BAG with all items to minimize the circulation of professionals between safe and contaminated areas.

The use of a HEPA or HME F filter, similar to the one recommended for orotracheal intubation[6] should be considered and connected to the vent of the collecting bottle interposed by a cut orotracheal tube, in order to reduce possible contamination of the environment in collecting bottle with two vents, one of this must be isolated. (Figure 1).

It has already been demonstrated in the laboratory that the use of an antiviral filter reduces the emission of aerosols when coupled to the collector flask, thus reducing the chances of contamination by the team[7].

The collection bottle mentioned here is a simple one, which works as a collector and water seal with two vents, widely used in hospitals of the Brazilian Unified Health System and other parts of the world (Figure 2).

It is recommended that the chest drain previously chosen for this purpose is already connected to the extension tube, to avoid an inadvertent exit from collections that may contaminate the team[8].

Some authors recommend that the distal 1/3 of the drain be clamped with a strong hemostat with the same purpose described[8].

Preemptive multimodal analgesia with analgesic, non-steroidal anti-inflammatory, and an opiate in awake patients to reduce the pain of the procedure and reflexes that lead to the discharge of secretions that may serve as contaminants[8].

In patients on mechanical ventilation, a neuromuscular blocker can be used as an additive to sedation to prevent coughing and viral contamination.

During the procedure

The recommended technique surgical chest tube insertion, the same recommended by the American College of Surgeons[9].

The number of people at the bedside should be kept to a minimum, as in other procedures during the Pandemic, and should include the doctor who will perform the procedure, an assistant (who may be a more senior resident), and someone to open and deliver materials, such as a nurse[10].

The physician responsible for the procedure must be the most experienced, and the presence of students or interns must be avoided to minimize the risk of contamination[10].

All Personal Protective Equipment (PPE) available must be used for procedures that may generate aerosols: sterile and liquid-impervious apron, double gloves, Face Shield, Mask N95/PFF2, or higher[11,12].

Wide skin antisepsis on the side to be drained, placement of sterile fields.

Full local anesthesia with 20ml of 1% lidocaine.

Small incision 2 to 3 cm;

Drain passage in superior and posterior direction;

Making stitches around the drain for the wound to be tightly closed thus avoiding the discharge of secretions;

For those who use the drainage technique with closed hemostatic forceps on the distal 1/3 of the drain, this should only be released when the drain has been connected to the extension tube;

After the procedure

In 2011, Cipriano and Dessote[13] recommended the use of hospital adhesive tape on the connectors between the extension tube and chest drain to prevent inadvertent disconnection; in 2020, the use of two plastic cable ties with the same purpose was indicated[14].

Change of water stamp only when indicated and by a properly trained nursing professional, using all indicated PPE.

Keep using the HEPA or HME F filter connected to the patient's collector bottle in order to reduce contamination of the environment, some filters provide an additional resistance of 1 to 2.3 cm H_2O to the system[14] (Figure 3).

One author recently recommended the use of

FIGURE 1

FIGURE 2

FIGURE 3

domestic liquid bleach (5.25 to 6.15%) on the water seal in a concentration of 1 part to 50 in order to minimize contamination, but we believe that this recommendation still requires further analysis[14].

Drain removal should be performed with as few people in the room as possible, prior to analgesia, with anesthesia around the drain, making a suture in the drain wound to keep it tightly closed at the end.

DISCUSSION

Although complications such as pneumothorax affect only 1% of patients with COVID-19, and pleural effusions with a possible indication for chest tube insertion have been reported in only 5% of cases, chest drainage continues to be performed in trauma victims and with its classic indications[15].

Old rules and precautions to avoid contamination such as keeping the drain clamped in its 1/3 distal or having the drain already attached to the extension tube at the time of insertion must be followed thoroughly[8].

The use of personal protective equipment complete with gloves, cap, N95 or PFF2 mask, face shield, and waterproof apron is essential[12].

During the patient's convalescence, whether in the ICU or in the wards, all care is necessary during the exchange of the water seals; it is advisable to reinforce the connections with adhesive tape or even with plastic clamps[13,14].

New approaches, such as the use of a filter with high particle detention power (HEPA), should be considered in order to reduce viral contamination[14].

Other conducts such as the addition of liquid bleach to the water seal require further analysis of the results before they are indicated[14].

CONCLUSIONS

Health officials are under increasing pressure to control the spread of COVID-19, which is a very virulent disease. In this context, many health professionals including doctors, nurses, physiotherapists, and nursing technicians have been contaminated, removed from work, and even lost their lives. Our analysis brought together old rules against contamination with new tactics for professionals who deal with chest drains in order to minimize contamination of the team during the Pandemic.

Author's Contributions

Bruno José da Costa Medeiros - Data Collection, Writing, Original preparation; Fernando Luíz Westphal - Conceptualization, Writing - Review and Editing, Visualization.

PALAVRAS-CHAVE: *Doenças Transmissíveis. Infecções por Coronavirus. Tubos Torácicos.*

REFERENCES

1. Johns Hopkins University & Medicine. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Baltimore: Johns Hopkins University & Medicine; 2020. [cited 2020 Jun 22]. Available from: https://coronavirus.jhu.edu/map.html
2. World Health Organization. OMS alerta sobre contaminação de profissionais de saúde por COVID-19. Geneva: World Health Organization; 2020. [cited 2020 Mar 19]. Available from: https://news.un.org/pt/story/2020/02/1704211
3. Conselho Federal de Enfermagem. Profissionais afastados por COVID-19. 2020. Brasília: Conselho Federal de Enfermagem; 2020. [cited 2020 May 26]. Available from: http://www.cofen.gov.br/brasil-tem-30-mortes-na-enfermagem-por-COVID-19-e-4-mil-profissionais-afastados_79198.html
4. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020;382(16):1564-7.
5. Bilkhu R, Viviano A, Saftic I, Bille A. COVID-19: chest drains with air leak: the silent 'super spreader'? CTSNet. 2020. doi.org/10.25373/ctsnet.12089130.v1. [cited 2020 May 26]. Available from: https://ctsnet.figshare.com/articles/COVID-19_Chest_Drains_With_Air_Leak_The_Silent_Super_Spreader_/12089130/1
6. Associação Brasileira de Medicina de Emergência - ABRAMEDE. Recomendações para intubação orotraqueal em pacientes portadores de COVID-19. 2020. [cited 2020 May 26]. Available from: http://abramede.com.br/wp-content/uploads/2020/04/Recomendacoes-IOT-FINAL-REVISAO-100420.pdf
7. Akhtar MR, Ricketts W, Fotheringham T. Use of an antiviral filter attached to a pleural drain bottle to prevent aerosol contamination with SARS-CoV-2. Clin Med (Lond). 2020;20(4):e60-1.
8. Medeiros BJC, Westphal FL, Lima LC. Cuidados padronizados em dreno de tórax: técnicas e manejo: técnicas e Manejo. São Paulo: Manole; 2019. p.41-6.
9. American College of Surgeons. ATLS Advanced Trauma Life Support: student course manual. 10th ed. Chicago: American College of Surgeons; 2018.
10. Lima DS, Ribeiro Junior MF, Vieira-Jr HM, Campos T, Savieiro S. Alternativas para o estabelecimento de via aérea cirúrgica durante a pandemia de COVID-19. Rev Col Bras Cir. 2020;47:e20202549.
11. Schultz P, Morvan JB, Fakhry N, Morinière S, Vergez S, Lacroix C, et al; French Society of Otorhinolaryngology, Head, Neck Surgery (SFORL); French Society of Head, Neck Carcinology (SFCCF). French consensus regarding precautions during tracheostomy and post-tracheostomy care in the context of COVID-19 pandemic. Eur Ann Otorhinolaryngol Head Neck Dis. 2020;137(3):167-9.
12. Center for Disease Control and Prevention. Coronavirus COVID-19. Atlanta: Center for Disease Control and Prevention; 2020. [cited 2020 May 28]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/index.html
13. Cipriano FG, Dessote LU. Drenagem pleural. Medicina (Ribeirão Preto). 2011;44(1):70-8.
14. Pieracci FM, Burlew CC, Spaim D, Livingston DH, Bulger EM, Davis KA, et al. Tube thoracostomy during the COVID-19 pandemic: guidance and recommendations from the AAST Acute Care Surgery and Critical Care Committees. Trauma Surg Acute Care Open. 2020;5(1):e000498.
15. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.

REVIEW ARTICLE

Ethical dilemmas in COVID-19 times: how to decide who lives and who dies?

Nedy M. B. C. Neves[1]
Flávia B. C. S. N. Bitencourt[2]
Almir G. V. Bitencourt[3]

1. Universidade Salvador (Unifacs), Salvador, BA, Brasil
2. Fleury Medicina e Saúde, São Paulo, SP, Brasil
3. A.C.Camargo Cancer Center, São Paulo, SP, Brasil

http://dx.doi.org/10.1590/1806-9282.66.S2.106

SUMMARY

The respiratory disease caused by the coronavirus SARS-CoV-2 (COVID-19) is a pandemic that produces a large number of simultaneous patients with severe symptoms and in need of special hospital care, overloading the infrastructure of health services. All of these demands generate the need to ration equipment and interventions. Faced with this imbalance, how, when, and who decides, there is the impact of the stressful systems of professionals who are at the front line of care and, in the background, issues inherent to human subjectivity. Along this path, the idea of using artificial intelligence algorithms to replace health professionals in the decision-making process also arises. In this context, there is the ethical question of how to manage the demands produced by the pandemic. The objective of this work is to reflect, from the point of view of medical ethics, on the basic principles of the choices made by the health teams, during the COVID-19 pandemic, whose resources are scarce and decisions cause anguish and restlessness. The ethical values for the rationing of health resources in an epidemic must converge to some proposals based on fundamental values such as maximizing the benefits produced by scarce resources, treating people equally, promoting and recommending instrumental values, giving priority to critical situations. Naturally, different judgments will occur in different circumstances, but transparency is essential to ensure public trust. In this way, it is possible to develop prioritization guidelines using well-defined values and ethical recommendations to achieve fair resource allocation.

KEYWORDS: *Ethics, Medical. Bioethics. Pandemics. Coronavirus Infections. Decision Making. Resource Allocation.*

INTRODUCTION

The respiratory disease caused by the Coronavirus 2019 (COVID-19) is a pandemic with serious clinical manifestations, including death, and affecting countries on all continents. The coronavirus type 2 was the virus that caused severe acute respiratory syndrome (Sars-Cov-2), a disease responsible for the infection of millions of individuals and hundreds of thousands of deaths worldwide[1].

Due to its high transmissibility, COVID-19 produces a simultaneous large number of patients with severe symptoms that require special hospital care, overloading the infrastructure of health services[2]. It has been demonstrated that no health system in the world is capable of managing all these patients if a large portion of the population is contaminated. The number of deaths in some countries has shocked the world and unveiled one of the biggest problems generated by the pandemic. The crisis due to the number of patients who require special care and hospitalizations, the resulting volume of equipment and multidisciplinary

DATE OF SUBMISSION: 10-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Almir Bitencourt
A.C.Camargo Cancer Center - Rua Professor Antonio Prudente, 211. Liberdade, São Paulo-SP, Brasil. CEP: 01509-010 - Tel.: (11) 2189-5000
Email: almir.bitencourt@accamargo.org.br

teams needed, all in discrepancy with the scarcity of such equipment, thus collapsing the health system.

All these demands made it necessary to ration equipment and interventions. The imbalance between supply and demand of resources leads to the question of how these resources can be allocated fairly[2]. As a consequence of this imbalance, there is the matter of how to, when to, and who will make such decisions, and, in addition to the underlying and inherent issues of human subjectivity, professionals who are at the frontline of care already have to cope with the impact of stressful systems. Thus arises the idea of using artificial intelligence (AI) algorithms to replace health professionals in this decision-making[3-5].

Considering the aspects mentioned and taking into account the crisis promoted by the discrepancy between the number of patients and the diagnostic and therapeutic tools of medical assistance, the questioning remains on how to manage the demands produced by the pandemic. The objective of this study is to reflect, from the point of view of medical ethics, on the basic principles of the choices made by health teams in the fight against the COVID-19 pandemic, dealing with scarce resources and having to make decisions that cause anguish and anxiety.

MEDICAL CARE NETWORK

In view of the facts mentioned in the introduction, it is worth reflecting on the scenario of the healthcare structures for critical patients who, consequently, require special equipment. These conditions are not related only to patients with positive results for COVID-19, but to any citizen whose pathology can weaken the health system, with a life-threatening risk. In this context, some authors have reported that the problem of hospital infrastructure with limited access is old and remains true in many regions. Goldwasser et al.[6], for example, relate a small number of units and demand, which generates a gap between availability and the admission flow. In short, the authors have reported that the system defends universal care, but there is no room for everyone.

The ICUs are key components in the care of patients with an imminent risk of death and chance of recovery[6]. Due to its high degree of complexity, ICUs are a costly resource in hospital units, corresponding to approximately 20% of the operational costs[7]. Given this, there is a reduced number of ICUs, which do not service everyone who needs them, thus rejecting patients and generating queues for hospitalizations. There is a gap between availability and the demand for ICU beds. In addition to the inadequate infrastructure, there is also an absence of protocols and a lack of trained human resources[6-8].

In isolation, some strategies have been developed to minimize these difficulties through regulatory policies that aim to organize the admission to services and procedures of high and medium complexity. A central manages the demands and resources available to provide the best care at an appropriate time. The regulation is based on technical criteria of priorities, following hierarchical protocols, based on a consensus by specialized medical societies, and prioritizing the most severe patients[9].

The planning of healthcare services is a complex social problem and requires multidisciplinary approaches. The organization of these systems is influenced by technical, epidemiological, ethical, educational, and cultural aspects. In order to substantiate the decision making that permeates medical conflicts, oftentimes it is mandatory to consult with and seek guidance from the institution's Ethics Committee[10]. All these arguments show that the ICU resources, with the necessary equipment for critical and serious health situations, are in deficit regardless of pandemics.

RATIONALIZATION OF CARE

How to make choices when there are numerous demands and lack of resources? Sartre[11] argues that: "Man is condemned to be free." To Sartre[11], our preferences are guided by what appears to be good, more specifically by an engagement in which represents good. Considering this scenario, the current question includes the approaches to allocate scarce resources. It is necessary to prepare to make tragic decisions, such as who lives and who dies. A utilitarian and pragmatic perspective would defend allocating resources to those with the greatest chance of survival and a greater time of remaining life. It is rationality based on cost-benefit that can have or not an ethical value.

Conversely, there are principles that propose saving as many lives as possible and ensuring no economic, racial, ethnic, or political bias. In this line of reasoning, it is not acceptable that financial conditions and social status are considered criteria of choice. Faced with this scenario, let's look at an example: a young 20-year-old man and a 60-year-old patient,

both with comparable forecasts, who would be given the benefit? Who will be saved? This and other challenges are in the hands of doctors at the frontline of emergency care. Faced with the anguish of this type of decision, it is believed that the task of allocating resources fairly could be shared with mechanisms that can minimize this overload of physicians.

MEDICAL AND TEAM CONFLICT

It is scientific knowledge that doctors work under pressure from their families, colleagues, and hospital managers to decide which patient will be benefited from the use of the ICU. In addition, the concept of priority varies based on individual judgment, interpretation, social responsibility, and transparency. Physicians who are in charge of the care of severe patients, deciding when and how the first support measures must be initiated, timely, are oftentimes young and unprepared. Considering this, it is essential to broaden the training of professionals[6]. Therefore, it is noted that the responsibility of deciding priorities is born by a single professional, the physician, with their human subjectivity and with risks of mistakes and successes. It is clear that these facts generate anguish and suffering in professionals.

There is no consensus in the literature of any scientific area; therefore, in some circumstances, the experience of a certain professional can guide the diagnostic and therapeutic determination, despite going against scientific evidence. Sometimes the best strategy is directly related to the experience of each service. Empiricism appears as a solution when it is acknowledged that the routine approach does not contemplate a routine situation[12].

An important milestone in the medical area was "evidence-based medicine". This pattern was built based on a mental process that evidences clinical reasoning, including the calculation of probabilities of outcomes, risks, and benefits in such a way that becomes relevant for the establishment of scientific evidence. This emerges as a tendency to replace subjectivity by technical objectivity. Following a new paradigm, protocols were created based on scientific studies in order to standardize the practice and make it safer to benefit patients and physicians alike[12]. In view of these facts, there are authors who advocate the introduction of protocols in medical practice, while others consider intersubjectivity restrictive to the construction of objective decisions as support of scientificity[13]. One must consider that all of these mechanisms were devised for the good of the patient; however, physicians risk becoming a "robot" that only follows frameworks and protocols without getting involved in the search for the best scientifically recognized solution at their disposal.

MODELING OF THE COVID-19 PANDEMIC

There are demonstrative data available to project the demands of resources. Estimates of the reproduction number of Sars-Cov-2 show that each infected person spreads the virus to at least two other, on average. Of all the patients infected with COVID-19, approximately 15% have severe diseases, and 5% have critical needs. The overall mortality ranges from 0.25% to 3.0%. Mortality is higher in vulnerable populations, such as people over 80 years old (>14%) and with comorbidities, 10% for patients with heart disease, and 7% for diabetics. Several factors, such as social distancing and other interventions can influence the calculation of the total population infected; however, the estimate is around 5%[14].

The model of scarcity previously observed extends to diagnostic, therapeutic, and preventive interventions[2]. Pharmaceutical products and experimental treatments are in the early stages of study[15]. In the same way, a vaccine will take time to be developed, produced, and distributed. Based on the foregoing, is it possible to predict that the time necessary to achieve the goals that can balance the system imposed by the pandemic is still long, requiring a structuring and making, therefore, the prognosis bleak.

AI IN PROBLEM SOLVING

AI can interfere and help in the creation of standards and protocols to assist physicians in making the previously mentioned choices in the face of severe patients in a critical situation. Currently, AI covers a huge variety of subfields. Among these is the study of connective models or neural networks (CNN, convolutional neural networks). A neural network can be seen as a simplified mathematical model of the functioning of the human brain[16].

One of the areas most studied by scientists about AI is the process of Problem Solving, which was developed by analyzing the behaviors of individuals who solve problems to simulate aspects of intelligent and rational behavior. The AI planning techniques have

allowed the generation of a plan that solved a problem in a few hours, something that would take other methods weeks to achieve. Among the software created are those for medical diagnosis based on probabilistic analysis, and they were able to execute tasks at the same level as a doctor who specializes in various areas of medicine. In this same line, the literature presents proposals for replacing causal, mechanistic, or structural clinical reasoning models for models of determining probabilistic that are typical of epidemiological reasoning[17,18]. These mechanisms include the assumptions of their knowledge pool and concepts of practical nature through methods and tools used in the examination of evidence and criteria to assess its results[12].

Therefore, is it possible to join strengths to develop effective and faster systems to reduce the shortage observed and, thus, fight the problems faced in this pandemic crisis[19].

ETHICAL VALUATION

From an ethical perspective, it can be argued that value judgment is an attempt of judgment based on a careful evaluation of the information available, taken as incomplete and evolving. It is worth exemplifying a value judgment on how to proceed in a medical emergency. In this case, the quality of judgment is incomplete since it is the result of cultural or personal limitations. Valuation is essential as an element for the contextualization of ethics in its broadest sense. Ethics is shaped based on the ingraining of values in subjects and the society in which they are inserted, and, from this set, each one proposes their actions[20]. That being said, it is necessary to valuate to intervene. It is worth noting that the medical field assigns a different value to life, according to age, providing distinct care to children, adults, and the elderly[12].

From this perspective, the ethical values necessary to ration healthcare resources in an epidemic have high prestige and can converge into some proposals based on fundamental values, such as maximizing the benefits produced by scarce resources, treating people equitably, promoting and recommending instrumental values, and giving priority to critical situations[21]. A recently published article taking into account the ethical particularities mentioned produced specific recommendations to allocate medical resources in the COVID-19 pandemic[2]:

1. Maximize benefits - the priority of limited resources should aim at saving as many lives as possible and maximizing improvements throughout life post-treatment. This premise is consistent both in the perspective of utilitarian and non-utilitarian ethics.

2. Prioritize health professionals - resources such as tests, PPE, ICU beds, ventilators, therapeutics, and vaccines should be directed initially to healthcare professionals, particularly those who face a high risk of infection and whose training makes them difficult to replace, which can cause insufficient assistance and, as a result, an increased number of deaths due to the decreased number of trained professionals.

3. Do not allocate based on the order of arrival - in case of patients with a similar prognosis, the operationalization should be random. Prioritizing those who arrived first would be unfair.

4. Be sensitive to the scientific evidence - protocols must follow scientific guidelines and be updated as they develop.

5. Reward research participants - people who participate in research to prove the safety and effectiveness of vaccines and therapeutic measures should receive some priority in interventions.

6. Apply the same principles to all COVID-19 and non-COVID-19 patients - the fair allocation of resources that prioritizes the value of maximizing benefits applies to all patients who need them.

It is necessary to implement policies of rationing in order to balance multiple ethical values. Naturally, there will be different judgments in different circumstances, but it is essential to maintain transparency to ensure public trust[2]. It is possible to draw up prioritization guidelines using well-established ethical values and recommendations to achieve fair procedures for resource allocation. That way, it is possible to prevent individual physicians from being faced with the grim task of improvising decisions.

FINAL CONSIDERATIONS

Certainly, there is much to be said about this topic; therefore, there are no pretensions of exhausting it here, given that in the history of humanity the evolution of thought is a historically recognized reality. In other words, problems are not impervious and solutions are changeable.

Despite what has been studied and seeking to achieve the objective proposed, many are the possibilities to contribute to the efforts of minimizing the dilemma of medical teams in circumstances of

a scarcity of resources in which they are coerced to make tragic decisions. In this aspect, it is worth reinforcing the six aforementioned recommendations that can ensure that physicians do not have to handle the task of deciding alone and can still count on a higher level of problem-solving in the organizational sphere the institution, relieving their emotional burden. In addition to that, there is the guarantee of equal treatment when patients are at the same level of prognosis, in the search for the equity of access to resources, something which must be considered in each case.

The defense of the creation of broad and well-defined scientific protocols to assist teams in making difficult decisions is advocated by several authors as one of the ways of distancing physicians at the frontline, from the responsibility of an inappropriate choice. There is validity in institutions creating models and parameters that can employ screening professionals, physicians who are not allocated to direct patient care, and medical committees specialized in ethics to apply guidelines that may help in making the decisions around the rationing and implementation of definitive choices. In this scenario, AI can assist in the generation of a multitude of probabilistic sets for hypothetical problems, comparing them with the similarity of the real problems, and from these events, cooperate for a more appropriate choice. In this same line of argument, governments have the legitimate right to draw up public policies that might hinder the scarcity of medical resources, such as ICU beds, respirators, monitors, and infusion pumps, in addition to PPE and testing for healthcare professionals who are at the frontline, preventing the risk of contamination. Therefore, AI algorithms can also be useful as an auxiliary tool to streamline inventory control, the standardization of purchases of raw materials, transport, and logistics.

The downside is that even well-designed guidelines can present challenging problems in decision-making. In other words, a well-defined protocol does not guarantee its applicability, nor its suitability of use. In addition, an excess of protocols and routines homogenize practices, and professionals start adopting intuitive and pragmatic approaches. Finally, a key point is the use of AI as an auxiliary strategy of this *praxis*. Given the above, it is possible to reframe healthcare through the work of teams composed of multiple players, even AI. This process aims to reduce problems while solutions are researched and answer questions to avoid anguish and suffering.

Author's Contribution

All authors contributed to the concept of the theme of the work, literature review, drafting, and revising the manuscript.

RESUMO

A doença respiratória provocada pelo coronavírus 2019 (COVID-19) é uma pandemia que produz uma grande quantidade simultânea de doentes com sintomas graves que necessitam de cuidados hospitalares especiais, sobrecarregando a infraestrutura dos serviços de saúde. Todas essas demandas geram a necessidade de racionar equipamentos e intervenções. Diante desse desequilíbrio, como, quando e quem decide, há o impacto dos sistemas estressores dos profissionais que se encontram na linha de frente do atendimento e, em segundo plano, questões inerentes à subjetividade humana. Nesse percurso, surge ainda a ideia do uso de algoritmos da inteligência artificial para substituir o profissional de saúde nessa tomada de decisão. Nesse contexto, fica o questionamento ético de como gerenciar as demandas produzidas pela pandemia. O objetivo deste trabalho é refletir, do ponto de vista da ética médica, sobre princípios basilares das escolhas executadas pelas equipes de saúde, no enfrentamento da pandemia da COVID-19, cujos recursos são escassos e as decisões ocasionam angústia e inquietação. Os valores éticos para o racionamento de recursos de saúde em uma epidemia devem convergir para algumas propostas embasadas em valores fundamentais, como maximizar os benefícios produzidos por recursos escassos, tratar as pessoas de forma igualitária, promover e recomendar os valores instrumentais, dar prioridade para situações críticas. Naturalmente ocorrerão julgamentos diferentes em circunstâncias distintas, mas é fundamental que haja transparência para garantir a confiança pública. Desse modo, é possível elaborar diretrizes de priorização utilizando valores e recomendações éticas bem delineados para atingir procedimentos justos de alocação de recursos.

PALAVRAS-CHAVE: *Ética médica. Bioética. Pandemias. Infecções por coronavírus. Tomada de decisões. Alocação de recursos.*

REFERENCES

1. Cespedes MS, Souza JCRP. Coronavirus: a clinical update of COVID-19. Rev Assoc Med Bras. 2020;66(2):116-23.
2. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair allocation of scarce medical resources in the time of COVID-19. N Engl J Med. 2020;382(21):2049-55.
3. Jiang X, Coffee M, Bari A, Wang J, Jiang X, Huang J, et al. Towards an artificial intelligence framework for data-driven prediction of coronavirus clinical severity. CMC. 2020;63(1):537-51.
4. Yan L, Zhang H-T, Xiao Y, Wang M, Sun C, Liang J, et al. Prediction of criticality in patients with severe COVID-19 infection using three clinical features:

a machine learning-based prognostic model with clinical data in Wuhan. medRxiv 2020;2020.02.27.20028027. doi: https://doi.org/10.1101/2020.02.27.20028027.

5. Naudé W. Artificial intelligence vs COVID-19: limitations, constraints and pitfalls. AI Soc. 2020;1-5. doi: 10.1007/s00146-020-00978-0.
6. Goldwasser RS, Lobo MSC, Arruda EF, Angelo SA, Ribeiro ECO, Silva JRLE. Planning and understanding the intensive care network in the State of Rio de Janeiro (RJ), Brasil: a complex societal problem. Rev Bras Ter Intensiva. 2018;30(3):347-57.
7. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368-77.
8. Halpern NA, Pastores SM. Critical care medicine in the United States 2000–2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med. 2010;38(1):65-71.
9. Bloomfield EL. The ethics of rationing of critical care services: should technology assessment play a role? Anesthesiol Res Pract. 2009;2009:915197.
10. Vecina Neto G, Malik AM. Tendências na assistência hospitalar. Cienc Saúde Coletiva. 2007;12(4):825-39.
11. Sartre J. O existencialismo é um humanismo. Petrópolis: Editora Vozes; 2014.
12. Uchôa SAC, Camargo Jr KR. Os protocolos e a decisão médica: medicina baseada em vivências e ou evidências? Cienc Saúde Coletiva. 2010;15(4):2241-9.
13. Eddy DM. Clinical decision making: from theory to practice. Resolving conflicts in practice policies. JAMA. 1990;264(3):389-91.
14. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020. doi: 10.1001/jama.2020.2648.
15. Harrison C. Coronavirus puts drug repurposing on the fast track. Nat Biotechnol. 2020;38(4):379-81.
16. Osaki MM. Inteligência artificial, prática médica e a relação médico-paciente. Rev Adm Saúde. 2018;18(72). http://dx.doi.org/10.23973/ras.72.134.
17. Beil M, Proft I, van Heerden D, Sviri S, van Heerden PV. Ethical considerations about artificial intelligence for prognostication in intensive care. Intensive Care Med Exp. 2019;7(1):70.
18. Kang DY, Cho KJ, Kwon O, Kwon JM, Jeon KH, Park H, et al. Artificial intelligence algorithm to predict the need for critical care in prehospital emergency medical services. Scand J Trauma Resusc Emerg Med. 2020;28(1):17.
19. Ienca M, Vayena E. On the responsible use of digital data to tackle the COVID-19 pandemic. Nat Med. 2020;26(4):463-4.
20. Neves NC. Ética para os futuros médicos. É possível ensinar? Brasília: Conselho Federal de Medicina; 2006.
21. Persad G, Wertheimer A, Emanuel EJ. Principles for allocation of scarce medical interventions. Lancet. 2009;373(9661):423-31.

REVIEW ARTICLE

Renal changes and acute kidney injury in covid-19: a systematic review

Samuel Átila Rodrigues Nogueira[1]
Samuel Ciríaco Silva de Oliveira[1]
Ana Flávia Moreira de Carvalho[1]
Julia Moreira Cavalcante Neves[1]
Leila Silveira Vieira da Silva[1]
Geraldo Bezerra da Silva Junior[2]
Maria Elizabeth Pereira Nobre[1]

1. Universidade Federal do Cariri, Faculdade de Medicina, Barbalha, CE, Brasil.
2. Universidade de Fortaleza, Curso de Medicina, Programas de Pós-Graduação em Saúde Coletiva e Ciências Médicas, Fortaleza, CE, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.112

SUMMARY

OBJECTIVE: *We aimed to present a review of renal changes in patients with COVID-19.*

METHODS: *We performed a systematic review of the literature to identify original articles regarding clinical, laboratory, and anatomopathological kidney changes in patients infected with SARS-CoV-2 published until May 7, 2020. The search was carried out across PubMed, Scopus, and Embase using the keywords "COVID-19", "coronavirus", "SARS-CoV-2", "kidney injury" and "kidney disease". Fifteen studies presented clinical and laboratory renal changes in patients with COVID-19, and three addressed anatomopathological changes.*

DISCUSSION: *Acute kidney injury (AKI) was a relevant finding in patients with COVID-19. There were also significant changes in laboratory tests that indicated kidney injury, such as increased serum creatinine and blood urea nitrogen (BUN), proteinuria, and hematuria. The presence of laboratory abnormalities and AKI were significant in severely ill patients. There was a considerable prevalence of AKI among groups of patients who died of COVID-19. Histopathological analysis of the kidney tissue of patients infected with SARS-CoV-2 suggested that the virus may directly affect the kidneys.*

CONCLUSION: *Although COVID-19 affects mainly the lungs, it can also impact the kidneys. Increased serum creatinine and BUN, hematuria, proteinuria, and AKI were frequent findings in patients with severe COVID-19 and were related to an increased mortality rate. Further studies focusing on renal changes and their implications for the clinical condition of patients infected with the novel coronavirus are needed.*

KEYWORDS: *Coronavirus. Coronavirus Infections. Betacoronavirus. Acute Kidney Injury. Renal Insufficiency.*

INTRODUCTION

The coronaviruses are RNA viruses of the *Coronaviridae* family and the *Nidovirales* order[1]. Many of them are zoonotic viruses that can infect humans, causing mild diseases, such as colds, or even serious illnesses, such as the betacoronaviruses, responsible for the epidemics of Severe Acute Respiratory Syndrome (SARS-CoV) and the Middle East Respiratory Syndrome (MERS-CoV)[2,3].

DATE OF SUBMISSION: 06-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Samuel Átila Rodrigues Nogueira
Faculdade de Medicina da Universidade Federal do Cariri. Rua Divino Salvador, 284 - Alto do Rosário, Barbalha - CE, 63180-000
Email: samuelatilanogueira@gmail.com

A new respiratory syndrome similar to those caused by SARS-CoV and MERS-CoV emerged in Wuhan, China, at the end of 2019[4,5]. The etiologic agent was identified as a new coronavirus, which received the name SARS-CoV-2, and the disease it causes was named Coronavirus Disease 2019 (COVID-19)[6]. Until the beginning of May 2020, there were over 4 million confirmed cases and 300,000 deaths due to SARS-CoV-2 throughout the world, a health crisis of proportions never before seen in the contemporary world[7].

The pathological characteristics of these diseases are similar, with the involvement of several tissues, such as the lungs, liver, intestine, and central nervous system[1,8-10]. There are also reports of compromised kidney function during MERS-CoV and SARS-CoV infections[11,12].

The main clinical manifestations of COVID-19 include fever, cough, fatigue, and dyspnea[13]. A large proportion of patients presented deregulation of organic functions, usually respiratory and of the heart[14]. However, a significant number of patients presented acute kidney injury (AKI) during the clinical course[15-17]. In the same line, some studies have reported a possible interface between SARS-CoV-2 and the kidney[18-20].

Given the urgency in getting answers about how the SARS-CoV-2 infection behaves, this work aims to present an update of the literature in order to understand the relationship between COVID-19 and its renal complications, particularly AKI.

METHODS

A systematic review of the literature was conducted in the PubMed, Scopus, and Embase electronic databases, using the keywords: "COVID-19", "coronavirus", "Sars-CoV-2", "kidney injury" and "kidney disease", according to PRISMA[21]. We selected original articles published up until May 7, 2020 and extracted the data related to clinical manifestations, laboratory findings, and pathological findings associated with kidney involvement in COVID-19. The primary outcome was to analyze the kidney effects and AKI in patients infected by SARS-CoV-2.

In the end, 18 papers were selected as relevant for the qualitative synthesis (Figure 1). Of these, 15 addressed the clinical and laboratory data of COVID-19 patients (Tables 1 and 2). Another 3 papers exposed anatomopathological alterations.

TABLE 2. STUDIES SHOWING PROTEINURIA AND HEMATURIA AMONG PATIENTS WITH COVID-19, DECEMBER 2019 TO MAY 2020*

Authors	Urinary Protein On Admission	Urinary Occult Blood On Admission
Cheng, et al., (2020)[19]	43.9%	26.7%
Chen, et al., (2020)[14]	60.24%[a]	50.6%[a]
Pei, et. al., (2020)[29]	65.8%	41.7%

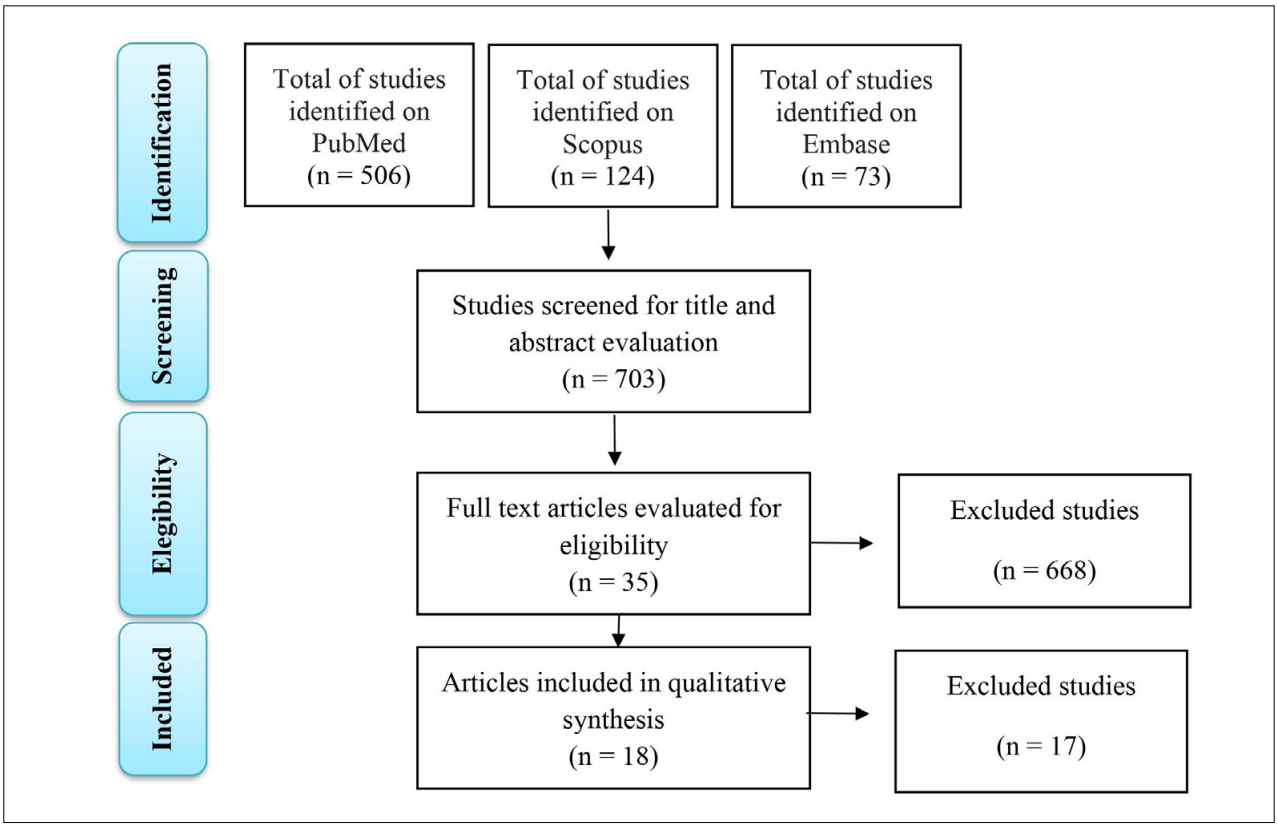
*By May 7, 2020; [a] Regarding patients who underwent routine urine testing (n = 166);

TABLE 1. STUDIES ON ACUTE KIDNEY INJURY (AKI) IN PATIENTS WITH COVID-19, DECEMBER 2019 TO MAY 2020*

Authors	Total Number of Patients	Incidence of AKI (%)	Serum Creatinine (µmol/L) On Admission	Blood Urea Nitrogen (mmol/L) On Admission
Zhang, et al., (2020)[17]	221	4.5[a]	69.0 (56.0-84.0)[b]	4.3 (3.4-5.6)[b]
Cheng, et al., (2020)[19]	701	5.1[c]	Elevated in 14.4% (77.0 ± 31.0)[d]	Elevated in 13.1% (5.7 ± 3.9)[d]
Shi, et al., (2020)[22]	416	1.9	59.23 (48.62-71.60)[b]	-
Chen, et al., (2020)[14]	274	11	76.0 (58.0-94.0)[b]	4.9 (3.5-7.9)[b]
Deng, et al., (2020)[23]	225	8.89	-	89.0 (72.0, 133.5) vs. 65.0 (54.6, 78.75)[e]
Yang, et al., (2020)[15]	52	29	-	76.3 (27.4) vs. 80.7 (32.3)[f]
Richardson, et al., (2020)[24]	2.634	22.2	-	-
Li, et al., (2020)[25]	54	70.7	-	-
Wang, et al., (2020)[26]	116	0.0	78.26 ± 25.14[g]	5.23 ± 1.72[g]
Li, et. al., (2020)[27]	25	-	66.0 (49.5-161.0)[b] 33.3%[h]	9.29 (6.07-16.4)[b] 43.5%[h]
Wang, et. al., (2020)[28]	107	13.1	71.0 (60.0-86.0)[b]	4.2 (3.2-5.6)[b]
Pei, et. al., (2020)[29]	333	10.5	70.0 (57.0-84.0)[i]	4.3 (3.2-5.7)[i]
Zhao, et al., (2020)[30]	91	5.5	≤ 97.0 (94.5%), > 97.0 (5.5%)[j]	≤ 417.0 (94.5%), > 417.0 (5.5%)[j]
Yang, et al., (2020)[31]	92	15.4	86.0 (34.0-428.0)[b]	8.9 (3.4-48.0)[b]

*By May 7, 2020; [a] Of the 221 patients, the majority were still hospitalized at the time of data collection; [b] Median (IQR); [c] Stage 1: 1.9%, Stage 2: 1.3%, Stage 3: 2%; [d] Mean ± SD; [e] Dead (n = 109) vs. Recovered (n = 116), Median (Q1, Q3); [f] Survivors (n = 20) vs. Non-survivors (n = 32), Mean (SD); [g] Number of patients without CKD (n = 111); [h] Above the upper limit of normality; [i] Median (25th-75th percentil); [j] Uric acid (µmol/L) instead of blood urea nitrogen (mmol/L);

FIGURE 1. FLOWCHART SUMMARIZING THE SEARCH STRATEGY FOR STUDIES (KIDNEY INJURY AND COVID-19). ADAPTED FROM MOHER ET AL. (DOI.ORG/10.1371/JOURNAL.PMED.1000097)©2009, UNDER TERMS OF CREATIV COMMONS ATTRIBUTION 4.0 INTERNATIONAL LICENCE (CREATIVECOMMONS.ORG/LICENSES/BY/4.0/LEGALCODE).



DISCUSSION

Studies show that SARS-CoV-2 can infect the alveolar epithelial cells of the lungs through the angiotensin-converting enzyme-II (ACEII) receptor, which is also expressed in other tissues, such as the kidneys[17]. After pulmonary infection, the virus would enter the bloodstream and accumulate in the kidneys, causing damage to the kidney tubular epithelial cells through an ACEII-dependent pathway[19]. Pei et al.[29] suggested that acute tubular necrosis (ATN) is the main cause of AKI in COVID-19. In their study, a patient with AKI had, in their urine protein electrophoresis, a high proportion of tubular renal protein.

Several studies have described renal involvement mainly due to AKI, which can affect up to 70% of COVID-19 patients (Table 1); the kidney is the second most affected organ in the disease, behind the lung and followed by the heart and the liver[25]. Li et al.[27] also found the kidney was the most affected organ, except for the lung and heart. In contrast, a study conducted by the University of Wuhan, China, showed that of the 116 hospitalized patients due to COVID-19, only 10.35% had a slight increase in the level of serum urea or creatinine, without meeting the criteria for AKI[26]. This study was an exception among those selected in our work.

In general, serum creatinine values were the main parameter for the diagnosis of AKI, following the criteria of the Kidney Disease: Improving Global Outcomes (KDIGO). In most studies, their values were measured at the time of patient admission (Table 1) and varied based on the severity of the condition. Yang et al.[32] found that 50% of the patients with AKI already had a high rate of serum creatinine at the time of admission. Patients with a normal rate of serum creatinine on admission had an increase in the second test, followed by a decrease in the glomerular filtration rate[32]. Among the values found for serum creatinine, the biggest alterations were in patients who needed intensive care and/or died due to the new coronavirus disease. According to Cheng et al.[19], patients with high basal serum creatinine had a higher leukocyte count and a lower count of lymphocytes and platelets. Abnormalities in the coagulation cascade, including extended activated partial thromboplastin time (aPTT) and higher D-dimer value, were common[19].

Cheng et al.[19] demonstrated an average of serum urea of 5.7 mmol/L in the patients of the study, reaching an average of 11 mmol/L in patients with increased serum creatinine. As to the rate of glomerular filtration, we observed an average of 87 mL/min/1.73m² when considering all the patients, and 48 mL/min/1.73m2 in patients with increased serum creatinine, which corroborates the development of kidney failure in the latter. Approximately 13.1% of the infected patients presented a glomerular filtration rate < 60 mL/min/1.73m2 at the time of hospital admission[19]. In the same sense, Yang et al.[31] found that, on admission, the median (IQR) of the glomerular filtration rate of the 92 patients included in the study was 89.6 mL/min/.73m² (9-135). Another study in China found proteinuria and microscopic hematuria in, respectively, 60.24% and 50.6% of the patients who underwent routine urine examination (Table 2)[14].

Kidney complications can occur at any time during the course of the disease and are increasingly being described as late[32]. The pathogenesis of kidney injury in COVID-19 has not yet been defined, but it has been observed that the presence of comorbidities can influence its development[32]. In this sense, Yang et al.[32] have shown an incidence of kidney injury in patients with renal comorbidities significantly higher than in those without comorbidities (54.5% vs 2.0%, p<0.001). Cheng et al.[19] found that out of all the patients with abnormalities in kidney function, 13% had an underlying kidney disease and 2% a history of chronic kidney disease (CKD). In addition, the percentage of patients who developed AKI was higher in the diabetic subgroup, compared to non-diabetic patients[15].

Cheng et al.[19] emphasize that patients with a history of CKD exhibit a pro-inflammatory state with functional defects in innate and acquired immunity and are recognized as a population at greater risk for infections. However, this alone is not enough to explain the frequent occurrence of AKI in COVID-19 patients, and perhaps it only corroborates what was demonstrated by Yang et al.[32], who demonstrated that patients with kidney comorbidities are more susceptible to the development of AKI, although this does not apply exclusively to them. Pei et al.[29] suggested that the severity of pneumonia was the main risk factor for the development of AKI in COVID-19 patients.

The risk factors and causes of AKI in COVID-19 are diverse. Serum creatinine was a widely used marker to detect kidney involvement. However, new biomarkers of kidney injury, such as neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemotactic protein-1 (MCP-1), and interleukins, have been applied to infectious diseases and could be valuable for detecting early kidney involvement in COVID-19[33].

SEVERITY AND MORTALITY

There is a link between the severity of COVID-19 patients and kidney status. AKI was a frequent finding in severe patients, found in 29% of them, while only 1.2% of non-severe cases developed this complication[17]. In the same way, the increase in basal serum creatinine was correlated with a worsening of clinical condition[17,19]. Cheng et al.[19] found a significant difference regarding the number of severe patients between the groups of patients with high and normal basal serum creatinine (52.5% vs. 40.7%, p= 0.026).

Many studies found higher mortality in COVID-19 patients who had kidney complications. Chen et al.[14] found that 25% of the patients who died presented AKI, while only 1% of the patients recovered presented this complication. Another important finding of this study was that, of the 29 patients who had AKI, 96.55% died[14]. Several studies presented similar data, with the presence of AKI in a considerable portion of dead patients: 62% in the study by Richardson et al.[24] and 32% in Yang et al.[15]. Wang et al.[28] highlighted a significant prevalence of AKI (73.7%) in dead patients and none in recovered ones.

In this sense, Cheng et al.[19] analyzed data from 701 patients in China. Part of the patients already presented renal alterations in hospital admission, such as increased serum creatinine (14.4%), high serum urea (13.1%), proteinuria (43.9%), and hematuria (26.7%). During the hospital stay, 5.1% of the studied group developed AKI. The authors concluded that the rate of in-hospital mortality was significantly higher in patients who presented these kidney alterations and that any degree of proteinuria, hematuria, elevated basal serum urea, peak serum creatinine > 133 µmol/L, and AKI above stage 2 are associated with in-hospital death of COVID-19 patients[19].

The mean serum urea of dead patients compared to the mean of recovered patients was 8.4 mmol/L and 4.0 mmol/L, respectively[14]. The same was observed in the comparison of serum creatinine means: 88 µmol/L in dead patients and 66 µmol/L in recovered patients[14]. The incidence of in-hospital death in patients with high basal serum creatinine was 33.7%, which was

considerably higher than in those with normal basal serum creatinine (13.2%)[19]. Upon analyzing the urine from COVID-19 patients, hematuria and proteinuria were frequent findings during the hospital stay, present in 82% and 86% of dead patients, respectively[14].

Pei et al.[29] found similar results, with a higher mortality rate in patients who had kidney involvement (11.2%), compared to those who had no kidney involvement (1.2%). In this study, 4.7% of the group presented AKI. Of these, 86.4% died, which was the outcome of 75% of the patients with stage 1 AKI, 85.7% of patients with stage 2 AKI, and 90.9% of the patients with stage 3 AKI.

As seen, a large proportion of patients with severe COVID-19 developed some type of kidney involvement. AKI seems to have affected particularly patients who died from COVID-19. There is a considerable prevalence of this alteration in patients who died, which could indicate a correlation with higher mortality in patients infected by SARS-CoV-2.

COVID-19 AND RENAL PATHOLOGY

SARS-CoV-2 is 79% homologous with SARS-CoV, and both belong to the betacoronavirus genera, which uses the same ACEII receptor as a means of entry into the target cells[20]. Therefore, it is likely that the new coronavirus uses a similar mechanism[20]. The high expression of the angiotensin-converting enzyme type II (ACEII) in the kidneys could explain why these organs are possible targets[34]. Su et al.[20], in a study with patients who died from COVID-19, found that the ACEII protein was abnormal in 60% of them.

In a renal histopathological analysis of COVID-19 patients, changes were found in the epithelial and endothelial cells[20,35]. There was a variety of cellular abnormalities, with acute injury of the proximal tubule present in all patients analyzed[20].

There is evidence suggesting that the SARS-CoV-2 virus can directly infect renal tissues[20,35]. In an ultrastructural and immunostaining analysis, it was observed that diffuse acute tubular injury with loss of brush border and non-isometric vacuolization could be partially caused by direct infection[20]. Wichmann et al.[34] detected viral RNA in 41.66% of the renal tissues. Similarly, Su et al.[20] assessed that AKI and proteinuria in these patients may be associated with the kidney tubule epithelial and podocyte infection by SARS-CoV-2.

CONCLUSION

COVID-19 is a disease that, despite affecting primarily the lungs, can also affect other organs such as the kidneys. The increase in nitrogenous waste, hematuria, proteinuria, and AKI were frequent findings in patients with severe COVID-19. These findings were correlated with a higher mortality rate. We emphasize the need for more studies focused on kidney alterations and biomarkers[34] since detection and early treatment can contribute to decreasing the severity and mortality in COVID-19.

Acknowledgments

We thank the Federal University of Cariri and all the scientists and health professionals who work hard in the fight against the SARS-CoV-2 pandemic.

The authors declare there are no conflicts of interest in professional or financial nature, and no direct or indirect benefits were obtained from this work.

Author's Contribution

Samuel Átila Rodrigues Nogueira, Samuel Ciríaco Silva de Oliveira, Ana Flávia Moreira de Carvalho, Julia Moreira Cavalcante Neves, Leila Silveira Vieira da Silva, Geraldo Bezerra da Silva Junior and Maria Elizabeth Pereira Nobre: made substantial contributions to the concept and design of the work, the collection, analysis, and interpretation of data, the drafting of the paper and its critical review, and the final approval of the version to be published.

RESUMO

OBJETIVO: *Apresentar uma revisão sobre as alterações renais nos pacientes com COVID-19.*

MÉTODOS: *Foi realizada uma revisão sistemática de literatura para buscar estudos referentes a pacientes com alterações renais clínicas, laboratoriais e anatomopatológicas durante a infecção por SARS-CoV-2. A busca foi realizada nas bases de dados eletrônicos PubMed, Scopus e Embase, com as palavras-chaves: "COVID-19", "coronavirus", "Sars-CoV-2", "kidney injury" e "kidney disease", para identificar artigos originais publicados na literatura até 07 de maio de 2020. Quinze estudos trouxeram alterações renais clínicas e laboratoriais dos pacientes com COVID-19, e três abordaram análises anatomopatológicas.*

DISCUSSÃO: *A Lesão renal aguda (LRA) foi um achado relevante nos pacientes com COVID-19. Houve também alterações significativas nos exames laboratoriais que indicam lesão renal, como o nível de creatinina e ureia séricas, proteinúria e hematúria. As alterações laboratoriais e a LRA foram importantes nos pacientes que desenvolveram o quadro grave da doença. Há considerável prevalência de LRA nos grupos de pacientes que vieram a óbito. Na análise histopatológica de pacientes com SARS-CoV-2 foram encontrados achados renais sugestivos que o vírus poderia ter efeitos diretos sobre o rim.*

CONCLUSÃO: *A COVID-19 é uma doença que, apesar de acometer principalmente os pulmões, também acomete os rins. Aumento das escórias nitrogenadas, hematúria, proteinúria e LRA foram achados frequentes em pacientes com quadros graves da COVID-19. Esses achados foram relacionados a maior mortalidade. É necessária a realização de mais estudos com enfoque nas alterações renais e suas implicações no quadro clínico causadas pelo novo coronavírus.*

PALAVRAS-CHAVE: *Coronavirus. Infecções por Coronavirus. Betacoronavirus. Lesão Renal Aguda. Insuficiência Renal.*

REFERENCES

1. Yin C. Genotyping coronavirus SARS-CoV-2: methods and implications. Genomics. 2020;S0888-7543(20)30318-9.
2. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al; SARS Working Group. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med. 2003;348(20):1953-66.
3. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. New Engl J Med. 2012;367(19):1814-20.
4. Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264-6.
5. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J Med Virol. 2020;92(4):401-2.
6. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. New Engl J Med. 2020;382(8):727-33.
7. Johns Hopkins University & Medicine. COVID-19 map [Internet]. Baltimore: Johns Hopkins Coronavirus Resource Center; 2020. [cited 2020 May 18]. Available from: https://coronavirus.jhu.edu/map.html
8. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Resp Med. 2020;8(4):420-2.
9. Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol. 2003;200(3):282-9.
10. Ng DL, Al Hosani F, Keating MK, Gerber SI, Jones TL, Metcalfe MG, et al. Clinicopathologic, immunohistochemical, and ultrastructural findings of a fatal case of Middle East respiratory syndrome coronavirus infection in the United Arab Emirates, April 2014. Am J Pathol. 2016;186(3):652-8.
11. Cha RH, Joh JS, Jeong I, Lee JY, Shin HS, Kim G, et al; Critical Care Team of National Medical Center. Renal complications and their prognosis in Korean patients with Middle East respiratory syndrome-coronavirus from the central MERS-CoV designated hospital. J Korean Med Sci. 2015;30(12):1807-14.
12. Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int. 2005;67(2):698-705.
13. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
14. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.
15. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.
16. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
17. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol. 2020;127:104364.
18. Pan XW, Xu D, Zhang H, Zhou W, Wang LH, Cui XG. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med. 2020;46(6):114-6.
19. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829-38.
20. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;S0085-2538(20)30369-0.
21. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
22. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;e200950.
23. Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. Chin Med J (Engl). 2020;133(11):1261-7.
24. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323(20):2052-9.
25. Li Y, Hu Y, Yu J, Ma T. Retrospective analysis of laboratory testing in 54 patients with severe- or critical-type 2019 novel coronavirus pneumonia. Lab Invest. 2020;100(6):794-800.
26. Wang L, Li X, Chen H, Yan S, Li D, Li Y, et al. Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. Am J Nephrol. 2020;51(5):343-8.
27. Li X, Wang L, Yan S, Yang F, Xiang L, Zhu J, et al. Clinical characteristics of 25 death cases with COVID-19: a retrospective review of medical records in a single medical center, Wuhan, China. Int J Infect Dis. 2020;94:128-32.
28. Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care. 2020;24(1):188.
29. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol. 2020;31(6):1157-65.
30. Zhao XY, Xu XX, Yin HS, Hu QM, Xiong T, Tang YY, et al. Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study. BMC Infect Dis. 2020;20(1):311.
31. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Analysis of 92 deceased patients with COVID-19. J Med Virol. 2020;10.1002/jmv.25891.
32. Yang R, Gui X, Zhang Y, Xiong Y. The role of essential organ-based comorbidities in the prognosis of COVID-19 infection patients. Expert Rev Respir Med. 2020;1-4.
33. Meneses GC, Silva Junior GBD, Tôrres PPBF, Castro VQ, Lopes RL, Martins AMC, et al. Novel kidney injury biomarkers in tropical infections: a review of the literature. Rev Inst Med Trop Sao Paulo. 2020;62:e14.
34. Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med. 2020;M20-2003.
35. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. Zhonghua Bing Li Xue Za Zhi. 2020;49(5):411-7.

REVIEW ARTICLE

Clinical and socioeconomic characteristics of older adults with COVID-19: A protocol for a rapid systematic review

Maycon Sousa Pegorari[1]
Areolino Pena Matos[1]
Natalia Camargo Rodrigues Iosimuta[1]
Vânia Tie Koga Ferreira[1]
Daniela Gonçalves Ohara[1]
Elane Priscila Rosa Santos[1]
Caroline de Fátima Ribeiro Silva[1]
Nara Loren Oliveira dos Santos[1]
Aline Pereira Rocha[2]
Álvaro Nagib Atallah[2]
Ana Carolina Pereira Nunes Pinto[1,2]

1. Universidade Federal do Amapá - Unifap, Macapá, AP, Brasil
2. Universidade Federal de São Paulo - Unifesp, São Paulo, SP, Brasil

http://dx.doi.org/10.1590/1806-9282.66.S2.118

SUMMARY

The aim of this rapid systematic review is to analyze the prevalence of clinical, socioeconomic, and demographic characteristics, laboratory and imaging findings, diagnostic tests, and treatment information of older adults with COVID-19. To conduct this systematic review, the Cochrane Handbook recommendations will be followed. Patients aged 60 years or older with a confirmed diagnosis of SARS-CoV-2 infection will be included. A comprehensive literature search will be performed in the following databases: MEDLINE via PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Latin American and Caribbean Health Sciences Literature (LILACS), Spanish Bibliographic Index on Health Sciences (IBECS) and Epistemonikos COVID-19 L·OVE platform. No language restrictions will be applied. To assess the methodological quality of the included studies and the certainty of the evidence, the Newcastle-Ottawa Scale, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used. The meta-analysis will be performed using R software. We believe this rapid systematic review will be able to summarize the currently available evidence on clinical, socioeconomic characteristics, and management of COVID-19 in older adults. Therefore, it will help implement adequate strategies to fight the pandemic and assist in understanding the clinical profile of older patients with COVID-19, providing data with due scientific support upon which to base future choices of procedures and interventions.

KEYWORDS: *Aged. Coronavirus Infections. Health of the elderly.*

DATE OF SUBMISSION: 09-Jun-2020
DATE OF ACCEPTANCE: 12-Jun-2020
CORRESPONDING AUTHOR: Maycon Sousa Pegorari
Departamento de Ciências Biológicas, Curso de Graduação em Fisioterapia, Universidade Federal do Amapá (Unifap)
Rodovia Juscelino Kubitschek, Km – 02, Jardim Marco Zero, Macapá – AP
CEP 68903-419 - Campus Marco Zero - Tel: (+55 96) 4009-2944
E-mail: mayconpegorari@yahoo.com.br

INTRODUCTION

In the last months, the world has been facing a pandemic unprecedented in human history[1]. Initially identified in China in December 2019, the novel coronavirus (SARS-CoV-2) has high transmissibility and is the cause of Coronavirus Disease 19 (COVID-19), a potentially deadly acute respiratory infection[2]. There are several clinical symptoms of COVID-19, but they resemble those of simple flu. The patients can have mild, moderate, severe, or critical illness[3]. Data from a large case series have shown that nearly 10-15% of patients have the severe form of the disease, and 5% have the critical form of the disease and require treatment in intensive care units (ICU)[4].

Older age and clinical comorbidities, such as hypertension, diabetes, and obesity are factors associated with evolution to the severe form of COVID-19 and death[3]. However, comorbidities are much more prevalent in older adults than in the general population[5]. Therefore, it is not well established whether chronological age alone would be a good predictor of worse outcomes or if comorbidities would have a stronger impact on the prognosis of patients with COVID-19.

Of note, as a diagnostic test for COVID-19 depends on the dynamics of the immunological response, it has been questioned whether the sensitivity of the current diagnostic tests is affected by age[6]. Additionally, as age is accompanied not only by changes in the immune response but also by multimorbidity and polypharmacy, it has also been suggested that the treatment of COVID-19 in older adults should be carefully evaluated[7].

Although there is a large number of reviews on COVID-19[8-10], to our knowledge, none of them have investigated several features specifically of the elderly population with COVID-19. Therefore, an accurate synthesis of the currently available evidence pointing out clinical, socioeconomic, demographic characteristics, and information on efficient diagnostic tests and specific treatments for COVID-19 in older adults is crucial and can help health professionals face the health emergency we are currently experiencing.

Thus, the purpose of this rapid systematic review is:

- To estimate the prevalence of clinical characteristics and comorbidities in older people with COVID-19;

- To analyze the prevalence of socioeconomic and demographic characteristics in older adults with COVID-19;

- To determine the prevalence of laboratory and imaging findings in older people with COVID-19;

- To analyze which diagnostic tests and treatments are most frequently used in older adults with COVID-19.

METHODS

To conduct a rapid systematic review, we will employ abbreviated systematic review methods. Therefore, we will not perform independent screenings of abstracts, nor will we search grey literature[11].

ELIGIBILITY CRITERIA

Types of studies

We will include clinical studies on COVID-19 that have included older adults and with availability of clinical, socioeconomic, and demographic characteristics, laboratory and imaging findings, diagnostic tests, or treatment information.

Types of participants

Patients aged 60 years or older with a confirmed diagnosis of SARS-CoV-2 infection.

Outcome measures

We aim to determine the prevalence of the following outcomes in older adults diagnosed with COVID-19:

Clinical characteristics: fever, cough, sore throat, difficulty breathing, diarrhea, nausea/vomiting, headache, runny nose, irritability/confusion, adynamia, pharyngeal exudate, seizure, conjunctivitis, coma, dyspnea/tachypnea, abnormal lung sounds, delirium, loss of taste or smell, chest pain or pressure, muscle pain; and previous characteristics or comorbidities: smoking status, cardiovascular disease, hypertension, diabetes, liver disease, chronic neurological or neuromuscular disease, immunodeficiency, HIV infection, kidney disease, chronic lung disease, neoplasia (solid or hematological tumor), or any other clinical characteristics and/or comorbidities reported in the primary studies.

Socioeconomic and demographic characteristics: such as gender, age, income, education, marital status, housing arrangement, country or continent, hospital, clinic, community, or long-term care institutions for the older people.

Laboratory findings: e. g. serum creatinine, platelets, hemoglobin, blood albumin, procalcitonin,

c-reactive protein, white blood cells, aspartate transaminase, alanine transaminase, ferritin, interleukins, international normalized ratio – INR; and imaging findings: chest x-ray and computed tomography abnormalities (multiple lobe lesion, single lobe lesion).

Most frequently used diagnostic tests: such as nucleic acid amplification tests (RT-PCR), serological tests for IgA, IgM, and/or IgG anti-SARS-CoV-2 antibodies, using ELISA, chemiluminescence or immunochromatographic methods, immunochromatographic test to search for viral antigens in upper respiratory tract samples.

Most frequently used treatments: such as oxygen therapy, mechanical ventilation (non-invasive and invasive), antiviral treatment, glucocorticoids, immunoglobulin, traditional Chinese medicine, antibiotics, thymopentin, continuous renal replacement therapy, immunobiologics, or any other treatment reported in the primary studies.

Data sources and searches

A comprehensive literature search will be performed in the following databases:

- MEDLINE via PubMed;
- Embase;
- Cochrane Central Register of Controlled Trials (CENTRAL);
- Latin American and Caribbean Health Sciences Literature (LILACS);
- Spanish Bibliographic Index on Health Sciences (IBECS);
- Epistemonikos COVID-19 L·OVE platform.

To identify potentially relevant studies, appropriate descriptors and synonyms will be used, adapting the search to the specifications of each database. We will also search the trials registry ClinicalTrials.gov. Studies published since December 2019 will be included and no language restrictions will be used in the selection. Finally, we will apply the technique of snowballing, searching the lists of references of the included studies.

Search strategy

We will use the terms related to the problem of interest, the intervention, and filter the date of publication. The search strategy in Medline via Pubmed is shown in Table 1.

Study selection

Two authors (E.P.R.S. and N.L.O.S.) will screen the studies retrieved during the searches and select them for inclusion in this review. If studies are found in more than one database, only one of them will be considered for inclusion. If reports using the same participants but different outcome measurements are found, both reports will be included, but they will be considered as parts of only one study.

After removing duplicated studies, the titles and abstracts will be read and those that clearly do not fulfill the eligibility criteria will be excluded. The remaining studies will then be fully read and assessed for inclusion in the review. Disagreements regarding the inclusion of studies will be solved by consulting a third author (C.F.R.S.). The reasons for any full-text paper exclusions will be documented. Rayyan application[12] will be used for the screening and selection of studies.

TABLE 1. SYSTEMATIC REVIEW SEARCH STRATEGY

Number	Combiners	Terms
1	Population of interest	Coronavirus[MeSH Terms] OR Coronaviridae[MeSH Terms] OR Coronavirus Infections[MeSH Terms] OR coronavirinae OR COVID-19 OR COVID OR COVID19 OR "severe acute respiratory syndrome coronavirus 2" OR SARS-CoV-2 OR SARS2 OR SARSCov2 OR ncov* OR betacoronavirus[MeSH Terms] OR Coronavirus* OR 2019-nCoV OR (Corona virus*)
2		Aged[MeSH Terms] OR Geriatrics[Mesh Major Topic] OR geriatric* OR gerontolog* OR older OR aging OR senior OR old OR elder* OR Aged, 80 and over[Mesh Terms] OR centenarian* OR nonagenarian* OR octogenarian* OR pensioner OR veteran* OR Health Services for the Aged[Mesh Terms] OR Homes for the Aged[Mesh Terms] OR (nursing home) OR (retirement home) OR old-age
	Filters	Publication date: 2019 - 2020
3		#1 AND #2 AND #3

The abovementioned search strategy will be used in Medline via Pubmed and will be adapted to the specifications of each database.

Data extraction

Two authors (E.P.R.S. and N.L.O.S.) will independently extract relevant data. Discrepancies in the data extraction will be solved by a third author (C.F.R.S.). To extract data from included studies, a predefined form will be used with the following information: (I) Demographic and clinical characteristics of the participants; (II) Socioeconomic characteristics of the participants; (III) Laboratory findings; (IV) Imaging findings; (V) Tests used to confirm diagnosis; (VI) Treatment; (VII) Sources of funding; (VIII) Possibility of conflict of interests.

Assessment of methodological quality in included studies and certainty of the body of evidence

The Newcastle-Ottawa Scale for assessing the methodological quality of observational studies will be used[13]. The certainty of evidence will be assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[14] using GRADE profiler software[15]. An assessment of risk of bias and of the certainty of evidence will be performed by two authors (E.P.R.S. and N.L.O.S.), and all disagreements will be solved through discussion or, if required, by consulting with a third author (C.F.R.S.).

Data Synthesis and Analysis

When at least two studies are found assessing the same clinical, epidemiological, or treatment characteristics of COVID-19 in older adults, we will assess the possibility of pooling the data into a meta-analysis. To perform the meta-analysis, R software[16] with the "meta" package (version 4.9–6), the "metaprop" function for proportion data, and the "metamean" function for continuous data will be used. We will present pooled results of proportion with their respective 95% confidence intervals (CI) by using the inverse variance method with a random-effects model. For continuous data, we will present pooled results of means with their respective 95% CI by the inverse variance method with a random-effects model. Heterogeneity will be assessed by Cochran's Q test considering a statistically significant value for $p < 0.1$ and Higgins I^2.

Reporting Characteristics

This rapid systematic review protocol was reported following the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance[17] and was registered in the Prospective Register of Systematic Reviews (PROSPERO) platform (CRD42020190951).

DISCUSSION

Our rapid systematic review planned with this protocol aims to estimate, analyze, and determine the sociodemographic, clinical, laboratory, and imaging findings, as well as the diagnostic tests and treatments of older adults with COVID-19. Since the first reports of COVID-19 cases in Wuhan, China, studies have shown that older adults are at a higher risk of complications when infected by SARS-CoV2[2,3], especially those with frailty and comorbidities. Of note, most publications have considered their results in the adult populations without providing specific information regarding older adults. As a huge amount of publications have addressed COVID-19, an updated synthesis compiling the best available evidence is critical and can help guideline developers and front-line health professionals create strategies to assist patients with due scientific support.

To ensure the methodological quality of this review, we will follow the Cochrane Handbook of the Systematic Reviews recommendations[18], search the largest electronic databases, assess the risk of bias of included studies using the Newcastle-Ottawa Scale[13], and, finally, evaluate the certainty of evidence with GRADE[14]. We believe this rapid systematic review will be able to summarize the currently available studies on the clinical profile and management of older adults with COVID-19. Therefore, it will not only guide future research but also help implement adequate strategies to fight the pandemic and provide critical data upon which future choices of procedures and interventions can be based.

Conflict of interest

There was no conflict of interest.

Author's Contributions

MSP, APM, NCRI, VTKF, DGO, APR, ANA, and ACPNP contributed to the study conception and design, article writing, and editing. EPRS, CFRS, and NLOS contributed to the article writing. All authors read and approved the final version of the article to be published.

APPENDIX

Search Strategy

EMBASE

#1 'coronavirinae'/exp OR coronavirinae OR 'COVID-19'/exp OR 'COVID-19' 'COVID-19' OR covid OR COVID-19 OR 'coronavirus'/exp OR coronavirus* OR 'corona virus*' OR 'coronaviral infection' OR 'coronaviridae'/exp OR coronaviridae OR 'coronavirus infection'/exp OR 'coronavirus infection' OR 'sars-cov-2' OR SARSCov2 OR ncov* OR coronaviruses OR 'severe acute respiratory syndrome coronavirus 2' OR 'SARS coronavirus'/exp OR 'SARS coronavirus' OR 'SARS-related coronavirus'/exp OR 'SARS-related coronavirus' OR 'betacoronavirus'/exp OR betacoronavirus

#2 'aged'/exp OR aged OR elder* OR 'geriatrics'/exp OR geriatric* OR 'geriatric patient'/exp OR gerontolog* OR 'geriatric care'/exp OR older OR old OR aging OR senior OR senium OR 'very elderly'/exp OR 'very elderly' OR centenarian* OR nonagenarian* OR octogenarian* OR pensioner OR veteran* OR 'nursing home' OR 'home for the aged'/exp OR 'retirement home' OR old-age

#3 #1 AND #2

#4 #3 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND [1-12-2019]/sd

LILACS AND IBECS VIA PORTAL BVS

mh:"Coronavirus" OR mh:"Infecções por Coronavirus" OR mh:"Coronaviridae" OR mh:"Betacoronavirus" OR mh:"Severe Acute Respiratory Syndrome" OR COVID-19 OR COVID-19 OR (COVID-19) OR 2019-ncov OR sars-cov-2 OR "Novo Coronavírus" OR mh:b04.820.504.540* OR "Coronavirus Infections" OR "novel coronavirus"

AND

mh:"Idoso" OR aged OR anciano OR Idosos OR (Pessoa Idosa) OR (Pessoa de Idade) OR (Pessoas Idosas) OR (Pessoas de Idade) OR (População Idosa) OR mh:"Idoso de 80 Anos ou mais" OR Centenários OR Nonagenários OR Octogenários OR Velhíssimos OR mh:"Instituição de Longa Permanência para Idosos" OR Ancianatos OR ILPI OR (Instituição Asilar) OR (Instituições Geriátricas de Longa Permanência) OR mh:"Geriatria" OR Geriatrics OR Geriatría OR Gerontologia

Filter: Year 2019-2020

COCHRANE

#1 MeSH descriptor: [Coronavirus] explode all trees

#2 MeSH descriptor: [Coronaviridae] explode all trees

#3 MeSH descriptor: [Coronavirus Infections] explode all trees

#4 MeSH descriptor: [Betacoronavirus] explode all trees

#5 coronavirinae OR COVID-19 OR COVID OR COVID-19 OR "severe acute respiratory syndrome coronavirus 2" OR Coronavirus* OR "2019-nCoV" OR nCoV* OR "SARS-CoV-2" OR SARS2 OR SARSCov2 OR "Corona virus*"

#6 #1 or #2 or #3 or #4 or #5

#7 MeSH descriptor: [Aged] explode all trees

#8 MeSH descriptor: [Geriatrics] explode all trees

#9 MeSH descriptor: [Aged, 80 and over] explode all trees

#10 MeSH descriptor: [Health Services for the Aged] explode all trees

#11 MeSH descriptor: [Homes for the Aged] explode all trees

#12 geriatric* OR gerontolog* OR older OR aging OR senior OR old OR elder* OR centenarian* OR nonagenarian* OR octogenarian* OR pensioner OR veteran* OR (nursing home) OR (retirement home) OR old-age

#13 #7 OR #8 or #9 or #10 or #11 or #12

#14 #6 AND #13

Filter: Year 2019-2020

EPISTEMONIKOS

https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d
Primary Studies
Reporting results

CLINICAL TRIALS

https://clinicaltrials.gov/ct2/results?cond=COVID-19
Filters:
-Age 18-65
-Age: (65+)
-With results

RESUMO

O objetivo desta rápida revisão sistemática é analisar a prevalência de características clínicas, socioeconômicas e demográficas, achados laboratoriais e de imagem, testes de diagnóstico e informações de tratamento de idosos com COVID-19. Para conduzir esta revisão sistemática, serão seguidas as recomendações do Manual Cochrane. Pacientes com 60 anos ou mais com diagnóstico confirmado de infecção por Sars-CoV-2 serão incluídos. Uma pesquisa bibliográfica abrangente será realizada nas seguintes bases de dados: Medline via PubMed, Embase, Cochrane Central Register of Controlled Trials (Central), Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs), Índice Bibliográfico Espanhol em Ciências da Saúde (Ibecs) e Epistemonikos Plataforma COVID-19 L · OVE. Nenhuma restrição de idioma será aplicada. Para avaliar a qualidade metodológica e a certeza das evidências dos estudos incluídos, serão utilizadas a Escala Newcastle-Ottawa e a abordagem Grading of Recommendations Assessment, Development and Evaluation (Grade). A meta-análise será realizada no software R. Acreditamos que esta revisão sistemática rápida será capaz de resumir as evidências atualmente disponíveis sobre as características clínicas, socioeconômicas e sobre o manejo de idosos com COVID-19. Portanto, ajudará a implementar estratégias adequadas para combater a pandemia e ajudará a entender o perfil clínico de pacientes idosos com COVID-19, fornecendo dados com o devido apoio científico sobre o qual basear futuras escolhas de procedimentos e intervenções.

PALAVRAS-CHAVE: *Idoso. Infecções por coronavírus. Saúde do idoso.*

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19) outbreak situation. Geneva: World Health Organization; 2020.
2. Sun H, Ning R, Tao Y, Yu C, Deng X, Zhao C, et al. Risk factors for mortality in 244 older adults with COVID-19 in Wuhan, China: a retrospective study. J Am Geriatr Soc. 2020;68(6):E19-E23.
3. Jain V, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health. 2020;1-14.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020. doi: 10.1001/jama.2020.2648.
5. Pereira DS, Nogueira JAD, Silva CAB. Quality of life and the health status of elderly persons: a population-based study in the central sertão of Ceará. Rev Bras Geriatr Gerontol. 2015;18(4):893-908.
6. Lithander FE, Neumann S, Tenison E, Lloyd K, Welsh TJ, Rodrigues JCL, et al. COVID-19 in older people: a rapid clinical review. Age Ageing. 2020;afaa093. doi: 10.1093/ageing/afaa093.
7. Lauretani F, Ravazzoni G, Roberti MF, Longobucco Y, Adorni E, Grossi M, et al. Assessment and treatment of older individuals with COVID-19 multi-system disease: clinical and ethical implications. Acta Biomed. 2020;91(2):150-68.
8. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020;87(4):281-6.
9. AminJafari A, Ghasemi S. The possible of immunotherapy for COVID-19: a systematic review. Int Immunopharmacol. 2020;83:106455.
10. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA. 2020. doi: 10.1001/jama.2020.6019.
11. Garritty C, Gartlehner G, Kamel C, King VJ, Nussbaumer-Streit B, Stevens A, et al. Cochrane rapid reviews: interim guidance from the Cochrane Rapid Reviews Methods Group. [cited 2020 Jun 1]. Available from: https://methods.cochrane.org/rapidreviews/cochrane-rr-methods
12. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
13. Wells GA, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. 2014.
14. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.
15. GDT G. Grade's software for summary of findings tables, health technology assessment and guidelines 2015.
16. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2013.
17. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.
18. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019). Oxford: Cochrane; 2019. [cited 2020 May 23]. Available from: www.training.cochrane.org/handbook

REVIEW ARTICLE

Safety alert for hospital environments and health professional: chlorhexidine is ineffective for coronavirus

Marcelo Souza de Assis[1]
Renata Alves de Andrade Moreira Araújo[1,2]
Angela Maria Moed Lopes[1,2]

1. Masters in Health Management Sciences – Must University, Boca Raton, FL, USA.
2. Capstone Course – Must University, Boca Raton, FL, USA.

http://dx.doi.org/10.1590/1806-9282.66.S2.124

SUMMARY

An alarming fact was revealed by recent publications concerning disinfectants: chlorhexidine digluconate is ineffective for disinfecting surfaces contaminated by the new coronavirus. This is a finding that requires immediate disclosure since this substance is widely used for the disinfection of hands and forearms of surgeons and auxiliaries and in the antisepsis of patients in minimally invasive procedures commonly performed in hospital environments. The objective of this study is to compare the different disinfectants used for disinfection on several surfaces, in a review of worldwide works. Scientific studies were researched in the BVS (Virtual Health Library), PubMed, Medline, and ANVISA (National Health Surveillance Agency) databases. The following agents were studied: alcohol 62-71%, hydrogen peroxide 0.5%, sodium hypochlorite 0.1%, benzalkonium chloride 0.05-0.2%, povidone-iodine 10%, and chlorhexidine digluconate 0.02%, on metal, aluminum, wood, paper, glass, plastic, PVC, silicone, latex (gloves), disposable gowns, ceramic, and Teflon surfaces. Studies have shown that chlorhexidine digluconate is ineffective for inactivating some coronavirus subtypes, suggesting that it is also ineffective to the new coronavirus.

KEYWORDS: *Coronavirus. Disinfection. Asepsis. Chlorhexidine.*

INTRODUCTION

COVID-19 is a pandemic caused by a new coronavirus, Sars-CoV-2, which, by 28 May 2020[1], had affected approximately 5,593,631 patients throughout the world, having been the cause of 353,334 deaths (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200528-COVID-19-sitrep-9.pdf?sfvrsn=5b154880_2)[2].

The exponential growth of the novel coronavirus resulted in the halting of the world economy. According to the United Nations Industrial Development Organization (UNIDO), the world is experiencing the greatest challenge of the post-war era due to the sudden stoppage of economic activity in developed and developing countries. The latest forecasts by the World Trade Organization (WTO) expect a global contraction of around 9% of the world economy[3].

Other pandemic outbreaks have happened before, including the Spanish flu (1917-1919), which killed

DATE OF SUBMISSION: 17-Jun-2020
DATE OF ACCEPTANCE: 28-Jun-2020
CORRESPONDING AUTHOR: Angela Maria Moed Lopes
N Ferderal Hwy, n° 2220, Boca Raton, FL 33431, USA. Tel: +1(561)465-3277.
E-mail: angela.lopes@mustedu.com.br

between 50 and 100 million people[4], and the black plague, which struck Europe between 1347 and 1352 and that, according to Alfani and Murphy[5], was the worst plague of all times, killing between one- and two-thirds of the European population and also affecting the north of Africa and most of Asia.

The coronaviruses comprise a large family of viruses, common in humans and some animals, such as camels, oxen, cats, and bats[6]. The most recent pandemic was caused by Sars-CoV-2, which, in its most severe presentation, causes severe acute respiratory failure. This pandemic began in December 2019, in the city of Wuhan, in the Chinese province of Hubei. It spread quickly through China and, soon after, worldwide. In March 2020, the World Health Organization (WHO) recognized the situation as a "pandemic" that, as defined by the entity, is a disease outbreak with a number of cases above the expected, affecting several countries and continents[7].

One of the factors that may be related to the rapid spread of the novel coronavirus is its great resistance to external environments, unlike other viruses, which are inactivated in seconds, which makes it a challenge regarding strategies of disinfection or adequate antisepsis[8].

Asepsis, antisepsis, and disinfection have different goals. Asepsis is the set of measures that we use to prevent the penetration of microorganisms in an environment that does not have them, i.e., which is free of infection. Antisepsis is the set of measures proposed to inhibit the growth of microorganisms or remove them from a particular environment, destroying them or not. Disinfection is the process of destroying microorganisms, pathogens or not, occurring in surfaces and objects by applying germicidal agents, classified as disinfectants[9].

In practice, the terms antiseptics and disinfectants are used as synonyms; however, they are characterized as antiseptics when used in living tissues, such as the skin and mucous membranes, and as disinfectants when used on inanimate objects, such as metals, wood, and latex[9].

Concern about the use of proper antiseptics and disinfectants is related to the health and safety of the people on the frontline of the pandemic. In this context, given the absence of a vaccine against Sars-CoV-2 and of effective treatments for the most acute stages of COVID-19, prevention and antisepsis measures, based on the use of effective disinfecting agents, according to the field of activity, are fundamental to control the dissemination of the disease.

Thus, this review aims to alert health authorities, health professionals, life maintenance agents, such as nurses, pharmacists, biomedicine professionals, paramedics, firefighters, police officers, among others, regarding the inefficiency of chlorhexidine digluconate against the new coronavirus and the need to use appropriate antisepsis and disinfection agents at a large scale.

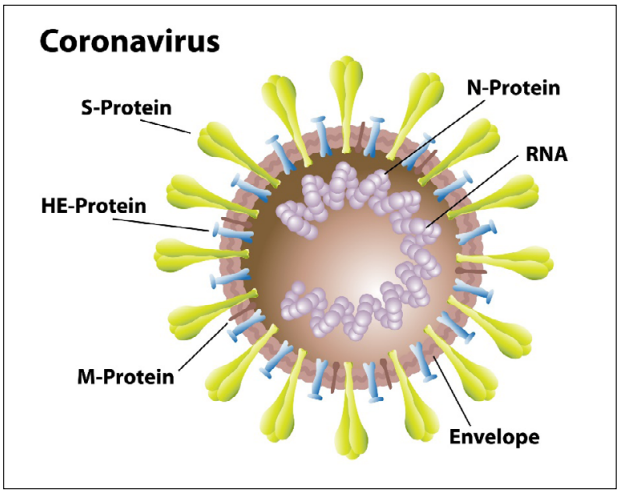
SARS-COV-2

According to the Pan American Health Organization (PAHO), seven human coronaviruses (HCoVs) have been identified: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, Sars-CoV (which causes severe acute respiratory syndrome), Mers-Cov (which causes the Middle Middle East respiratory syndrome), and, most recently, the novel coronavirus (which at first was temporarily called 2019-nCoV and, on 11 February 2020, received the name of Sars-CoV-2), which is responsible for causing the COVID-19 disease[10].

The coronavíruses belong to the Coronaviridae family and are responsible for a variety of diseases in man and animals, affecting, in particular, the respiratory system. They are composed of single-stranded, positive-sense RNA, containing from 26 to 32 kilobases, and are associated with proteins, forming a nucleocapsid. Its particles present projections on their envelope shaped like spicules, formed by *S* protein (Spike protein) trimers. These projections look like a crown, hence the name coronavirus[10,11] (Figure 1).

Sars-CoV-2 is transmitted mainly by respiratory droplets and has an incubation period of about 4-5 days before the onset of symptoms, which include

FIGURE 1. MOLECULAR STRUCTURE OF THE NOVEL CORONAVIRUS (SARS-COV-2).



Source: Shutterstock (license number 1684060378).

fever, cough, breathing difficulties, headaches, muscle and/or joint pain, diarrhea, and nausea. In more severe cases, COVID-19 patients develop acute respiratory distress syndrome (ARDS). The severity of the disease is related not only to the viral infection but also to the host's response, who may succumb to other underlying comorbidities[12].

Some studies have shown that the human coronaviruses are very resistant outside a host and may remain active on various surfaces for up to nine days[8], which may explain the effectiveness of contagion and the unbridled spread of the novel coronavirus. According to a study published by Doremalen and collaborators[13], Sars-CoV-2 viruses have been detected in up to 72 hours after their application in plastic and stainless steel.

GERMICIDES USED AGAINST THE CORONAVIRUS

According to Geller, Varbanov, and Duval (2012)[14], a good germicide is considered effective as a disinfectant and antiseptic if it can induce, in well-defined contact time, a reduction in viral titers greater than 3 or 4 $\log_{10}$, depending on the American and European regulatory agencies.

The sensitivity of HCoV 229E, a subtype of human coronavirus, to the action of antiseptic disinfectants was evaluated in a study published by Sattar and collaborators[15], which validated disinfecting agents that reduced viral titers of 3 $\log_{10}$ after exposure for 1 minute (Table 1).

Table 1 shows that chlorhexidine alone, associated to cetrimide or associated to less than 70% ethanol, which is widely used in medicine, is ineffective against the HCOV 229E, one of the lightest variants of the coronavirus, since reaches only 0.008-0.8 $\log_{10}$ of inactivation, except when associated with 70% ethanol[15].

The biocidal agent chlorhexidine is widely used in hospitals for antisepsis of cutaneous and mucosal surfaces in the antisepsis of the hands and forearms of surgeons and asepsis and antisepsis of surgical patients or patients undergoing invasive and minimally invasive procedures, such as peripheral punctures, placement of catheters, vesical tubes, drains, central venous catheters, and tracheostomies, all common procedures in patients admitted to intensive care units (ICUs)[16].

TABLE 1. ANTISEPTIC AND DISINFECTANT AGENTS THAT WORK AGAINST THE HCOV (HUMAN CORONAVIRUS).

Tested disinfectant antiseptics	Concentration	Reduction of the viral titer ≥ 3 $\log_{10}$ after 1 min
Sodium hypochlorite	0.10% and 0.50%	YES
Chloramine-T	0.10% and 0.30%	YES
Sodium hypochlorite/ Potassium bromide	0.05% and 0.10%	YES
Povidone-iodine	10%	YES
Ethanol	70%	YES
Glutaraldehyde	2%	YES
Chlorhexidine + Cetrimide	0.008% + 0.08%	NO
Chlorhexidine + Cetrimide + Ethanol	0.05% + 0.5% + 70%	YES

Source: Adapted from Sattar and colleagues (1989) 15.

TABLE 2. PERSISTENCE OF THE CORONAVIRUS IN DIFFERENT INANIMATE SURFACES.

Surfaces	Virus	Inoculum (viral titer)	Temperature	Persistence
Steel	MERS-CoV	105	20o to 30°C	8h to 48h
Aluminum	HCoV	5x103	21oC	2-8h
Metal	SARS-CoV	105	Room temp.	5 days
Wood	SARS-CoV	105	Room temp.	4 days
Paper	SARS-CoV	105	Room temp.	4-5 days
Glass	SARS-CoV HCoV	105 103	Room temp. 21oC	4 days 5 days
Plastic	SARS-CoV MERS-CoV	105 105	22o to 25oC 20°C	≤ 5 days 48h
PVC	HCoV	103	21o	5 days
Silicone	HCoV	103	21o	5 days
Gloves (latex)	HCoV	5X103	21o	8h
Disposable apron	SARS-CoV	106	Room temp.	2 days

Source: Adapted from Sattar and colleagues (2020) 8.

TABLE 3. INACTIVATION OF THE CORONAVIRUS BY DIFFERENT DISINFECTANTS.

Biocidal Agent	Concentration	Virus	Exposure Time	Reduction of viral activity (log10)
Ethanol	70%	MHV	10 min.	≥ 3.9
Sodium hypochlorite	0.21%	MHV	30 s	≥ 4.0
Hydrogen peroxide	0.5%	HCoV	1 min.	>4
Povidone-iodine	0.23% 0.23%	SARS-CoV MERS-CoV	15 s 15 s	≥ 4.4 ≥ 4.4
Glutaraldehyde	2.0%	HCoV	1 min.	>3
Chlorhexidine gluconate	0.02%	MHV	10 min.	0.7-0.8

Source: Adapted from Sattar and colleagues (2020) 8.

They are usually used at a concentration of 0.5% and may be associated with antiseptic solutions, aqueous or alcoholic, and are excellent germicides, according to Moriya and Modena[9]. This is the option of choice against gram-positive bacteria, but its action is ineffective for the coronavirus family[9,16].

According to Colares (2015)[17], the microbicidal activity of chlorhexidine is mainly against gram-positive and gram-negative vegetative bacteria. It does not act on sporulating forms, except at high temperatures. Some lipophilic viruses, such as influenza, herpes virus, and HIV, are quickly inactivated.

Another study that is very relevant to this topic was conducted by the University of Medicine of Greifswald, Germany. It described the persistence of various strains of coronavirus, including Sars-CoV, Mers-CoV, and HCoV, on different surfaces. The authors demonstrated that these variants of the coronavirus can persist on inanimate surfaces, such as metal, glass, or plastic for between two hours and nine days[8].

In addition, this study also described the action of some disinfectant agents, including alcohol 70%, hydrogen peroxide 0.5%, sodium hypochlorite 0.1%, benzalkonium hydrochloride 0.05-0.2%, povidone-iodine 10%, and 0.02% chlorhexidine digluconate, comparing the inactivity of the several strains mentioned in several inanimate surfaces, such as metal, aluminum, paper, glass, plastic, PVC, silicone, latex (gloves), disposable aprons, ceramics, and Teflon (Table 2). In this table, it is possible to observe that certain strains of coronaviruses are capable of resisting up to five days on metal, paper, glass, plastic, PVC, and silicone surfaces[8].

The data in Table 3 are even more alarming, because they demonstrate that chlorhexidine reduces the titer of the MHV virus, a murine strain of the coronavirus, only in 0.7-0.8 $\log_{10}$, and the standard level established by international bodies is ≥3 $\log_{10}$ of inactivation in 1 minute of exposure[8].

The study by Koh (2020) demonstrates a great increase of cases of COVID-19 infections among health professionals, making this a high-risk group. From 138 cases of patients treated at the Hospital of Wuhan, 40 (29%) were health professionals. Among those affected, 31 (77%) worked in general activities, seven (17.5%) in the emergency room, and two (5%) in the ICU[18].

The Federal Nursing Council (COFEN) (2020) published that already over 10,000 nurses, technicians, and nursing assistants have been removed from work due to COVID-19 in Brasil, with 88 deaths by May 2020. According to the Council, this figure is more than double than that of contaminated professionals in Italy (http://www.cofen.gov.br/cofen-publica-observatorio-diario-da-COVID-19-entre-profissionais-de-enfermagem_79551.html)[19]. However, to date, no study has assessed the possible association between the use of chlorhexidine as a disinfection agent as a possible cause of dissemination of the novel coronavirus among health professionals, but this could be a potential factor for greater infection due to its inefficiency in inactivating the virus.

PROTECTIVE AND ANTISEPSIS MEASURES AGAINST THE NOVEL CORONAVIRUS

The Regional Council of Pharmacy of Minas Gerais created a booklet called PADM - Protocol for Antisepsis of Massive Disinfection in response to the novel coronavirus; we suggest its adoption as complementary care for the protection of the population and mainly of healthcare professionals who are at the frontline of the pandemic [20].

The PADM includes actions of antisepsis of the hands and forearms to eliminate a possible viral load; lips, tongue, and mucous membranes of the oral cavity; nostrils and oropharyngeal mucosa; eyeballs and lacrimal ducts; and dermis and mucosae of infected and hospitalized. The booklet also advocates for defining clean and dirty areas, based on green, yellow, and red areas, with basic cleaning actions for non-disposable PPE and measures for handling disposable materials[20].

In addition, based on the data from Kampf (2020)[8], solutions of ethanol (78-95%), 2-propranolol 45%, in combination with 1-propanolol 30%, glutaraldehyde (0.5-2.5%), formaldehyde (0.7-1%), and povidone-iodine (0.23-7.5%) were the most effective agents for antisepsis, with a reduction of the viral load of 4 $\log_{10}$ or more, i.e., above the value recommended by the American and European authorities.

For the disinfection of rooms, patient waiting areas, surgical centers, and all common areas of hospitals, outpatient clinics, and other clinics, we suggest using pressurized backpack sprayers to massively apply sodium hypochlorite solutions at 0.1-0.5%, between 100 and 300 ml per m^2, and in open areas (CCDCP, 2020)[21], since this has been proven to be greatly effective against the coronavirus, in addition to being very accessible.

According to a technical note published by the Brazilian Health Regulatory Agency (Anvisa), common household disinfectants, including water and soap or a solution of diluted bleach can deactivate the novel coronavirus on surfaces. This is due, mainly, to the fact that these disinfectants destroy the lipid layer that surrounds the coronavíruses[22].

In addition, the note also informs about alternatives to alcohol 70% that cannot be used to disinfect objects and surfaces, including sodium hypochlorite 0.1%, bleaches containing hypochlorite (sodium or calcium) 0.1%, povidone-iodine 1%, hydrogen peroxide 0.5%, peracetic acid 0.5%, benzalkonium chloride 0.05%, phenolic compounds, and disinfectants for general use approved by Anvisa.

In a decision published on 17 March of this year[23], Anvisa exceptionally authorized the selling of chlorhexidine digluconate 0.5%, provided it is prepared according to the guidelines of the 2nd edition, Revision 2, of the Brazilian Pharmacopoeia National Form[24], which recommends adding other components to chlorhexidine, including isopropyl alcohol, benzalkonium chloride, polysorbate, lactic acid, and purified water. It is worth mentioning that, alone, chlorhexidine, as well as benzalkonium chloride, are not effective against the coronavirus[8].

According to these data, it is suggested that chlorhexidine at the usual concentrations of 0.5% and 2% marketed in Brasil, alone or associated with cetrimide or alcohol at less than 70%, is completely ineffective against the novel coronavirus[8], putting healthcare professionals at a greater chance of contamination.

CONCLUSION

According to the data found in the literature, chlorhexidine is ineffective for the disinfection of surfaces containing coronavirus subtypes, which leads us to believe that it is also ineffective against the novel coronavirus. These data lead to a great concern regarding the spread of the novel coronavirus among health professionals, in particular physicians and nurses and other life and order maintenance agents since chlorhexidine is widely used in surgical and invasive procedures in ICUs, particularly in view of the great resistance of the novel coronavirus on surfaces such as plastic, face shields, latex gloves, masks, and disposable aprons.

Therefore, the use of other disinfectant agents is recommended, among them alcohol 70%, sodium hypochlorite 0.1%, bleach containing hypochlorite (sodium or calcium) 0.1%, povidone-iodine 1%, which have proved to be more effective. In addition, we suggest the completion of studies to prove the effectiveness of the disinfecting agents listed in the paper against the novel coronavirus, Sars-CoV-2, in view of its high degree of dissemination and the absence of studies related to this type of virus.

Acknowledgments

We would like to thank the Must University for their support.

Author's Contribution

Marcelo Souza de Assis, Angela Maria Moed Lopes - Definition of the theme and data collection, tabulation, data analysis, and creation of tables and figures.

Marcelo Souza de Assis, Angela Maria Moed Lopes, Renata Alves de Andrade Moreira Araújo - Drafting of the text and adjustments according to the standards of the periodical.

Angela Maria Moed Lopes, Renata Alves de Andrade Moreira Araújo - Revision of the text and adding of significant parts.

RESUMO

Um dado alarmante revelado por publicações a respeito dos agentes desinfetantes: o digluconato de clorexidina é ineficaz para desinfecção de superfícies contaminadas por coronavírus. Trata-se de uma constatação que reclama imediata divulgação, uma vez que essa substância é amplamente usada para degermação de mãos e antebraços dos cirurgiões e auxiliares e na antissepsia dos pacientes, em procedimentos minimamente invasivos, comumente em ambientes hospitalares. O objetivo deste trabalho foi comparar os diferentes desinfetantes usados para desinfecção em diversas superfícies em revisão de trabalhos mundiais. Foram pesquisados trabalhos científicos na BVS (Biblioteca Virtual de Saúde), PubMed, Medline e Anvisa (Agência Nacional de Vigilância Sanitária). Foram estudados os seguintes agentes: álcool 62-71%, peróxido de hidrogênio 0,5%, hipoclorito de sódio 0,1%, cloreto de benzancônio 0,05-0,2%, iodo povidina 10% e digluconato de clorexidina 0,02%, em superfícies de metal, alumínio, madeira, papel, vidro, plástico, PVC, silicone, látex (luvas), avental descartável, cerâmica e teflon. Os estudos demonstraram que o digluconato de clorexidina é ineficaz para a inativação de alguns subtipos de coronavírus, sugerindo que também seja ineficaz contra o novo coronavírus.

PALAVRAS-CHAVE: *Coronavírus. Desinfecção. Assepsia. Clorexidina.*

REFERENCES

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):105924. doi:10.1016/j.ijantimicag.2020.105924
2. Organização Mundial da Saúde (OMS). *Novo coronavírus (2019-nCoV). Relatório de situação*. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200528-COVID-19-sitrep-29.pdf?sfvrsn=5b154880_2 [acessado em 29 de maio de 2020].
3. United Nations Industrial Development Organization (UNIDO). *Coronovírus – O impacto econômico*. https://www.unido.org/stories/coronavirus-economic-impact.
4. He CQ, He M, He HB, Wang HM, Ding NZ. The matrix segment of the "Spanish flu" virus originated from intragenic recombination between avian and human influenza A viruses. *Transbound Emerg Dis*. 2019;66(5):2188-2195. doi:10.1111/tbed.13282.
5. Alfani G, Murphy TE. Plague and Lethal Epidemics in the Pre-Industrial World. *The Journal of Economic History*. 2017;77(1):314-343. doi:10.1017/S0022050717000092.
6. Decaro N, Lorusso A. Novel human coronavirus (SARS-CoV-2): A lesson from animal coronaviruses. *Vet Microbiol*. 2020;244:108693. doi:10.1016/j.vetmic.2020.108693.
7. Acter T, Uddin N, Das J, Akhter A, Choudhury TR, Kim S. Evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as coronavirus disease 2019 (COVID-19) pandemic: A global health emergency [published online ahead of print, 2020 Apr 30]. *Sci Total Environ*. 2020;730:138996. doi:10.1016/j.scitotenv.2020.138996.
8. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. *J Hosp Infect*. 2020;104(3):246-251. doi:10.1016/j.jhin.2020.01.022.
9. Moriya T, Modena L P. Assepsia e antissepsia: técnicas de esterilização. Medicina (Ribeirão Preto) 2008; 41 (3): 265-73. doi: 10.11606/issn.2176-7262
10. Yang Y, Peng F, Wang R, et al. The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China [published correction appears in J Autoimmun. 2020 May 15; 102487]. *J Autoimmun*. 2020;109:102434. doi:10.1016/j.jaut.2020.102434
11. Yoshimoto FK. The Proteins of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2 or n-COV19), the Cause of COVID-19 [published online ahead of print, 2020 May 23]. *Protein J*. 2020;1-19. doi:10.1007/s10930-020-09901-4
12. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention [published online ahead of print, 2020 Apr 28]. *Nat Rev Immunol*. 2020;1-12. doi:10.1038/s41577-020-0311-8
13. Van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med*. 2020;382(16):1564-1567. doi:10.1056/NEJMc2004973
14. Geller C, Varbanov M, Duval RE. Coronavírus humanos: insights sobre a resistência ambiental e sua influência no desenvolvimento de novas estratégias anti-sépticas. *Vírus*. 2012; 4 (11): 3044-3068. Publicado em 2012. 12. Nov. Doi: 10.3390 / v4113044
15. Sattar SA, Springthorpe VS, Karim Y, Loro P. Chemical disinfection of non-porous inanimate surfaces experimentally contaminated with four human pathogenic viruses. *Epidemiol Infect*. 1989;102(3):493-505. doi:10.1017/s0950268800030211
16. Chiewchalermsri C, Sompornrattanaphan M, Wongsa C, Thongngarm T. Chlorhexidine Allergy: Current Challenges and Future Prospects. *J Asthma Allergy*. 2020;13:127-133. Published 2020 Mar 9. doi:10.2147/JAA.S207980
17. Colares A 2015. *Clorexidine indicação para uso em serviços de saúde* [tese]. São Paulo: Faculdade Método de São Paulo; 2015.
18. Koh D. Occupational risks for COVID-19 infection. *Occup Med (Lond)*. 2020;70(1):3-5. doi:10.1093/occmed/kqaa036
19. Conselho Federal de Enfermagem (COFEN). *Cofen registra 10 mil casos de COVID-19 entre profissionais de enfermagem*. http://www.cofen.gov.br/cofen-publica-observatorio-diario-da-COVID-19-entre-profissionais-de-enfermagem_79551.html.
20. Conselho Regiona de Farmácia de Minas Gerais (CRFMG). *CORONAVÍRUS. PADM – Protocolo de Antissepsia e Desinfecção Massiva frente ao n-CoV-2.* https://www.crfmg.org.br/site/uploads/areaTecnica/20200427[164659]coronaviruscartilhaPADM27042020.pdf
21. Chinese Center for Disease Control and Prevention. *Handbook of COVID-19 Prevention and Treatment*. https://irp-cdn.multiscreensite.com/a3b631e7/files/uploaded/02.%20Handbook%20of%20COVID-19%20Prevention%20and%20Treatment.pdf.pdf
22. Agência Nacional de Vigilância Sanitária (ANVISA). *Nota técnica no 47/2020/SEI/COSAN/GHCOS/DIRE3/ANVISA*. Processo no. 25351.911971/2020-80. http://portal.anvisa.gov.br/documents/219201/4340788/Nota+T%C3%A9cnica+47.pdf/242a3365-2dbb-4b58-bfa8-64b4c9e5d863
23. Agência Nacional de Vigilância Sanitária (ANVISA). *RESOLUÇÃO - RDC No 347, DE 17 DE MARÇO DE 2020.* http://www.in.gov.br/web/dou/-/resolucao-rdc-n-347-de-17-de-marco-de-2020-*-250404851
24. Agência de Vigilância Sanitária (ANVISA). *Formulário Nacional de Farmacopeia Brasileira, 2° Edição, Revisão 2*. http://portal.anvisa.gov.br/documents/33832/259372/FNFB+2_Revisao_2_COFAR_setembro_2012_atual.pdf/20eb2969-57a9-46e2-8c3b-6d79dccf0741

REVIEW ARTICLE

Current evidence of SARS-CoV-2 vertical transmission: an integrative review

Lisiane Vital de Oliveira[1]
Camila Radelley Azevedo Costa da Silva[2]
Lorenna Peixoto Lopes[1,2]
Isabela Karine Rodrigues Agra[1,2]

1. Faculdade de Medicina – Centro Universitário Cesmac, Maceió, AL, Brasil
2. Faculdade de Medicina – Universidade Federal de Alagoas, Maceió, AL, Brasil

http://dx.doi.org/10.1590/1806-9282.66.S2.130

SUMMARY

OBJECTIVE: *To review the current scientific evidence of vertical transmission related to coronavirus disease 2019 (COVID-19).*

METHODS: *An integrative review was performed by two independent researchers, based on the literature available in the MEDLINE (via PubMed) and LILACS databases, using the descriptors "pregnancy" AND "COVID-19" AND "vertical transmission". This search included case reports or case series published up until 17th June 2020 in English or Portuguese. After reading the articles available in their entirety, those related specifically to the potential risks of vertical transmission of COVID-19 during pregnancy were selected. We initially found a total of 57 articles; 26 were carefully screened and 15 were finally selected.*

RESULTS: *Pregnancy can make women more susceptible to infections, especially by viral pathogens, given the various physiological and immunological changes that occur to maintain maternal-fetal balance. It is speculated that the fetus may be a possible target for COVID-19. Few studies (3 out of 15) in our analysis have found positive results for SARS-CoV-2 in fetal membranes, placenta, and in newborns right after birth. Additionally, no difference was noticed when comparing different modes of delivery, and seems reasonable to assume that pregnant women with stable clinical conditions can be encouraged for vaginal delivery.*

CONCLUSION: *Further studies with a great number of cases are warranted to elucidate whether the virus may be vertically transmitted to the fetus and if any maternal conditions can influence that. Our findings seem to demonstrate that vertical transmission is possible but quite unusual.*

KEYWORDS: *Pregnancy. Coronavirus Infections. Infectious Disease Transmission, Vertical.*

INTRODUCTION

The current coronavirus disease (COVID-19) pandemic emerged in China at the end of 2019[1]. Although this new severe acute respiratory syndrome coronavirus (SARS-CoV-2) has a generally low fatality rate calculated at 2.3%, it is highly contagious, causing more deaths in absolute numbers than other similar specimens[2]. So far, there is still great concern about the possible consequences of this infection in pregnancy.

Data published up until recently indicate that pregnant women do not seem to be at a higher risk of developing COVID-19 compared to the general population[3]. However, this group may have a greater risk of obstetric morbidity associated with the virus infection,

DATE OF SUBMISSION: 28-Jun-2020
DATE OF ACCEPTANCE: 11-Jul-2020
CORRESPONDING AUTHOR: Isabela Karine Rodrigues Agra
Faculdade de Medicina da Universidade Federal de Alagoas (Ufal) - Campus A. C. Simões, Av. Lourival Melo Mota s/n
Tabuleiro dos Martins – Maceió – Alagoas - CEP: 57072-900 -Tel.: (82) 3214-1858
E-mail: agraisabela@gmail.com

since small series of cases reported an increased risk of premature birth, rupture of membranes, placental abruption, and fetal distress[4,5]. Moreover, in low- to middle-resource countries, evidence suggests the possibility of increased postpartum death rates, possibly due to inadequate prenatal and postnatal care[6].

The possibility of transmission from mother to fetus in COVID-19 is considered controversial, as the number of confirmed cases for the disease increases all over the world[7]. Reports of neonatal infection shortly after birth may suggest transplacental infection (vertical transmission) or horizontal transmission via direct surface contact at delivery or during breastfeeding[8]. Furthermore, if this route of intrauterine infection is proven possible, it is also important to determine the moment of the pregnancy when the virus crossed the placenta, in order to establish the possibility of injuries to the fetal organ formation and their well-being.

Considering the lack of consensus on vertical transmission in SARS-CoV-2 infection, in this review, we assembled the most recent studies involving this subject in an attempt to summarize the current understanding of congenital infection by COVID-19.

METHODS

This integrative literature review was conducted in the Medical Literature Analysis and Retrieval System on-line (Medline, through access to the PubMed) and in the Latin America and Caribbean Health Sciences Literature (Lilacs) databases. The descriptors – and their combination in Portuguese and English – used were "pregnancy" and "COVID-19" and "vertical transmission", crossed using the Boolean operator "AND". This search included articles published up until 17th June 2020.

The inclusion criteria defined to first select articles were case series and case reports published in English or Portuguese – review articles, short communications, dissertations, and management guidelines were not included. Then, studies that were not available on the internet databases in its entirety were excluded. After reading the full extent of the articles, those studies that did not address specifically the vertical transmission or congenital infection by COVID-19 were also excluded. For that, two independent researchers performed the search strategy in the scientific databases and, if there were disagreements regarding the final inclusion, a third senior researcher was consulted.

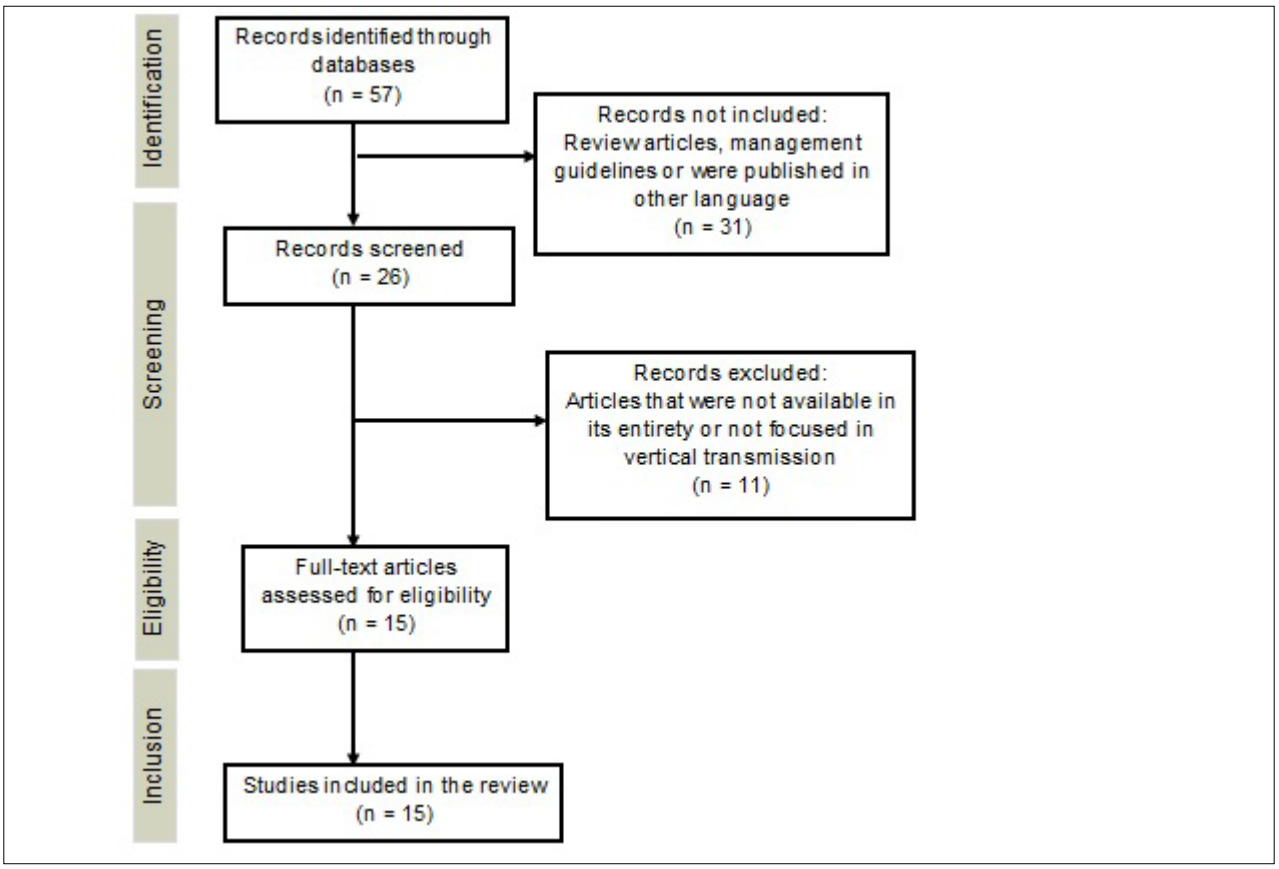


FIGURE 1. PRISMA 2009 FLOW DIAGRAM FOR ARTICLE'S INCLUSION ON VERTICAL TRANSMISSION OF COVID-19

TABLE 1. PUBLICATIONS INCLUDED IN THIS INTEGRATIVE REVIEW.

Author	Date of publication	Number of pregnant women (n)	Number of neonates (n)	Pregnancy: Amniotic fluid		Pregnancy: Placenta tissues		Mother: Maternal Serum		Mother: Vaginal swab		Mother: Throat swab		Mother: Breastilk		Neonates: Umbilical cord blood		Neonates: Anal swab		Neonates: Throat swab	
				+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
Fan et al.[9]	17 Mar 2020	2	2		2		2		2		2	2			2		2				2
Yang et al.[10]	10 Apr 2020	7	7		5							7					5				6
Xiong et al.[11]	10 Apr 2020	1	1		1		1				1	1			1				1		1
Peng et al.[12]	11 Apr 2020	1	1		1		1				1	1			1		1		1		1
Liu et al.[13]	13 Apr 2020	19	19		19							10			10		19				19
Alzamora et al.[14]	18 Apr 2020	1	1					1				1					1			1	
Yan et al.[15]	23 Apr 2020	116	100		10						6	65			12		10				86
Qiancheng et al.[16]	27 Apr 2020	28	23									*									23
Lu et al.[17]	30 Apr 2020	1	1									1					1				1
Kalafat et al.[18]	5 May 2020	1	1				1					1			1		1				1
Penfield et al.[19]	8 May 2020	11	11			3	8														11
Kuhrt et al.[20]	8 May 2020	1	2									1									2
Mehta et al.[21]	16 May 2020	1	2									1								1	1
Pereira et al.[22]	22 May 2020	60	23				6					60									23
Li et al.[23]	17 Jun 2020	1	1		1		1		1		1	1			1		1				1
Total		251	195	0	39	3	20	1	3	0	11	152	0	0	28	0	41	0	2	2	178

* All the COVID-19 patients had either positive reverse transcription polymerase chain reaction (RT-PCR) from respiratory samples or positive serological test of specific IgM antibody to SARS-CoV-2 – with no further specifications

This review was performed according to a standard protocol for systematic reviews, which was based on the methodological manuals of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We initially found a total of 57 articles; 26 were carefully screened and, according to the inclusion and exclusion criteria adopted, 15 papers were finally selected. Figure 1 summarizes the studies' selection.

RESULTS AND DISCUSSION

The articles selected are shown in Table 1, which summarizes their main information and findings regarding maternal and neonatal exam results[9-23].

Pregnancy consists of complex physiological and immunological processes that can make this period more susceptible to infections, including by viral pathogens[24]. The maternal immune response may play a crucial role in the pathophysiology of coronavirus infections since important changes need to happen to ensure maternal-fetal balance. For this, throughout gestation, the female body changes from a pro-inflammatory to an anti-inflammatory state, depending on the needs of the fetus[25].

Although SARS-CoV-2 infection may cause a cytokine storm and induces a more severe inflammatory state in the maternal-fetal placental interface[25], the available scientific evidence is still inconclusive regarding aspects of vertical transmission during pregnancy.

Lamouroux et al.[26] and Mahyuddin et al.[27], mention that many microorganisms are able to violate the maternal immune system barrier through the placenta and result in severe fetal consequences. Viruses can exert dynamic fluctuations in the immune environment of the placenta throughout pregnancy and contribute to changes in fetal susceptibility[27]. Thus, SARS-COV-2 has also become a major concern in pregnancy, although few case reports with a small number of subjects have shown positive results in placental tissue or in newborns[14,19,21].

Penfield et al.[19] published the first study that found the presence of viral RNA in the placenta/membranes. Details regarding the histological examination of the placentas (3 out of 11) that tested positive (for PCR analysis of placental tissue or membranes) were not provided. Besides that, none of the 11 neonates tested positive right after birth or in the first 5 days of life. The authors also mention that given the mixing of maternal and fetal fluids and tissue at the time of

delivery, the origin of the detected SARS-CoV-2 RNA in their series is unclear.

Low cellular expression of the angiotensin-converting enzyme 2 (ACE2) on the trophoblast, especially in the first trimester, may explain the small amount of evidence attesting vertical transmission. It has been shown that ACE2 is a functional receptor for SARS-CoV-2 infection[28]. In addition, COVID-19 does not appear to have sufficient evolution to use perivascular cluster cells (PV1) to overcome the immune system and affect the fetus during pregnancy[29].

Rajewska et al.[30] and Panahi et al.[31] describe that most of the evidence, so far, does not suggest vertical transmission and that the reported cases were possibly infected after pregnancy and delivery. In many studies, RT-PCR tests in neonates were performed several hours after birth, when horizontal transmission cannot be ruled out.

Thus, much has been discussed about the mode of delivery for pregnant women with COVID-19, which should be guided mainly according to the maternal-fetal hemodynamic status. Therefore, different recommendations for cesarean delivery have been described, even in mild cases, initially assuming that the newborn's passage through the birth canal could increase their chances of viral infection.

However, recent evidence failed to prove the benefits of cesarean compared to vaginal birth in stable cases[14]. It is important to highlight that the choice of the mode of delivery must take into account the maternal clinical condition, signs of fetal distress, gestational age, and maternal complications[11]. Corroborating this, Pereira et al.[22] evidenced that during the study period, 18 of the women included in their analysis (78%) delivered vaginally. All newborns tested negative for SARS-CoV-2 and none of them were infected during breastfeeding. No SARS-CoV-2 was detected in placental tissue. Accordingly, it seems reasonable to assume that pregnant women and their fetuses with stable clinical conditions can strongly benefit from this mode of delivery[17,19].

Zimmermann and Curtis[32] noticed that even with strict infection control and prevention procedures during and after cesarean delivery, four neonates tested positive for SARS-CoV-2 (one healthy newborn and three who presented pneumonia), and three of them also expressed IgM and IgG antibodies at birth, suggesting the possibility of vertical transmission. Zeng et al.[33] corroborate that with the report of six neonates – all born by cesarean delivery in an isolated room with negative pressure and immediate separation from their mothers – that exhibited high concentrations of IgG and IgM antibodies right after birth, as well as high inflammatory levels of interleukin-6.

It is believed that maternal IgM antibodies do not cross the placental barrier because it is a macromolecule when compared to IgG, which is passively transferred through the mother's placenta to the fetus[26,33,34]. Therefore, it is speculated that the IgM presented in the newborn is produced by the baby when in contact with the virus that has possibly crossed the placental barrier, since the IgM molecule usually does not appear until 3-7 days after infection[33,34].

This subject still remains questionable, since Xiong et al.[11] and Alzamora et al.[14], on the other hand, reported negative IgG and IgM serological results in all the newborns studied right after birth. Therefore, the maternal-fetal transmission of SARS-CoV-2 is still a controversial subject.

CONCLUSION

Further studies with a great number of cases are warranted to elucidate whether the virus may be vertically transmitted to the fetus and if any maternal conditions can influence that. Our findings seem to demonstrate that vertical transmission is possible but quite unusual. Complications related to newborns are apparently more related to the aspects of prematurity than to the impairment caused by the virus itself.

Since uncertainties remain without robust scientific answers, infection control will be the basis for preventing further spread among pregnant women, combined with social distance and universal testing in areas of high prevalence[27].

Conflicts of interest

The authors declare that they have no conflicts of interest.

Author's Contribution

Lisiane V. de Oliveira: Data management/analysis, manuscript writing

Camila R. A. C. da Silva: Data management/analysis, manuscript writing

Lorenna P. Lopes: Project development, data management/analysis, manuscript writing

Isabela K. R. Agra: Project development, data management/analysis, manuscript editing

RESUMO

OBJETIVO: *Revisar as evidências científicas atuais sobre a transmissão vertical relacionada à infecção pelo novo coronavírus 2019 (COVID-19).*

MÉTODOS: *Uma revisão integrativa foi realizada por dois pesquisadores independentes, com base na literatura disponível nas bases de dados Medline (via PubMed) e Lilacs, utilizando os descritores "gravidez" e "COVID-19" e "transmissão vertical". Esta pesquisa incluiu relatos de caso ou séries de casos publicados até 17 de junho de 2020, em inglês ou português. Após a leitura integral dos artigos, foram selecionados aqueles relacionados especificamente aos riscos potenciais da transmissão vertical do COVID-19 durante a gravidez. Encontramos inicialmente um total de 57 artigos; 26 foram cuidadosamente analisados e 15 artigos foram finalmente selecionados.*

RESULTADOS: *A gravidez pode tornar as mulheres mais suscetíveis a infecções, principalmente patógenos virais, dadas as várias alterações fisiológicas e imunológicas que ocorrem para manter o equilíbrio materno-fetal. Especula-se que o feto possa ser um possível alvo para a COVID-19. Poucos estudos (3 em 15) em nossa análise encontraram resultados positivos para Sars-CoV-2 em membranas fetais, placenta e em recém-nascidos logo após o nascimento. Além disso, nenhuma diferença foi observada ao comparar diferentes tipos de parto e parece razoável supor que mulheres grávidas com condições clínicas estáveis podem ser incentivadas para o parto vaginal.*

CONCLUSÃO: *Mais estudos com maior número de casos são necessários para elucidar se o vírus pode ser transmitido verticalmente ao feto e se alguma condição materna pode influenciar isso. Nossas descobertas parecem demonstrar que a transmissão vertical é possível, mas bastante incomum.*

PALAVRAS-CHAVE: *Gravidez. Infecções por coronavírus. Transmissão vertical de doença infecciosa.*

REFERENCES

1. Anesi GL. Coronavirus disease 2019 (COVID-19): critical care and airway management issues. UpToDate Jun 2020. [cited 2020 Jul 7]. Available from: https://www.uptodate.com/contents/coronavirus-disease-2019-COVID-19-critical-care-issues
2. Wang L, Shi Y, Xiao T, Fu J, Feng X, Mu D, et al; Working Committee on Perinatal and Neonatal Management for the Prevention and Control of the 2019 Novel Coronavirus Infection. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection (First edition). Ann Transl Med. 2020;8(3):47.
3. Dotters-Katz SK, Hughes BL. Considerations for obstetric care during the COVID-19 pandemic. Am J Perinatol. 2020;37(8):773-9.
4. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020;9(1):51-60.
5. Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) coronavirus 2019-nCoV infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. Viruses. 2020;12(2):194.
6. Amorim MMR, Takemoto MLS, Fonseca EB. Maternal deaths with coronavirus disease 2019: a different outcome from low-to middle-resource. Am J Obstet Gynecol. 2020;S0002-9378(20)30471-3.
7. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al; UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in the UK: a national population based cohort study. BMJ. 2020;369:m2107.
8. Tosone G, Maraolo AE, Mascolo S, Palmiero G, Tambaro O, Orlando R. Vertical hepatitis C virus transmission: main questions and answers. World J Hepatol. 2014;6(8):538-48.
9. Fan C, Lei D, Fang C, Li C, Wang M, Liu Y, et al. Perinatal transmission of COVID-19 associated SARS-CoV-2: should we worry? Clin Infect Dis. 2020;ciaa226.
10. Yang P, Wang X, Liu P, Wei C, He B, Zheng J, et al. Clinical characteristics and risk assessment of newborns born to mothers with COVID-19. J Clin Virol. 2020;127:104356.
11. Xiong X, Wei H, Zhan Z, Chang J, Ma X, Gao X, et al. Vaginal delivery report of a healthy neonate born to a convalescent mother with COVID-19. J Med Virol. 2020;10.1002/jmv.25857.
12. Peng Z, Wang J, Mo Y, Duan W, Xiang G, Yi M. Unlikely SARS-CoV-2 vertical transmission from mother to child: a case report. J Infect Public Health. 2020;13(5):818-20.
13. Liu W, Wang J, Li W, Zhou Z, Liu S, Rong Z, et al. Clinical characteristics of 19 neonates born to mothers with COVID-19. Front Med. 2020;14(2):193-8.
14. Alzamora MC, Paredes T, Caceres D, Webb CM, Valdez LM, La Rosa M. Severe COVID-19 during pregnancy and possible vertical transmission. Am J Perinatol. 2020;37(8):861-5.
15. Yan J, Guo J, Fan C, Juan J, Yu X, Li J, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. Am J Obstet Gynecol. 2020;223(1):111.e1-111.e14.
16. Qiancheng X, Jian S, Lingling P, Lei H, Xiaogan J, Weihua L, et al; sixth batch of Anhui medical team aiding Wuhan for COVID-19. Coronavirus disease 2019 in pregnancy. Int J Infect Dis. 2020;95:376-83.
17. Lu D, Sang L, Du S, Li T, Chang Y, Yang XA. Asymptomatic COVID-19 infection in late pregnancy indicated no vertical transmission. J Med Virol. 2020;10.1002/jmv.25927.
18. Kalafat E, Yaprak E, Cinar G, Varli B, Ozisik S, Uzun C, et al. Lung ultrasound and computed tomographic findings in pregnant woman with COVID-19. Ultrasound Obstet Gynecol. 2020;55(6):835-7.
19. Penfield CA, Brubaker SG, Limaye MA, Lighter J, Ratner AJ, Thomas KM, et al. Detection of SARS-COV-2 in placental and fetal membrane samples. Am J Obstet Gynecol MFM. 2020;100133.
20. Kuhrt K, McMicking J, Nanda S, Nelson-Piercy C, Shennan A. Placental abruption in a twin pregnancy at 32 weeks' gestation complicated by COVID-19, without vertical transmission to the babies. Am J Obstet Gynecol. 2020;100135.
21. Mehta H, Ivanovis S, Cronin A, VanBrunt L, Mistry N, Miller R, et al. Novel coronavirus-related acute respiratory distress syndrome in a patient with twin pregnancy: a case report. Case Rep Womens Health. 2020;27:e00220.
22. Pereira A, Cruz-Melguizo S, Adien M, Fuentes L, Marin E, Perez-Medina T. Clinical course of coronavirus disease-2019 in pregnancy. Acta Obstet Gynecol Scand. 2020;99(7):839-47.
23. Li Y, Zhao R, Zheng S, Chen X, Wang J, Sheng X, et al. Lack of vertical transmission of severe acute respiratory syndrome coronavirus 2, China. Case Infect Dis. 2020;26(6):1335-6.
24. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: a systematic review of 108 pregnancies. Acta Obstet Gynecol Scand. 2020;99(7):823-9.
25. Silva CRAC, Oliveira LV, Lopes LP, Santos WAGD, Agra IKR. Immunological aspects of coronavirus disease during pregnancy: an integrative review. Rev Assoc Med Bras. 2020;66(5):696-700.
26. Lamouroux A, Attie-Bitach T, Martinovic J, Leruez-Ville M, Ville Y. Evidence

for and against vertical transmission for severe acute respiratory syndrome coronavirus 2. Am J Obstet Gynecol. 2020;223(1):91.e1-91.e4.

27. Mahyuddin AP, Kanneganti, A, Wong J, Dimri PS, Su LL, Biswas A, et al. Mechanisms and evidence of vertical transmission of infections in pregnancy including SARS-CoV-2. Prenat Diagn. 2020;10.1002/pd.5765.

28. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-80.

29. Zheng QL, Duan T, Jin LP. Single-cell RNA expression profiling of ACE2 and AXL in the human maternal-fetal interface. Reprod Develop Med. 2020;4(1):7-10.

30. Rajewska A, Mikolajek-Bedner W, Lebdowicz-Knul J, Sokolowska M, Kwiatkowski S, Torbé A. COVID-19 and pregnancy: where are we now? A review. J Perinat Med. 2020;48(5):428-34.

31. Panahi L, Amari M, Pouy S. Risks of novel coronavirus disease (COVID-19) in pregnancy: a narrative review. Arch Acad Emerg Med. 2020;8(1):e34.

32. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. Pediatr Infect Dis J. 2020;39(6):469-77.

33. Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, et al. Antibodies in infants born to mothers with COVID-19 pneumonia. JAMA. 2020;323(18):1848-9.

34. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020;323(18):1846-8.

REVIEW ARTICLE

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

Laura Faustino Gonçalves[1]
Ana Inês Gonzales[2]
Fernanda Soares Aurélio Patatt[3]
Karina Mary de Paiva[4]
Patrícia Haas[4]

1. Graduanda em Fonoaudiologia pela Universidade Federal de Santa Catarina – UFSC, Florianópolis, SC, Brasil
2. Doutora e Fisioterapeuta UDESC - Universidade do Estado de Santa Catarina, Florianópolis, SC, Brasil
3. Doutora pela Universidade de Brasília (UnB), Brasília, DF, Brasil
4. Professora Doutora do Curso de Fonoaudiologia pela Universidade Federal de Santa Catarina – UFSC, Florianópolis, SC, Brasil

http://dx.doi.org/10.1590/1806-9282.66.S2.136

SUMMARY

OBJECTIVE: *To present scientific evidence based on a systematic literature review (PRISMA) evaluating the association of Kawasaki Disease (DK) and COVID-19 in children.*

METHODS: *For the selection of studies, a combination based on the Medical Subject Heading Terms (MeSH) was used. The Medline (Pubmed), LILACS, SciELO, COCHRANE, and BIREME databases were used. The search period for the articles comprised the last 10 years (2010 to 2020).*

RESULTS: *840 articles with potential for inclusion were retrieved, one of which met the inclusion criteria and the guiding question that consisted of evaluating the association of Kawasaki disease and COVID-19 in children.*

CONCLUSION: *A significant increase in the incidence of Kawasaki-type diseases after the onset of the epidemic has been reported, suggesting an association between the COVID-19 epidemic and the high incidence of a severe form of KD. However, further studies are needed to conduct an investigation of the association between these two diseases.*

KEYWORDS: *Mucocutaneous Lymph Node Syndrome; Coronavirus infections; Kid; Vasculitis; Kawasaki Disease; COVID-19*

INTRODUCTION

Kawasaki Disease (KD), first described in 1967, is characterized by a multisystemic disorder with acute inflammatory processes in small and medium vessels, particularly in the coronary arteries[1,2]. If left untreated, it can lead to several complications and even sudden death[1]. KD affects predominantly children, usually younger than 5 years old, and is the second most common vasculitis in this population, with a risk 1.5 times higher of occurring in boys than in girls; however, it is considered rare in children younger than 6 months old[1].

The epidemiological patterns of KD are quite

DATE OF SUBMISSION: 13-Jun-2020
DATE OF ACCEPTANCE: 27-Jun-2020
CORRESPONDING AUTHOR: Patrícia Haas
Departamento de Fonoaudiologia, Universidade Federal de Santa Catarina – UFSC, Campus Trindade, Florianópolis (SC), Brasil.
E-mail: patrícia.haas@ufsc.br

distinct regarding geographical location, with different incidence values between continents. In the countries of northeast Asia, including Japan, South Korea, China, and Taiwan, the incidence is 10 to 30 times higher than in the United States and Europe, with indices that have been increasing continuously[1,3,4]. In the USA, the incidence of KD is estimated to be between 17.5 and 20.8 per 100,000 children aged less than 5 years, while in Canada it is 19.6 per 100,000. Whereas in Europe it is around 5 to 10/100,000[3.4].

The diagnosis of KD is a clinical challenge, given its large variety of signs and symptoms since it may resemble other viral and bacterial infections[1]. In this sense, the clinical diagnosis is achieved by identifying signs and symptoms, as well as using various laboratory parameters that can complement the final diagnosis[5].

Some parameters are considered at the time of the diagnosis, such as the presence of fever for five or more days, accompanied by chapped lips, cervical lymphadenopathy, erythema, or polymorphic rash[6]. Given the high rate of cardiac complications from this disease, cardiac biomarkers are used for diagnostic purposes[1]. Heart sequelae are mainly related to the coronary arteries. For these patients, regular monitoring by imaging is paramount, and techniques such as myocardial perfusion imaging, angiography, and, more recently, magnetic resonance imaging are ideal[1,7].

Medical reports have described the presence of a hyperinflammatory response resulting from viral infection by the novel coronavirus (COVID-19) in children, with changes in the coronary arteries similar to KD. The hypotheses presented indicate that some children might be genetically predisposed to a more robust inflammatory response to the virus. These recent findings demonstrate the need for further efforts in order to elucidate the reasons behind these outcomes, which remain unknown[8].

The incidence of COVID-19 worldwide has significantly increased and accelerated. To date, 215 countries, areas, or territories have reported cases and over 254,000 deaths have been attributed to the virus, in addition to over 4 million confirmed cases[9].

Although it is still early to confirm the association between KD and COVID-19 infections, studies show the incidence of KD cases during spring and winter, suggesting its association with some types of viral infections, such as those by adenovirus, enterovirus, parvovirus, rhovírus, varicella, Epstein Barr, measles, and dengue[10-24]. Studies have described an association between viral respiratory infections and KD, ranging from 9% to 42% of patients with a positive test for viral respiratory infection within 30 days before the diagnosis of KD[15,25-27].

An initial analysis of the data obtained from adult patients with COVID-19 in China showed a significant increase with high rates of cardiac troponin, a parameter that is associated with an increase in mortality. It has been reported that, in COVID-19 patients, the microvascular damage in the heart cause perfusion effects, vessel hyperpermeability, and vasospasm, leading to myocardial injury[28].

Faced with the current pandemic and the uncertainties still generated around the association between KD and COVID-19 infections, this systematic review aims to present the scientific evidence available, up until now, about the association between Kawasaki Disease and COVID-19 in children.

METHODS

Research characterization and search strategies

A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma)[29].

The searches for scientific articles were carried out by two independent researchers in the Medline (PubMed) (https://www.ncbi.nlm.nih.gov/pubmed/), Lilacs (http://lilacs.bvsalud.org/), SciELO (http://www.scielo.br/), Cochrane (https://www.cochrane.org/), and Bireme (https://bvsalud.org/) electronic databases, with no language or location restrictions, from April to May 2020.

The research was structured and organized according to the PICO methodology, which is an acronym for Population, Intervention, Control, Outcomes, Study (Table 1).

TABLE 1. DESCRIPTION OF THE PICOS COMPONENTS

Acronym	Definition
P	Children
I	Kawasaki Disease
C	Association
O	Coronavirus
S	Descriptive study/Cross-sectional study Observational study

Source: Prepared by the authors.

The descriptors were selected from the dictionary

the Health Sciences Descriptors (DeCS) and Medical Subject Heading Terms (MeSH). The following keywords and boolean operators were proposed for the searches: [((*kawasaki syndrome*)) AND ((*COVID-19*) OR *(Coronavirus disease))* AND ((children)) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR singleblind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])).

The use of the keywords and boolean operators was adjusted according to the databases searched. As a complement, a manual search was carried out in the references of the papers included in the search, and gray literature was searched on Google Scholar.

SELECTION CRITERIA

Inclusion criteria

The designs of the studies selected included descriptive studies, randomized or non-randomized controlled clinical trials, cross-sectional studies, cohort studies, and case studies. We included studies with no language or location restrictions, published from January 2010 to May 2020.

Exclusion criteria

Were excluded studies published in the format of letters to the editor, guidelines, literature reviews, systematic reviews, meta-analyses, and summaries. Table 2 presents the inclusion and exclusion criteria used in this research.

DATA ANALYSIS

The extraction of data for the eligibility process was performed using a form specifically for systematic reviews prepared by the researchers in Excel®, in which the extracted data were added initially by one of the researchers, and then revised by another researcher. The data obtained from eligible studies were also added to a spreadsheet in the same software, in order to organize the results. The data extracted from the studies were analyzed descriptively, and the following were extracted: year of publication, place where the research was carried out, type of study design, assessments and tests performed, as well as the methods, used, and the results found. These studies had a score greater than 6 on the modified protocol by Python et al.[30] to assess their quality.

TABELA 2. SUMMARY OF THE INCLUSION/EXCLUSION CRITERIA

Inclusion criteria	
Design	Case reports Case-control studies Controlled clinical trials Cohort Studies Screening studies Observational studies
Location	No restrictions
Language	No restrictions
Exclusion criteria	
Design	Letters to the editor Guidelines Literature reviews Systematic reviews Meta-analyses
Studies	Unclear studies Poorly described or inappropriate
Type of publication	Only summary

Source: Prepared by the authors.

RESULTS

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. Thus, one article was eligible according to the Prisma[29] criteria used for the development of this research. We proceeded to carefully read the study in full and, after applying the eligibility criteria, the study[31] on the association between Kawasaki Disease and COVID-19 in children was selected to be the object of this analysis.

The study selected for this systematic review was a case study with descriptive analysis. In the analysis, they were categorized according to the theme investigated, Kawasaki Disease, and its possible association with the novel coronavirus.

The study[31] was carried out on a female patient, 6 months of age, full-term, previously healthy, who initially attended the pediatric emergency care with fever, agitation, and refusal to eat. On the second day of fever, she developed an erythematous rash and, on the fourth day, persistent skin rash and possible mild congestion, but without coughing. In addition

to these symptoms, the child presented irritability, limbus-sparing conjunctivitis, and chapped and dry lips. On the fifth day of fever, the child remained with limbus-sparing conjunctivitis, in addition to presenting prominent papillae of the tongue, maculopapular, polymorphic, throbbing rash, and swelling of the hands and lower extremities, thus meeting the classic criteria for KD. Initially, the patient was diagnosed with a viral infection. A chest X-ray showed a low opacity in the left lung, however, clinical laboratory examinations showed altered blood levels.

Due to the fever, possible mild congestion, as well as the radiographic chest findings, the child was referred to COVID-19 testing, although there was no history of contact with other patients or recent travels, and the family had been in isolation for a week. The night before the discharge, the tests for COVID-19 came back positive.

Table 3 shows the main characteristics described in the study included for analysis.

DISCUSSION

KD is an acute vasculitis of childhood and the main cause of acquired heart disease in children, with 50% of the cases occurring in children younger than 2 years old and 80% in those younger than 5 years[32]. The child of the study selected for this review is at the beginning of the age group affected by the disease, 6 months old, and KD is rare in children younger than 6 months old[1].

The diagnosis of KD is based on the observation of signs and symptoms such as high fever persistent for at least five days, in association with four of five diagnostic criteria, such as alterations in the oral cavity, conjunctival hyperemia, changes in the extremities, and cervical lymphadenopathy[33]. The exact cause of KD still remains unknown. The factor most considered up until now suggests contagion by various viral infections with an expansion of infectious agents, particularly in the period between winter and spring[26].

However, although knowledge of its etiology is still incipient, studies have been developed in recent years. Recent research has described an association between viral respiratory infections and KD, ranging from 9% to 42 % of patients DK with a positive test for viral respiratory infection within 30 days before the diagnosis of KD[15,25,27].

In the study selected in this review, although there was evidence of a viral infection with positive results for COVID-19 in a child treated for KD, the association between the positive results and the configuration of KD was not established[31]. Because this is a case study, the data presented are initial and encourage further and more robust clinical research and analyses to elucidate findings for a better clinical implication.

After the study was published in a scientific journal in mid-April 2020, there was greater attention from researchers and pediatricians of various countries

TABLE 3. SUMMARY OF THE RESULTS FOUND IN THE ARTICLE INCLUDED IN THE REVIEW

Author/Year/Location/Type of Study	Objective	Results	Conducts/Conclusion
Jones, et al. (2020) United States Case study	Describe the case of a pediatric patient diagnosed with and treated for KD in the context of confirmed infection by COVID-19	*Body temperature: 38.3 °C for over 4 days *Complete blood count: CRP ↑13.3mg/dl; hyponatremia; normocytic anemia; hypoalbuminemia; ↑erythrocyte sedimentation rate *Hemodynamic parameters: Sinus tachycardia (200 bpm), and tachypnea *Parameters of oxygenation and respiratory assessment: SpO_2 - 100%; mild subcostal retractions; small opacity in the left lung base *Echocardiogram: without evidence of coronary dilation, without pericardial effusion, and with normal ventricular and valvular function. *Testing for Influenza:negative *Testing for Covid - 19: positive *Assessment with marked signs of: Irritability, conjunctivitis, skin rashes, dry and chapped lips. Swelling in the hands and lower limbs	- Patient treated with a single dose of 2 g/kg of intravenous immunoglobulin (IVIG) and a high dose of acetylsalicylic acid (ASA 20 mg/kg four times a day) - Clinical Course of mild COVID-19 - Since this is a description of a single case, more detailed studies on pediatric patients diagnosed with COVID-19 are required, mainly regarding its association with KD.

Legend: KD = Kawasaki Disease; COVID-19 = coronavirus; SpO_2 - Partial oxygen saturation; °C - degrees Celsius; bpm - beats per minute; ↑ high; mg/dl - milligrams per deciliters.
Source: Jones, et al., 2020.

regarding the possible association between COVID-19 and KD[34].

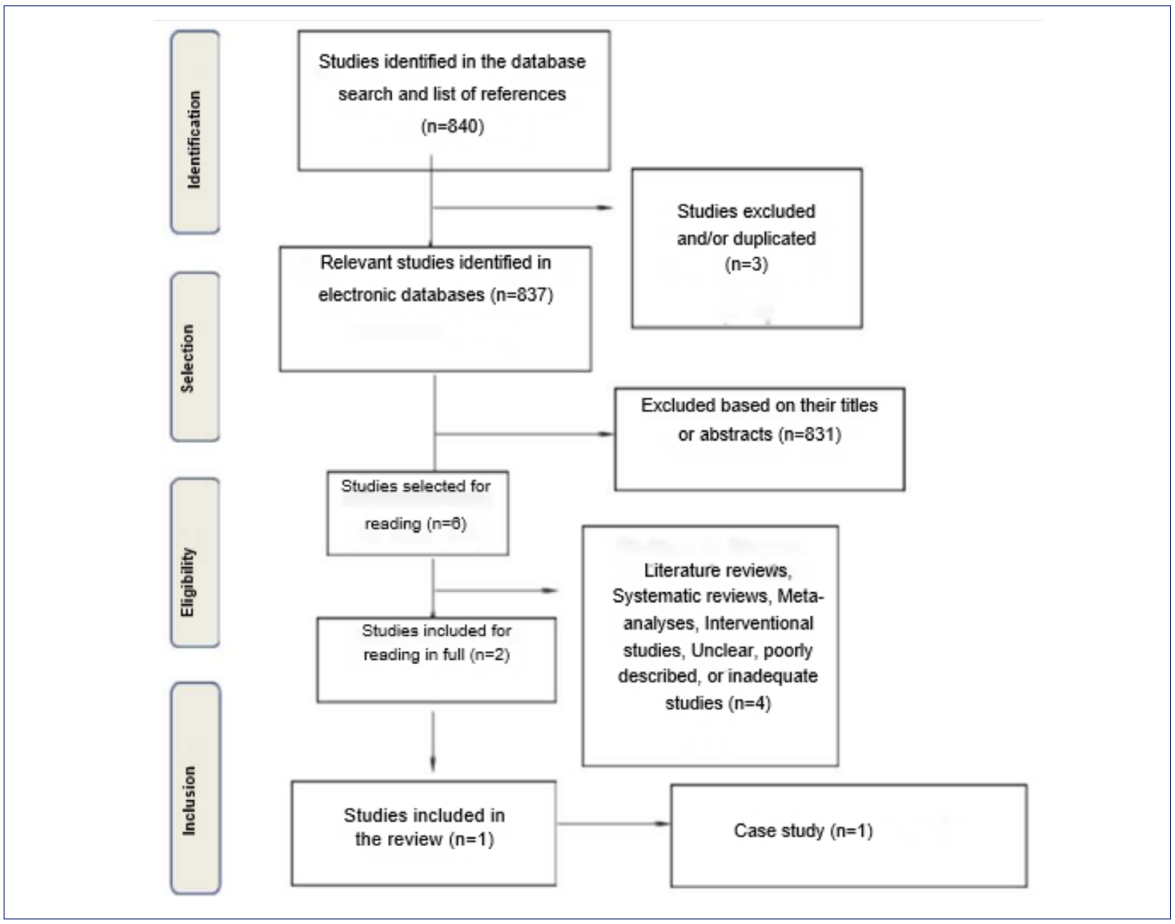
On 4 May 2020, the department of health of the city of New York issued a health alert describing 15 cases of a multisystem inflammatory syndrome with characteristics of KD in children[34]. Despite the lack of details inherent to these types of reports, deciphering the exact nature and severity of the cases admitted in a hospital environment is still a challenge. Additionally, due to the pandemic scenario in which we are still living and the recent nature of the topic, studies under development have not yet been completed and published in scientific journals[34].

A study developed by researchers from Bergamo, an Italian city widely affected by the COVID-19 epidemic, found an increase of 30 times in the incidence of Kawasaki Disease after the start of the epidemic. The children diagnosed during this period showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, characteristics of macrophage activation syndrome, and required adjuvant treatment with steroids. The COVID-19 epidemic was associated with a high incidence of a severe form of DK. The authors also estimate that a similar outbreak of Kawasaki Disease can occur in the countries involved in the pandemic[35].

At the time of hospital discharge of the patient described in the study, the World Health Organization had reported nearly 180,000 confirmed cases of COVID-19 globally, with 7,426 deaths[9]. Despite the growing number of cases reported, little is known about the infectious, clinical, and epidemiological aspects associated with COVID-19, particularly in the pediatric population[36].

Up until now, the pediatric presentation known from COVID-19 infections encompasses a variety of signs and symptoms, such as fever, fatigue, myalgia, cough, sore throat, runny nose, congestion, and shortness of breath. In more severe cases, symptoms can include gastrointestinal alterations and patients can progress to respiratory failure, shock, coagulation dysfunction, and renal injury. In addition to the cases with clear and detectable signs and symptoms, completely asymptomatic infections can occur[36]. In

FIGURE 1. FLOWCHART OF STUDY SEARCH AND ANALYSIS



Source: Prepared by the authors.

the patient of the study selected[31], the symptoms that led professionals to request COVID-19 testing were mild fever, congestion, and the radiological findings, which showed low opacity in the left lung, with most of the symptoms characteristic of COVID-19 absent, which has also been reported in the literature[36].

Although it is still early, the emergence of patterns that seem quite similar in several cities certainly points to a causal association between COVID-19 infection and KD. The alerts from Italy and France contain little data, and further publications will probably be released[34].

At the moment, around 5,014,943 cases of COVID-19 have been documented worldwide, with children also being infected with an increasing number of reported cases; however, with minimal load[37].

Epidemiological data from many countries show that children are a small group of COVID-19 cases. Patients younger than 18 years old accounted for only 1.7% of the national population of cases in the USA, 1% of the cases in Holland, and 2.0% of a large observational cohort study in the United Kingdom[37].

With respect to the COVID-19 infection, the clinical course, and presentation of the patient in the study were mild. Throughout hospitalization, she showed no remarkable respiratory symptoms with characteristic clinical signs of KD and was treated with a single dose of 2 g/kg of intravenous immunoglobulin (IVIG) and a high dose of acetylsalicylic acid (ASA 20 mg/kg four times a day) in a hospital environment[31]. Both the clinical characteristics and the treatment diverged from the evidenced in a recent study that found major complications in children with KD, in addition to requiring adjuvant treatment with steroids[35].

Post-discharge recommendations for monitoring included echocardiography after 1-2 weeks and 4-6 weeks after the treatment[31]. The approach to the pediatric population with a clinical spectrum must still be clearly defined; patients who present fever alone or mainly involvement of other organs, such as gastrointestinal symptoms, might not be submitted to COVID-19 testing if this remains restricted to those with respiratory complaints.

The COVID-19 pandemic has been characterized by uncertainty. Faced with a severe pandemic, taking early actions in the absence of solid data is understandable and often necessary. With the increase of cases reported worldwide, data shows that it is plausible that associations between COVID-19 infections and other conditions could be found in the future[34].

Although medical entities and researchers have increased their attention to the association between COVID-19 infections and possible complications in children, more detailed descriptions about the clinical course of this population are still necessary, mainly regarding its possible association with KD.

However, studies have already reported an association between viral respiratory infections and KD, in addition to finding a significant increase in the incidence of diseases like Kawasaki after the start of the epidemic, suggesting an association between the COVID-19 epidemic and the high incidence of a severe form of KD.

Finally, data shows that associations between COVID-19 infections and other conditions are likely to be found in the future.

Author's Contribution

All authors contributed equally to this work.

RESUMO

OBJETIVO: *Apresentar evidências científicas com base em revisão sistemática da literatura (Prisma) avaliando a associação da Doença de Kawasaki (DK) e COVID-19 em crianças.*

MÉTODOS: *Para a seleção dos estudos foi utilizada a combinação baseada no Medical Subject Heading Terms (MeSH). Foram utilizadas as bases de dados Medline (PubMed), Lilacs, SciELO, Cochrane e Bireme.O período de busca dos artigos compreendeu os últimos dez anos (2010 a 2020).*

RESULTADOS: *Foram recuperados 840 artigos com potencial de inclusão, sendo que um respondeu aos critérios de inclusão e à pergunta norteadora que consistiu em avaliar a associação da Doença de Kawasaki e COVID-19 em crianças.*

CONCLUSÃO: *Um aumento significativo na incidência de doenças do tipo Kawasaki após o início da epidemia já foi relatado, sugerindo a associação entre a epidemia de COVID-19 e a elevada incidência de uma forma grave da DK. Contudo, mais estudos são necessários para conduzir a investigação da associação entre essas duas doenças.*

PALAVRAS-CHAVE: *Síndrome de Linfonodos Mucocutâneos. Infecções por coronavírus. Criança. Vasculite. Doença de Kawasaki. COVID-19*

REFERENCES

1. Agarwal S, Agrawal DK. Kawasaki disease: etiopathogenesis and novel treatment strategies. Expert Rev Clin Immunol. 2017;13(3):247-58.
2. Rodrigues M, Oliveira CJ, Carvalho F, Silva H, Moreira C, Granja S, et al. Doença de Kawasaki e Complicações Cardiovasculares em Pediatria. Nascer e Crescer Birth and Growth Medical Journal. 2018; 27(1): 54-8.
3. Lin MT, Wu MH. The global epidemiology of Kawasaki disease: Review and future perspectives. Glob Cardiol Sci Pract. 2017; 3: 3-6.
4. Kim, BG. Reality of Kawasaki disease epidemiology. Korean J Pediatr. 2019; 62(8): 292-96.
5. Sharma D, Singh S. Kawasaki disease – A common childhood vasculitis. Indian J Rheumatol. 2015; 10: 578-83.
6. Saguil A, Fargo A, Grogan S. Diagnosis and management of kawasaki disease. Am Fam Physician. 2015; 91(6): 365-71.
7. Castro AP, Costa CMI, Urbano, FML. Kawasaki disease. An Bras Dermatol. 2009;84(4):317-31.
8. Loomba, RS, Villarreal, E,Flores, S.COVID-19 and Kawasaki syndrome: should we really be surprised?. Cardiology in the Young. 2020; 1-5.
9. WHO: World Health Organization. Doença de coronavírus (COVID-19) Pandemia [internet]. 2020. [Acesso em: 7 maio 2020]. Disponível em: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAjw4871BRAjEiwAbxXi29gEUGkT-x1I583SlRVeCvzOYufu1EWhdMb60_9_G_ZOII69vN_5tRoCt_kQAvD_BwE.
10. Catalano-Pons C, Quartier P, Leruez-Ville M. Primary cytomegalovirus infection, atypical Kawasaki disease, and coronary aneurysms in 2 infants. Clin Infect Dis. 2005;41(5):53-6.
11. Shike H, Shimizu C, Kanegaye JT. Adenovirus, adeno-associated virus and Kawasaki disease. The Pediatric infectious disease journal. 2005;24(11):1011-14.
12. Ferraz C, Cunha F, Mota TC, Carvalho JM, Simoes JS, Aparicio JM. Acute respiratory distress syndrome in a child with human parvovirus B19 infection. The Pediatric infectious disease journal. 2005;24(11):1009-10.
13. Turkay S, Odemis E, Karadag A. Kawasaki disease onset during concomitant infections with varicella zoster and Epstein-Barr virus. Journal of the National Medical Association. 2006;98(8):1350-52.
14. Sopontammarak S, Promphan W, Romanew S, Phetpisan S. Positive serology for dengue viral infection in pediatric patients with Kawasaki disease in southern Thailand. Circulation journal: official journal of the Japanese Circulation Society. 2008;72(9):1492-94.
15. Jordan-Villegas A, Chang ML, Ramilo O, Mejias A. Concomitant respiratory viral infections in children with Kawasaki disease. The Pediatric infectious disease journal. 2010;29(8):770-2.
16. Huang X, Huang P, Zhang L. Influenza infection and Kawasaki disease.Rev Soc Bras Med Trop. 2015;48(3):243-8
17. Joob B, Wiwanitkit V. Kawasaki Disease in a 2-year-old Child with Dengue Fever: Correspondence. Indian journal of pediatrics. 2016;83(9):1054.
18. Hu P, Guan Y, Fan XC, Lu FY, Song LM. Incomplete Kawasaki disease induced by measles in a 6-month-old male infant. International journal of dermatology. 2016;55(1):34-36.
19. Jagadeesh A, Krishnamurthy S, Mahadevan S. Kawasaki Disease in a 2-year-old Child with Dengue Fever. Indian journal of pediatrics. 2016;83(6):602-3
20. Weng KP, Cheng-Chung Wei J, Hung YM. Enterovirus Infection and Subsequent Risk of Kawasaki Disease: A Population-based Cohort Study. The Pediatric infectious disease journal. 2018;37(4):310-15.
21. Guleria S, Jindal AK, Pandiarajan V, Singh MP, Singh S. Dengue-Triggered Kawasaki Disease: A Report of 2 Cases. J Clin Rheumatol. 2018;24(7):401-4.
22. Thissen JB, Isshiki M, Jaing C A novel variant of torque teno virus 7 identified in patients with Kawasaki disease. PloS one. 2018;13(12):e0209683.
23. Wang J, Sun F, Deng HL, Liu RQ. Influenza A (H1N1) pdm09 virus infection in a patient with incomplete Kawasaki disease: A case report. Medicine. 2019;98(15):e15009.
24. Maggio MC, Cimaz R, Alaimo A, Comparato C, Di Lisi D, Corsello G. Kawasaki disease triggered by parvovirus infection: an atypical case report of two siblings. J Med Case Reports. 2019;13(1):104.
25. Kim JH, Yu JJ, Lee J. Detection rate and clinical impact of respiratory viruses in children with Kawasaki disease. Korean J Pediatr. 2012; 55:470-3.
26. Chang LY, Lu CY, Shao PL, Lee PI, Lin M, Fan TY, Cheng AL, Lee WL, Hu JJ, Yeh SJ, Chang CC, Chiang BL, Wu MH, Huang LM. Viral infections associated with Kawasaki disease. J Formos Med Assoc. 2014; 113(3):148-54.
27. Turnier JL, Anderson MS, Heizer HR, Jone PN, Glode MP, Dominguez SR. Concurrent Respiratory Viruses and Kawasaki Disease. Pediatrics. 2015;136:e609-614.
28. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with Coronavirus Disease 2019 (COVID-19): possible mechanisms. Journal of Cardiac Failure. 2020; 1-16.
29. Moher D, Shamseer L, Clarke M. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. Published 2015 Jan 1.
30. Pithon MM, Santanna LIDA, Baião FCS, Santos RL, Coqueiro RS, Maia LC. Assessment of the effectiveness of mouthwashes in reducing cariogenic biofilm in orthodontic patients: a systematic review. J Dent. 2015; 43:297–308.
31. Jones GV, Milles M, Suarez D, Hogan AC, Yeh D,Segal BJ, et al. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. Hospital Pediatrics. Hospital Pediatrics. 2020; 1-11. Hosp Pediatr. 2020;10(6):537-540.
32. Rowley AH, Shulman ST. The Epidemiology and Pathogenesis of Kawasaki Disease. Front Pediatr. 2018;6:374.
33. Almeida RGD, Goldenzon AV, Rodrigues MCF, Sztajnbok FR, Elsas MICG, Oliveira SKFD. Perfil da doença de Kawasaki em crianças encaminhadas para dois serviços de reumatologia pediátrica do Rio de Janeiro, Brasil. Bras J Rheumatol. 2010; 50(5): 529-38.
34. Schroeder, AR, Wilson KM, Ralston AL. COVID-19 and Kawasaki Disease: Finding the Signal in the Noise. Hosp Pediatr. 2020; doi: 10.1542/hpeds.2020-000356
35. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasakilike disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020; 395:1771-8.
36. Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics. 2020; 145(6):e20200702.
37. Viner RM, Whittaker E. Kawasaki-like Disease: Emerging Complication During the COVID-19 Pandemic. Lancet. 2020;395(10239):1741-3.

REVIEW ARTICLE

Sleep and immunity in times of COVID-19

Eduardo de Sousa Martins e Silva[1]
Ben Hur Vitor Silva Ono[2]
José Carlos Souza[3]

1. Universidade Federal do Triângulo Mineiro (UFTM), Uberaba, MG, Brasil.
2. Universidade para o Desenvolvimento do Estado e da Região do Pantanal (Uniderp), Campo Grande, MS, Brasil.
3. Universidade Estadual de Mato Grosso do Sul (UEMS), Campo Grande, MS, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S2.143

SUMMARY

BACKGROUND: *Analyze how the COVID-19 (SARS-CoV-2) pandemic and its social restriction measures affect sleep quality and the immunological system.*

METHODS: *An integrative bibliographical review was carried out using scientific articles from the last five years, from the PUBMED databases, with the descriptors: Sleep; Quarantine; COVID-19; Immunity; Mental Health. Besides the books "Oxford textbook of sleep disorders", "Cellular and molecular immunology", and "Treaty of Infectology".*

RESULTS: *Sleep affects immunity. This happens through the regulation of immunological markers and their cells. Therefore, the COVID-19 pandemic can promote sleep disturbances and harm the immune system function.*

CONCLUSION: *Sleep exercises a direct influence on immunity maintenance and immunological response. Circadian rhythm alterations, associated with the psychological problems imposed by the COVID-19 pandemic compromise the quality of sleep and, for that reason, the immune system.*

KEYWORDS: *Sleep. Quarantine. Coronavirus Infections. Immunity. Mental Health.*

INTRODUCTION

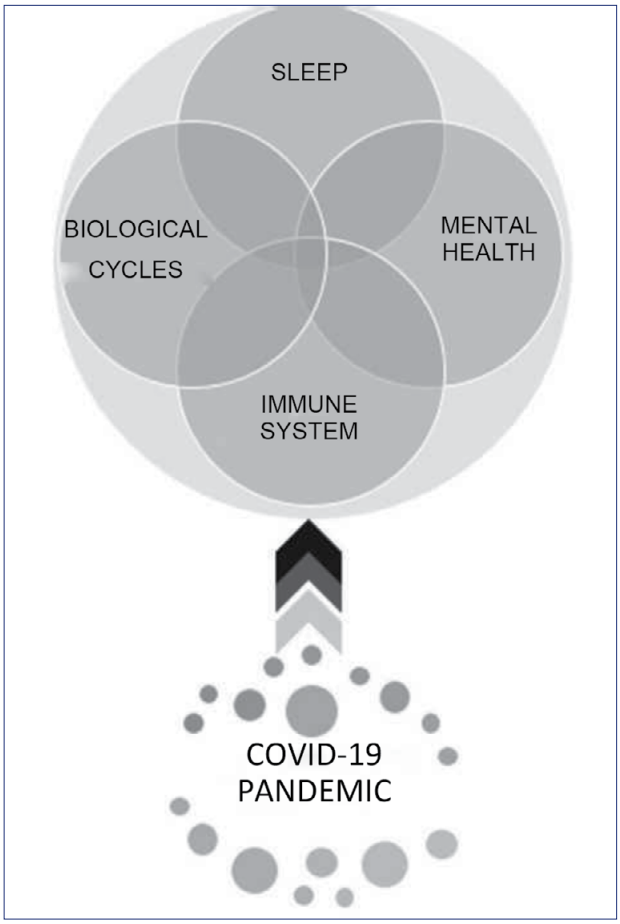
Sleep is a vital process for maintaining homeostasis and the quality of human life. Good sleep quality has impacts on well-being and mental health. Research over the last decade has increasingly validated the claim that sleep disorders have a strong influence on the risk of infectious diseases, the occurrence and progression of a series of diseases, and the incidence of depression[1].

The COVID-19 pandemic (Sars-Cov-2) not only altered the routine of a large portion of the population but also affected their quality of sleep. Much has been discussed about sleep and its immune function, something more evident when evaluating individuals under sleep deprivation, when there is an increase in the activity of cytokines, such as interferon (IFN), tumor necrosis factor-alpha (TNF-α), and interleukin-1-beta (IL-1-beta), in addition to an increase of inflammatory markers such as C-reactive protein[2]. This contributes to the general idea that a reduction in the quality of sleep negatively affects immunity. This relationship corroborates the consequences that the changes in routine caused by the pandemic, linked to their psychosocial impact, have on the health and sleep of the population, affecting, therefore, their immune system. The purpose of this article, therefore, is to analyze the influence of sleep on the immune system during the

DATE OF SUBMISSION: 19-Jun-2020
DATE OF ACCEPTANCE: 03-Jul-2020
CORRESPONDING AUTHOR: Eduardo Silva
Rua Castro Alves, 600, Uberaba, MG, Brasil – 38025-380
Tel: +55 61 99697-7851
E-mail: eduardosousa25@gmail.com

COVID-19 pandemic, which allows for an increase in the onset of sleep disorders correlated with a worsening of mental health, making the body more vulnerable to diseases.

FIGURE 1. FLOWCHART OF THE RELATIONSHIPS BETWEEN SLEEP, MENTAL HEALTH, IMMUNE SYSTEM, AND THE COVID-19 PANDEMIC.



Sleep and biological clock

The perception of time is crucial for the body to adapt to the needs of each period of the day. That way, there are cycles linked to the oscillation of temperature, hormones, sleep-wakefulness, among other processes that promote the maintenance of the body's physiological systems over the course of life, and, when imbalanced, they can harm health. Disturbances of circadian cycles are involved with the onset of metabolic diseases, such as obesity and diabetes, cardiovascular diseases, and cancer[3]. In the same way, a lifestyle that is not in sync with the circadian rhythm or abrupt changes in routine, such as those arising from the COVID-19 pandemic, favor these disorders and are risk factors for the onset of diseases.

The process of sleep is not simply the absence of alertness and perception, nor is it the suspension of sensory processes, but the combination of a passive withdrawal of afferent stimuli to the brain, linked to functional activation of certain brain regions[4]. In this way, far from being a simple process, sleep, in addition to its considerable influence in regulating mood, concentration, memory, body temperature, among other processes, is also an essential regulator of the immune system and response. Lack of sleep, therefore, can negatively compromise immunity, increasing the chances of illnesses. Prather et al.[5] found that there was greater susceptibility to colds related to shorter durations of sleep. There is also the influence of sleep in emotional processing, with a role in the maintenance of mood and emotional state[6]. In the same way, sleep deprivation can have a strong negative impact on daily behavior and, consequently, on everyday mental health.

However, excess sleep is also harmful. In addition to being associated with metabolic diseases, excess sleep (more than 10 hours per day), in comparison with lower durations, with insufficient exposure to sunlight in both cases, was associated with lower levels of circulating 25-hydroxyvitamin D (25OHD) stock[7]. Vitamin D (1.25-$(OH)_2D_3$), in addition to its metabolites, of which 25-hydroxyvitamin D is part, are actively related to immune regulation, and its deficit is linked to an increase of pathologies such as infections, autoimmune diseases, and allergic diseases[8]. Changes in routine, along with increased sleep time, both very common during the pandemic, can facilitate inadequate exposure to sunlight, affecting not only the metabolism of vitamin D but also the biological clock and immune system.

The sleep-wakefulness cycle acts as an "internal clock" of the human body, regulating sleep and wakefulness processes and, consequently, the various circadian cycles that influence the functioning of human metabolism. There is evidence that typical symptoms of depression can sometimes be related to disturbances of the circadian rhythms, reinforcing the notion that changes in sleep or in other cycles can affect mental health[9]. Some of the strategies adopted to reduce the contamination by the novel coronavirus during the pandemic, such as isolation and social distancing, dramatically change routines, which may decrease the intensity of the *Zeitgebers* (environmental

cues such as sunlight, alarm clocks, and social interactions, all of which help govern the circadian cycle), thus disturbing sleep quality[10].

One study showed that individuals who adopted an irregular sleep pattern were subject to a variable light pattern that encouraged delays in the circadian cycle and, consequently, could also lead to sleep delays and irregularity, suggesting a possible feedback loop[11]. Changes in routine, thus, facilitate the oscillation of sleep times, increasing the chances of compromising the quality of sleep. In addition, the contrast between the endogenous circadian rhythm system and the 24-hour environment cycle, both very common in those who work in irregular shifts and thus have frequent changes in routine, is a risk factor for cardiovascular and inflammatory diseases and is associated with increased blood pressure and inflammatory markers[12].

Immunity and sleep

Sleep plays a unique role in the maintenance of immunity; the circumstances that affect its quality have been associated with a reduction in the response to vaccines and an increase in vulnerability to infectious diseases[1]. In social contexts, such as this of the COVID-19 pandemic, which naturally promote an increase in anxiety and stress, sleep can be affected and, with that, contribute to the deregulation of inflammatory and antiviral responses.

When discussing immunity, it can be divided into innate immunity and adaptive immunity, both having an important component of communication, the cytokines[13]. Cytokines are proteins produced by cells of the immune system that promote intra- and intercellular immune responses[4]. Some important cytokines involved in sleep and in the innate immunity are the interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α)[1]. IL-6 is a pro-inflammatory cytokine that plays a role in the reduction of anabolic pathways and increase of catabolic pathways, resulting in an increased expenditure of energy to decrease the weight gain[14]. Whereas the function of TNF-α, which is also a pro-inflammatory cytokine, is centered on lipolysis and in changes of the adipose tissue[14], immunomodulation, apoptosis, proliferation, and pathological responses[15].

In a study with people who had chronic fatigue syndrome, those who had the worst quality of sleep were associated with higher severity of fatigue and with a higher interference in daily activities, with increased levels of pro-inflammatory interleukins (IL-1□, TNF-α, and IL-6)[16]. Previous studies with groups of participants who got little slept (<6 h) detected a decline of T lymphocytes, lower activity of natural killer cells (NK), shorter telomere length of T-cells, and increased inflammatory markers (C-reactive protein and IL-6)[17]. Compared with people who slept seven to eight hours per day, those who slept less than five hours were more likely to report rhinopharyngitis and acute bronchitis[18].

The impaired mitogenic proliferation of lymphocytes, decreased HLA-DR expression, positive regulation of CD14+, and variations in CD4+ and CD8+ T lymphocytes appear to be a possible explanation for the higher susceptibility to infections after a worsening of sleep[19]. Combined with this, the physiological response to psychological stressors, which can affect sleep, also proved to be able to negatively influence the immune system, demonstrating that sleep, immunity, and mental health are invariably intertwined[20].

Sleep disorders and the COVID-19 pandemic

The assessment of the psychological and emotional impact of the COVID-19 pandemic in the Chinese population, during the months of January and February 2020, clearly demonstrated the harm caused by the spread of the disease on the mental health of individuals[21]. The growth of COVID-19 cases has been accompanied by an increase in the levels of anxiety, stress, depression, and poor sleep quality in the population of the United States[22].

Sleep disorders occur due to a malfunction of its various regulatory mechanisms. Insomnia, the most common sleep-related complaint, is a multidimensional condition, reflecting the physical and mental state of an individual. It is defined as a difficulty in initiating, maintaining, and consolidating sleep or a worsened overall quality of sleep, leading to physical and mental damage[23]. Depression and the widespread increase in anxiety are risk factors associated with the onset of insomnia. Excessive concern with the progress of the pandemic, their own health, or that of people close to them, and with financial aspects, in addition to social restrictions, collaborate to the impairment of sleep and, due to the role of sleep in emotional stabilization, this can impair mental health even further[6]. In a study performed with American soldiers from West Africa, during 2014, in the outbreak of Ebola, who were placed in quarantine, 29.8%

reported sleep problems[24]. The deterioration in the quality of sleep, therefore, should be expected at a global level during the social restrictions adopted during the COVID-19 pandemic. Even though it is difficult to measure the prevalence of insomnia in these circumstances, it is expected that there will be a large number of underreported cases of this public health problem.

When associating immunity, sleep, and depression, patients with depression, which naturally go through great psychological stress, have increased pro-inflammatory markers, particularly the marker of C protein (CRP) and IL-6. In addition, an increase in inflammation increases depressive symptoms. Moreover, sleep disorders such as insomnia are linked with the incidence of depression, in addition to promoting an increase in inflammation[25].

CONCLUSION

The COVID-19 pandemic is one of the biggest challenges ever faced by world health systems in this century. Beyond the physical and geographical boundaries, the novel coronavirus greatly changed the daily lives of people; however, at the same time that measures restricting the viral infection should be a priority, the effects that emerge from these actions also need to be considered and handled. Sleep is affected in this scenario and, due to its relationship with the immune system and mental health, bad sleep impairs the immune response, facilitating the spread of infectious diseases and the worsening of mental health and quality of life.

Author's Contribution

All authors contributed equally to this work.

RESUMO

OBJETIVOS: *Analisar como a pandemia de COVID-19 (Sars-CoV-2) e as medidas de restrição social afetam a qualidade do sono e o sistema imunológico.*

MÉTODOS: *Fez-se uma revisão bibliográfica integrativa usando-se artigos científicos dos últimos cinco anos, das bases de dados PubMed, com os descritores: Sono; Quarentena; COVID-19; Imunidade; Saúde mental. Além dos livros Oxford textbook of sleep disorders, Cellular and molecular immunology e Tratado de infectologia.*

RESULTADOS: *O sono afeta a imunidade. Isso se dá por meio da regulação de marcadores imunológicos e suas células. Dessa forma, a pandemia de COVID-19 pode corroborar distúrbios de sono e prejudicar o funcionamento do sistema imune.*

CONCLUSÃO: *O sono exerce influência direta na manutenção da imunidade e da resposta imunológica. A alteração do ritmo circadiano, atrelada aos problemas psicológicos impostos pela pandemia de COVID-19, compromete a qualidade do sono e, dessa forma, o sistema imune.*

PALAVRAS-CHAVE: *Sono. Quarentena. Infecções por coronavírus. Imunidade. Saúde mental.*

REFERENCES

1. Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol. 2015;66:143-72.
2. Ruiz FSA, Tufik S. Aspectos imunológicos do sono. In: Paiva T, Andersen ML, Tufik S, eds. O sono e a medicina do sono. Barueri: Manole; 2014. p.124-31.
3. Farhud D, Aryan Z. Circadian rhythm, lifestyle and health: a narrative review. Iran J Public Health. 2018;47(8):1068-76.
4. Chokroverty S, Ferini-Strambi L. Oxford textbook of sleep disorders. Oxford: Oxford University Press; 2017.
5. Prather AA, Janicki-Deverts D, Hall MH, Cohen S. Behaviorally assessed sleep and susceptibility to the common cold. Sleep. 2015;38(9):1353-9.
6. Tempesta D, Socci V, De Gennaro L, Ferrara M. Sleep and emotional processing. Sleep Med Rev. 2018;40:183-95.
7. Choi JH, Lee B, Lee JY, Kim CH, Park B, Kim DY, et al. Relationship between sleep duration, sun exposure, and serum 25-hydroxyvitamin D status: a cross-sectional study. Sci Rep. 2020;10(1):4168.
8. Trochoutsou AI, Kloukina V, Samitas K, Xanthou G. Vitamin-D in the immune system: genomic and non-genomic actions. Mini Rev Med Chem. 2015;15(11):953-63.
9. Reddy S, Reddy V, Sharma S. Physiology, circadian rhythm. [Updated 2020 May 24]. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2020. [cited 2020 May 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519507/#
10. Guichard K, Geoffroy PA, Taillard J, Micoulaud-Franchi J-Arthur, Royant-Parola S, Poirot I, et al. Stratégies de gestion de l'impact du confinement sur le sommeil: une synthèse d'experts. Medecine du Sommeil. 2020. doi: https://doi.org/10.1016/j.msom.2020.04.003
11. Phillips AJK, Clerx WM, O'Brien CS, Sano A, Barger LK, Picard RW, et al. Irregular sleep/wake patterns are associated with poorer academic performance and delayed circadian and sleep/wake timing. Sci Rep. 2017;7(1):3216.
12. Morris CJ, Purvis TE, Hu K, Scheer FA. Circadian misalignment increases cardiovascular disease risk factors in humans. Proc Natl Acad Sci U S A. 2016;113(10):E1402-11.
13. Abbas AK, Lichtman AH, Pillai S. Cellular and molecular immunology. 9ª ed. Philadelphia: Elsevier; 2017.
14. Veronesi R, Focaccia R. Tratado de infectologia. 5ª ed. São Paulo: Atheneu; 2015. p.334-5.

15. Holbrook J, Lara-Reyna S, Jarosz-Griffiths H, McDermott M. Tumour necrosis factor signaling in health and disease. F1000Res. 2019;8:F1000 Faculty Rev-111.

16. Milrad SF, Hall DL, Jutagir DR, Lattie EG, Ironson GH, Wohlgemuth W, et al. Poor sleep quality is associated with greater circulating pro-inflammatory cytokines and severity and frequency of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) symptoms in women. J Neuroimmunol. 2017;303:43-50.

17. Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in health and disease. Physiol Rev. 2019;99(3):1325-80.

18. Prather AA, Leung CW. Association of insufficient sleep with respiratory infection among adults in the United States. JAMA Intern Med. 2016;176(6):850-2.

19. Ibarra-Coronado EG, Pantaleón-Martínez AM, Velazquéz-Moctezuma J, Prospéro-García O, Méndez-Díaz M, Pérez-Tapia M, et al. The bidirectional relationship between sleep and immunity against infections. J Immunol Res. 2015;2015:678164.

20. Bailey MT. Psychological stress, immunity, and the effects on indigenous microflora. Adv Exp Med Biol. 2016;874:225-46.

21. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health. 2020;17(5):1729.

22. Voitsidis P, Gliatas I, Bairachtari V, Papadopoulou K, Papageorgiou G, Parlapani E, et al. Insomnia during the COVID-19 pandemic in a Greek population. Psychiatry Res. 2020;289:113076.

23. Bacelar A. Insônia: do diagnóstico ao tratamento. São Caetano do Sul: Diffusion; 2019. p.17-27.

24. Adler AB, Kim PY, Thomas SJ, Sipos ML. Quarantine and the U.S. military response to the Ebola crisis: soldier health and attitudes. Public Health. 2018;155:95-8.

25. Irwin MR, Opp MR. Sleep health: reciprocal regulation of sleep and innate immunity. Neuropsychopharmacology. 2017;42(1):129-55.