

Can the exacerbated synthesis of inflammatory markers in COVID-19 impair the response to treatments in patients with coronavirus?

A síntese exacerbada de marcadores inflamatórios na COVID-19 pode prejudicar a resposta aos tratamentos em pacientes com coronavírus?

¿La síntesis exacerbada de marcadores inflamatorios en COVID-19 puede afectar la respuesta a los tratamientos en pacientes con coronavirus?

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Abstract

In addition to chronic diseases and empirical therapies against COVID-19, other factors are responsible for the high mortality rate associated with COVID-19. The objective of this study was to verify whether the exacerbated synthesis of inflammatory markers resulting from COVID-19 could compromise patients with coronavirus. The bibliographic research was performed in the Pubmed, LILACS, and SciELO databases between December 2020 and July 2021. For this study, the terms "COVID-19," "Biomarkers," "SARS-COV-2," and "Coronavirus 2019" are in advanced mode to gather the best evidence for the proposal of this manuscript. In the present construct, it is argued that COVID-19 increases the susceptibility of patients to a high stage of inflammation, increasing the virulence factors of the virus and its dissemination through the human body, where the synthesis of inflammatory factors plays a crucial role in the worsening of the cases. The virulence of the virus can be decreased by correcting the synthesis of these inflammatory markers, as it can prevent a less ineffective immune response and even increase the resistance of patients. Consequently, clinical trials in this direction should be carried out from the perspective of modulating responses at the molecular level, to find out how they work and how the underexpression of inflammatory cytokines may reduce the aggravation of patients with coronavirus.

Keywords: COVID-19; Pandemic; SARS-CoV-2; Inflammatory markers.

Resumo

Além das doenças crônicas e do uso de terapias empíricas contra a COVID-19, acredita-se que outros fatores podem ser responsáveis pela alta taxa de mortalidade associada à COVID-19. O objetivo deste estudo foi verificar se a síntese

exacerbada de marcadores inflamatórios decorrentes da COVID-19 poderiam comprometer os pacientes com coronavírus. A pesquisa bibliográfica foi realizada nas bases de dados Pubmed, LILACS e SciELO entre dezembro de 2020 e julho de 2021. Para este estudo, os termos "COVID-19", "Biomarcadores", "SARS-COV-2" e "Coronavírus 2019" foram usados em modo avançado para reunir as melhores evidências para a proposta deste manuscrito. No presente constructo, argumenta-se que a COVID-19 aumenta a susceptibilidade dos pacientes a um elevado estágio de inflamação, aumentando os fatores de virulência do vírus e sua disseminação pelo corpo humano, onde a síntese de fatores inflamatórios desempenha papel crucial no agravamento dos casos. A virulência do vírus pode ser diminuída corrigindo a síntese desses marcadores inflamatórios, pois pode prevenir uma resposta imunológica menos ineficaz e ainda aumentar a resistência dos pacientes. Consequentemente, os ensaios clínicos nesse sentido devem ser realizados sobre a perspectiva de modular as respostas a nível molecular, para descobrir como elas atuam e como a subexpressão de citocinas inflamatórias pode reduzir a agravamento dos pacientes com coronavírus.

Palavras-chave: COVID-19; Pandemia; SARS-CoV-2; Marcadores inflamatórios.

Resumen

Además de las enfermedades crónicas y el uso de terapias empíricas contra la COVID-19, se cree que otros factores son responsables de la alta tasa de mortalidad asociada con la COVID-19. El objetivo de este estudio fue verificar si la síntesis exacerbada de marcadores inflamatorios resultante de la COVID-19 podría comprometer a los pacientes con coronavirus. La búsqueda bibliográfica se realizó en las bases de datos Pubmed, LILACS y SciELO entre diciembre de 2020 y julio de 2021. Para este estudio se utilizaron los términos "COVID-19", "Biomarcadores", "SARS-COV-2" y "Coronavirus 2019" están en modo avanzado para recopilar la mejor evidencia para la propuesta de este manuscrito. En el presente constructo se argumenta que el COVID-19 aumenta la susceptibilidad de los pacientes a un estadio alto de inflamación, aumentando los factores de virulencia del virus y su diseminación por el cuerpo humano, donde la síntesis de factores inflamatorios juega un papel crucial en la el empeoramiento de los síntomas casos. La virulencia del virus se puede disminuir corrigiendo la síntesis de estos marcadores inflamatorios, ya que se puede evitar una respuesta inmune menos ineficaz e incluso aumentar la resistencia de los pacientes. En consecuencia, los ensayos clínicos en esta dirección deberían realizarse desde la perspectiva de modular las respuestas a nivel molecular, para conocer cómo actúan y cómo la infraexpresión de las citocinas inflamatorias puede reducir el agravamiento de los pacientes con coronavirus.

Palabras clave: COVID-19; Pandemia; SARS-CoV-2; Marcadores inflamatorios.

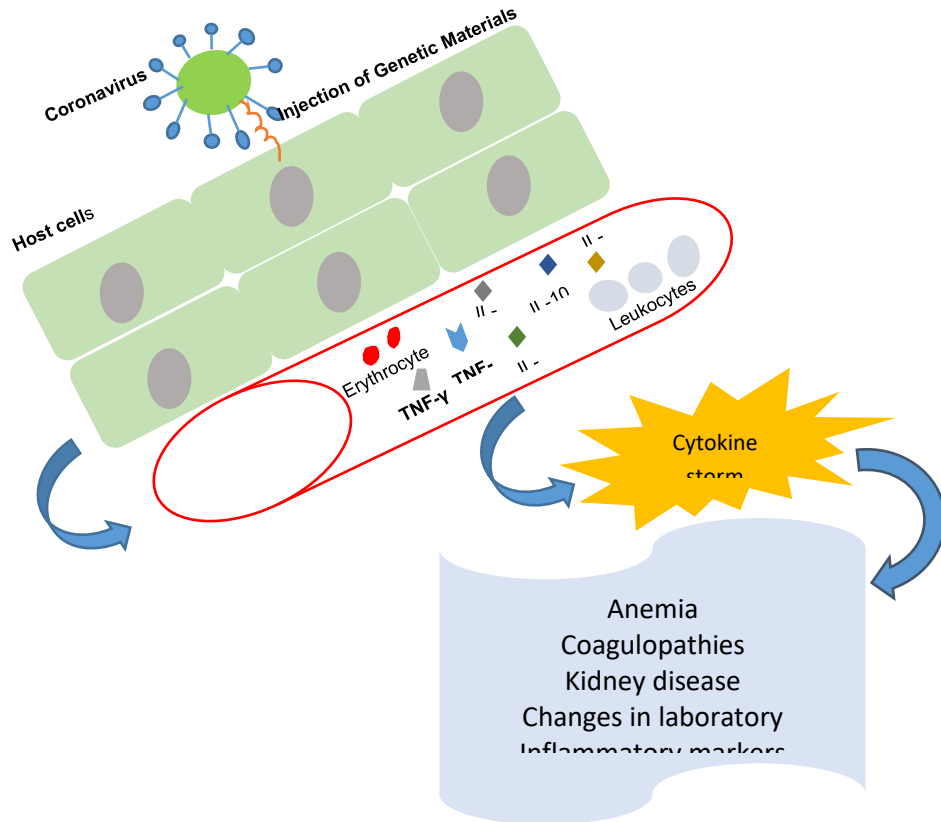
1. Introduction

The first records of the coronavirus disease (COVID-19) were identified in Wuhan, province of China, in 2019. Since then, the disease has spread quickly, with episodes of pneumonia associated with Severe Acute Respiratory Syndrome (SARS). COVID-19 is a severe infection caused by coronavirus species with a high capacity to infect humans (HCoV) (Fakhroo et al., 2021; Satış et al., 2021). Major risk factors for COVID-19 include hypertension, diabetes, obesity, cardiovascular disease, chronic lung disease, chronic kidney disease, and asthma (Fakhroo et al., 2021).

The highest incidence of this disease occurs mainly in individuals with diabetes mellitus, obesity, hypertension, and heart failure, where the virus seems to maintain greater infectability and virulence (Satış et al., 2021). The mechanisms that lead to the development of this phenomenon are associated with adhesion, fixation, penetration, incorporation of genetic material into the host genome, maturation, and formation of new viral copies that will be exposed to the extracellular environment (Ponti et al., 2020).

The virus will trigger several immunological reactions that provoke the cytokine storm upon penetrating the host cells. This phenomenon is characterized by the exacerbated response of interleukins-6 (IL-6), IL-1, IL-8, IL-10, in addition to Tumor Necrosis Factor-alpha (TNF- α) and Interferon-gamma (IFN- γ) of the immune system, resulting in metabolic failures such as anemia, coagulopathies, kidney disease and laboratory alterations such as ferritin, transaminases, coagulation parameters (prothrombin activity time) and elevation of C-reactive protein, according to Figure 1 (Upadhyay et al., 2020; Shimabukuro-Vornhagen et al., 2018; Mehta et al., 2020).

Figure 1. Schematic representation of the mechanism of production of the cytokine storm induced by SARS-CoV-2.



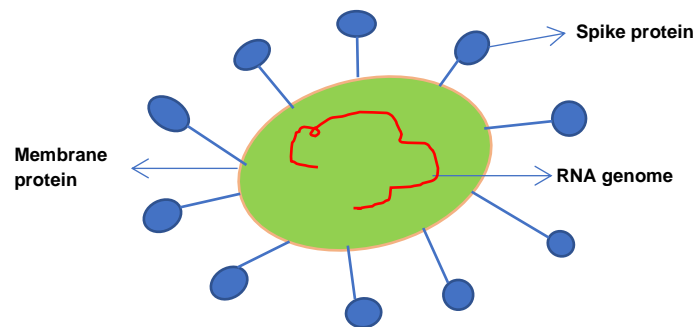
Source: Authors (2022).

Among the central cytokines frequently increased in the serum of patients with cytokine storm are IL-6, IL-10, and interferon IFN- γ . The secreted IFN- γ stimulates the activation of macrophages, which, when activated, produce high amounts of cytokines such as IL-6, TNF- α , and IL-10. TNF- α and IL-6 appear to play a critical role in the pathophysiology of the cytokine storm, as their extremely high levels are observed in these patients (Shimabukuro-Vornhagen et al., 2018).

Severe or prolonged cases of COVID-19 are associated with the absence of pre-existing immunity (previous contact with the pathogen or its similar), especially in elderly patients or those with pre-existing chronic comorbidities such as diabetes (Lughetti et al., 2020), hypertension (Santos 2021), and obesity (McNeill et al., 2021). These individuals manifest an excessive inflammatory response characterized by increased serum levels of biomarkers, exacerbated inflammatory reaction, and usually an unfavorable prognosis for the clinical situation (McNeill et al., 2021; Sabbatinelli et al., 2021).

Interestingly, the SARS-CoV-2 species has a rounded structure measuring ~80-120 nm. In its constitution, there is a protein called Spike in a helical shape with the ability to produce a type 1 glycoprotein in the surface region of the virion (Figure 2), which gives it a structural characteristic similar to a crown (Upadhyay et al., 2020; Pelle et al., 2020).

Figure 2. Schematic summary of the SARS-Cov-2 virus particle and genome.



Source: Authors (2022).

Usually, its structure favors favorable conditions for infection in host cells because the virus uses the host's angiotensin-converting enzyme-2 (ACE-2) enzyme as a co-receptor to penetrate its cells. In addition, virus surface proteins bind to ACE-2 receptors activating proteases that contribute to the adhesion of the coronavirus to the host cell, inflammatory events in the respiratory, digestive, nervous, and cardiocirculatory systems (Garg et al., 2021).

The incubation period varies between 5-7 days, and in most individuals, the disease ceases without therapeutic intervention. Pulmonary infection is physiologically involved with chemokines and inflammatory cytokines, causing an immunological imbalance through the stimulation of macrophages in the alveoli (Martinez-Urbistondo et al., 2020; Hariyanto et al., 2021).

In humans, the most prevalent clinical forms of the disease are muscle pain, cough, fever, and gastrointestinal complications accompanied by episodes of diarrhea. Other circumstances, such as the beginning of the conversion of IgG immunoglobulins and dysregulation of the immune system, lead to an exacerbated multiplication of the virus, causing severe injury to the alveoli and worsening symptoms and hospitalization (Upadhyay et al., 2020; Martinez-Urbistondo et al., 2020).

The most complex form of the disease is characterized by severe lung inflammation, causing severe acute respiratory syndrome (SARS), where special care is required, such as in Intensive Care Units (ICU). With the spread and severity of the infection and the lack of control of virulence factors in the host, one of the main outcomes is the patient's death. (Upadhyay et al., 2020; Smith et al., 2020).

It is also known that individuals with comorbidities such as diabetes, kidney disease, heart disease, hypertension, obesity have a greater tendency to progress to more severe cases of the disease when compared to those without comorbidities. Individuals with more than one comorbidity tend to have a more severe prognosis and greater risk of death (Fakhroo et al., 2021).

Despite all the studies related to the predictive role of biomarkers on poor prognosis in SARS-CoV-2 infection, it is known that, given the changes in the immune system and the inflammatory response of patients with chronic diseases, the association of biomarkers in this specific group is not fully elucidated, requiring further studies to understand the causal relationship entirely (Smith et al., 2020).

Currently, inflammatory biomarkers such as Lactate Dehydrogenase (LDH), IL-6, D-dimer are recommended to evaluate possible clinical complications in patients diagnosed with SARS-CoV-2. However, these are not part of the laboratory routine due to their high cost. Thus, many health services have adopted CBC, Ferritin, Transaminases, Prothrombin Activity Time, Erythrocyte Sedimentation Rate, and C-Reactive Protein as relevant tests to identify possible clinical complications in patients with COVID-19 (Ponti et al., 2020; Hill et al., 2021).

1.1. Hypothesis

Given the fact that COVID-19 is an unexpected health problem both in Brazil and in the world and that the use of drug therapy is still at an experimental stage, in addition to the large number of people who suffer from systemic diseases /metabolic: hypertension (16.9%), diabetes (8.2%), chronic heart disease (31%), uncomplicated diabetes (21%), non-asthmatic chronic lung disease (18%) and chronic kidney disease (16%) (Fakhroo et al., 2021), it is considered that high levels of inflammatory markers may also be responsible for the increase in severe cases and mortality of COVID-19.

The present study proposes that uncontrolled predisposing factors and high levels of inflammatory molecules play an essential role in coronavirus virulence. It is also argued that, by correcting the dysregulation of inflammatory levels, the morbidity of the disease can be stopped, and, consequently, the susceptibility of the patient to develop more severe cases is significantly reduced.

2. Methodology

The narrative review (Sauntally et al., 2021) was performed through research in the Pubmed, LILACS, and SciELO databases between December 2020 and July 2021. For this study, the terms "COVID-19," "Biomarkers," "SARS-COV-2," and "Coronavirus 2019" are in advanced mode to gather the best evidence for the proposal of this manuscript.

The bibliographic consultation resulted in 1,370 articles whose titles and abstracts were evaluated, leaving 56 for full-text reading and possible exclusion. After a complete reading of the 56 selected articles, 22 articles were chosen for inclusion, and 34 were excluded because they did not present data significantly related to the present study.

Inclusion criteria were case reports, cross-sectional studies, and randomized clinical trials on inflammatory markers in patients with COVID-19. Exclusion criteria were studies with inconsistent data, animal models, and cell culture.

3. Results and Discussion

3.1 Inflammatory biomarkers and severity of COVID-19

The panel of laboratory data on SARS-CoV-2 infected individuals was investigated, revealing a significant increase in inflammatory markers such as Total Bilirubin (BT), Ferritin, Transaminases, Prothrombin Activity Time (TAP), Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). It implies that in COVID-19, metabolic functions change as a function of the immune response and the activation of an inflammatory mechanism associated with the attempt to regulate the physiological situations of the host (Ponti et al., 2020).

In COVID-19, the increase in CRP represents the infection progress for supposedly more severe patients, determining the investigation pattern of systemic inflammation and severe coronavirus infection. An acute phase biomarker, CRP binds to phosphocholine in pathogens and host cell membranes, promoting opsonization, phagocytosis, and antigen exclusion. CRP also activates the classical pathway of the complement system, an essential component of the innate host defense to fight infection (Smilowitz et al., 2021).

Although TAP is within the reference values in most patients, high levels of this test are often associated with severe and fatal cases of COVID-19, showing an increase of up to six seconds compared to the most severe cases of the disease. Therefore, even if still hypothetical, this biomarker may be an essential ally to predict an unfavorable prognosis for regulating blood clotting in COVID-19 (Hadid et al., 2021).

Lu et al. reported that COVID-19 positive patients with high ferritin levels were among the most severe cases with the highest morbidity rate. Increased ferritin levels were also observed in more severe patients and among those admitted to the hospital than in the group of less severe patients, regardless of age, sex, and the number of cases. Likewise, Sun et al. revealed

that critically ill patients have more significant proportions of increased ferritin levels than non-serious patients and hospitalized patients, suggesting that elevated serum ferritin levels may be a risk factor for poor prognosis in COVID-19 patients.

The ferritin is a predictive marker of severe COVID-19, as many inflammatory cytokines are rapidly produced during the cytokine storm in COVID-19 (IL-6, TNF- α , IL-1 β , IL-12, and IFN- γ), which stimulate hepatocytes, Kupffer cells, and macrophages to secrete ferritin. Such exacerbated and dysfunctional immune responses associated with macrophage activation and hyperferritinemia can further cause multiple organ failures. Notably, ferritin is the result of marked inflammation. It also plays a pathogenic role in the inflammation process through its binding to T-cell immunoglobulin, stimulating the expression of multiple pro-inflammatory mediators (Cheng et al., 2020; Iba et al., 2020).

The direct cytopathic effects induced by SARS-CoV-2 may play an essential role in the liver abnormalities of COVID-19. Abnormal liver enzyme measurements are consistently seen in patients with COVID-19, although it has been suggested that elevated aminotransferases may also originate from myositis rather than liver injury. In a study of 156 patients (Yang et al., 2020), 64 patients were reported to have abnormal liver enzymes, with alanine aminotransferase (ALT) being the most common disorder described. It has been shown that approximately 45% of individuals admitted with COVID-19 had elevated levels of aspartate aminotransferase (AST) and about 36% had elevated levels of alanine aminotransferase (ALT) at admission, suggesting that both AST as ALT act as adjuvants in the pathogenesis of COVID-19 (Luan et al., 2019; Bertolini et al., 2020).

3.2 How does the synthesis of inflammatory markers happen in COVID-19?

The pathogenesis of COVID-19-induced clotting mechanisms has not yet been fully understood; however, the mechanisms may partly apply to septic coagulopathy and bacterial-induced disseminated intravascular coagulation. Increased production of pro-inflammatory cytokines, stimulation of cell death mechanisms, and vascular endothelial damage are the leading causes of disorders involving markers such as prothrombin time (Iba et al., 2020).

The C-reactive protein (CRP) is an acute-phase protein that increases rapidly in the circulation in infectious conditions, is synthesized mainly by hepatocytes, and macrophages produce a small amount in inflammatory areas. In hepatocytes, CRP stimulation is specifically regulated by IL-6 at the transcriptional level, which can be optimized by IL-1 β , both of which induce the expression of many acute-phase protein genes. CRP elevations have also been reported in severe viral infections, including H1N1 influenza pneumonia and SARS-CoV-2 infection (Smilowitz et al., 2021; Luan et al., 2019).

Several mechanisms are proposed to explain how the liver injury caused by the coronavirus causes changes in liver markers. Hypoxia and heart failure in critically affected COVID-19 cases can predispose to hypoxic hepatitis leading to marked increases in AST and ALT levels. Investigations in liver ductal organoids from SARS-CoV-2 infected individuals showed overexpression of viral mRNA after the first day of infection. In these organoids, 3% of the cells co-expressed ACE2 and bile markers, causing an increase in bilirubin (Bertolini et al., 2020).

The erythrocyte sedimentation rate (ESR) is influenced by the size, shape, and concentration of erythrocytes and plasma characteristics. It is believed that SARS-CoV-2 triggers a change in the shape of erythrocytes or plasma properties, including the immune system, causing an imbalance in the functions of this biomarker (Pu et al., 2021).

3.3 Is the immune system modified in COVID-19?

The initial communication of the coronavirus with the immune system begins with the impairment of pattern recognition receptors responsible for presenting signals to attract and activate cells of the innate system, which in turn produces cytokines such as Interferon type I (IFN I), TNF, IL-6, IL-1 β and nitric oxide (ON). These cytokines inhibit virus replication and command the adaptive immune response to the viral infection. During COVID-19, low levels of IFNs are released by the immune cells of the innate system, causing a delay in biosynthesis and antibody response against the antigen. Differently from this behavior,

biosynthesis of higher levels of IL-1 β , IL-6 occurs, inducing infiltration of inflammatory cells and increasing inflammation (Iwamura et al., 2021).

Another SARS-CoV-2 mechanism is modifying the immune system by binding the virus with the ACE2 membrane and internalizing the complex by the host cell. The effect and cause of this circulating enzyme in COVID-19 are not yet fully understood, although levels may be increased in diabetes, chronic kidney disease, and hypertension. As the primary function, ACE2 physiologically counterbalances ACE and regulates angiotensin II (Ang II), converting Ang I to Ang-(1-9), Ang II to Ang-(1-7), whose function is to protect the tissue (Ponti et al., 2020; Iwamura et al., 2021).

3.4 Can correction of overexpression of inflammatory biomolecules constrain coronavirus virulence?

Recent investigations have shown that individuals with high levels of serum vitamin D (Vit. D) manifest milder symptoms of COVID-19, proposing its essential role in decreasing inflammatory overexpression in COVID-19 cases. Some evidence still under consolidation mentions it. D can increase the production of various antimicrobial peptides and modulate the immune system according to the internal environment, reducing the exacerbated production of pro-inflammatory cytokines, stimulating the expression of anti-inflammatory cytokines by immune cells (Lakkireddy et al., 2021). Assuming that Vitamin D reduces the response by Th1 lymphocytes (T helper 1) and pro-inflammatory cytokines, the production of anti-inflammatory cytokines increases in cases of immune overexpression. Still, under this same perspective, the authors revealed through the analysis of inflammatory markers, there was a decrease in ferritin and C-reactive protein levels after Vitamin D treatment. The study also demonstrated that the elevation of serum levels of vitamin D significantly reduced inflammatory markers without any adverse effects (Lakkireddy et al., 2021). However, from the point of view of evidence-based medicine, these studies still have insufficient scientific evidence, requiring new randomized, double-blind, and controlled clinical trials to infer a low risk of bias.

More recently, some postulates have suggested the control of overexpression and reduction of inflammatory cytokines present in COVID-19 from the administration of tocilizumab, which is a recombinant monoclonal antibody of the IgG1 subtype capable of inhibiting the effects of IL-6 through its antagonist action on the IL-6 receptor, a substance capable of provoking a cytokine storm (Hill et al., 2021). Glycyrrhetic acid, another IL-6 signaling inhibitor, was proposed as an alternative to reduce the body's exacerbated response. In addition, mesenchymal stem cell infusions have been highlighted for their immunomodulatory and anti-inflammatory potential of these cells et al., (Yang et al., 2020). Still incipient, it becomes indispensable that these therapies be investigated through randomized clinical trials for a long time to prove their efficiency and safety to patients.

3.5 Consequences and action of the hypothesis

In line with the difficulties that still exist to identify the fundamental mechanisms that seem to induce the exacerbated inflammatory response in certain groups of individuals with COVID-19, it is clear that the overexpression of inflammatory cytokines drastically contributes to the worsening of cases in more susceptible individuals. Therefore, it is identified that the systemic inflammatory picture installed by the storm of inflammatory cytokines is caused by immunomodulators, reflecting a more severe state of health.

This situation of accentuated inflammation in individuals with COVID-19 in the most severe form seems to be a great challenge to treatments since the therapy implies action on the symptoms and complications resulting from the infection, not acting directly on the cause (overexpression of inflammatory cytokines), where the outcome can naturally evolve to an improvement or worsening of the clinical picture. That said, randomized controlled molecular trials aimed at protecting ACE-2 receptors in humans could be a progressive ruse to block the adhesion of the coronavirus to human cells, preventing the development of local and systemic inflammatory events.

4. Conclusion

This proposed mechanism envisions therapies starting from the molecular principle to decrease the most severe cases and morbidity and mortality rates from adverse events of COVID-19 in at-risk individuals, keeping them safe from all other variants of the virus. Given the experimental cause, this hypothesis offers a way to improve treatments against COVID-19 for the benefit of global health. Nonetheless, new studies molecular are needed to test this hypothesis.

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