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SYSTEMATIC REVIEWS AND META ANALYSES

Biochemical and Immune Indicators of COVID-19 Severity

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Abstract

Background: Coronaviruses (CoVs) are a class of RNA viruses that infect humans and various animals. They enter host cells via ACE2 receptors, which are widely distributed in organs such as the heart, lungs, kidneys, and the digestive tract. COVID-19 infection causes systemic illness, characterized by fever, cough, fatigue, sputum production, dyspnea, appetite loss, and sometimes diarrhea. It can disrupt, damage, or even cause failure of multiple organs, particularly the lungs, kidneys, and sites of prior injury. Immune activation is marked by heightened T-lymphocyte and macrophage responses, producing elevated levels of cytokines, notably interleukins such as IL-2, IL-4, and IL-6, which play complex and sometimes antagonistic roles in immune regulation.
Objective: To investigate alternative laboratory markers for the diagnosis and prognosis of COVID-19, particularly in settings where RT-PCR testing is unavailable, focusing on the role of inflammatory markers and biochemical parameters.
Methods: During periods when RT-PCR testing was inaccessible because of logistical constraints, conventional laboratory tests were utilized to establish diagnostic and prognostic criteria for COVID-19. These included measurement of serum ferritin, interleukin-6 (IL-6), lactate dehydrogenase (LDH), and hematological parameters such as hemoglobin levels to assess anemia and iron status.
Results: Patients with COVID-19 frequently exhibited rapid elevation of ferritin levels, which correlated with increased IL-6 concentrations. Hyperferritinemia was associated with anemia and excessive iron loss. LDH levels were also elevated and served as an independent predictor of mortality, regardless of underlying conditions.
Conclusion: In the absence of RT-PCR testing, routine laboratory markers—including ferritin, IL-6, LDH, and hematological profiles—can serve as valuable tools for the diagnosis and prognostic assessment of COVID-19. Elevated ferritin and LDH levels, in particular, are linked to increased disease severity and higher mortality risk.

1. Introduction

The respiratory ailment later known as COVID-19 was disseminated by the severe acute respiratory syndrome coronavirus 2 after it was firstly discovered in Wuhan, China, in 2019. Coronaviridae has a further subfamily classification; Orthocoronaviridae; which consists of four genera; (α – Coronaviridae & β – Coronaviridae) mostly; or exclusively, infects mammals, where (γ – Coronaviridae & δ– Coronaviridae) especially affect many avian species; As a result, humans and their animals came under a heavy burden of infections, both directly and through their effects on nutrition in various ways [1]. Severe acute respiratory syndrome coronavirus 2, as it was nomenclated by WHO, or COVID-19, where they took "CO" from corona, "VI" from virus & "D" for disease, and "19" flagged the year of exposure.

Symptoms of COVID-19 varied among people. Some experienced general tiredness, others had dyspnea, and still others had arthralgia and/or diarrhea. The prominent symptoms were headache and fever, in addition to loss of taste and smell. Secondary diseases were the

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biggest challenge for the medical staff during the period of infection, due to their wide spectrum and spread among patients. Pneumonia, with all its types was leading cause of secondary illness, which furtherly led to more thoracic ailments.

Lung and heart problems whether by causing thrombosis or inducing vascular disorders affecting the pulmonary and cardiac systems—may arise mainly due to excessive blood pressure or instability of blood pH, related to renal or hepatic regulation dysfunction, or even failure. These conditions can occur during or after recovery from the acute phase of COVID-19 [4].

Younger and healthier individuals were in more favorable conditions and were less likely to follow instructions and recommendations at the beginning, these unrelated criteria were linked to cytokine storms that that took place inside healthy bodies because of the severity of interleukin reaction toward the virus, Itself, or its related factors—especially interleukin-6 (IL-6)—play a key role in determining the course of preventing further complications. This is achieved by reducing IL-6 levels through the use of hydrocortisones, primarily dexamethasone. Such intervention has later proven effective in stopping or delaying acute respiratory distress syndrome (ARDS), septic shock, disseminated intravascular coagulation (DIC), or multiple organ failure—all of which can lead to death due to dysfunction, arrest, or embolism, particularly pulmonary embolism (PE) [5].

Most common laboratory tests or markers were conducted to help estimate diagnostic indicators for the presence of COVID-19, rather than relying solely on RT-PCR, which was not available in many locations. therefore; because of the sudden blockage that had occurred, getting use of old profiles and tests was the only and the most reliable way to establish new criteria to help in diagnosis. Rapid elevation of ferritin level, accompanied by IL-6 anemia that accompanies hyperferritinemia correlated excessive loss of iron in addition to the ascending level of iactate – dehydrogenase (LDH), increased the mortality rate, regardless of the prevalent conditions [6]. Impaired kidney function and elevated glucose levels were associated with systemic viral infections that caused organ dysfunction, while thrombosis and embolism were caused by cytokine reactions to the infection, or in many cases, cytokine storms that restricted the patient to a very severe condition, necessitating admission to the intensive care unit (ICU) [7]. Therefore, analyzing these correlations and interpretations, while utilizing tests to monitor the condition of patients during and after recovery from COVID-19, contributes to predicting potential future consequences.

1.1. Anti – Cardiolipin – Antibody

This group of negatively charged phospholipids, which are biological components of cell membranes, indicates that anticardiolipin antibodies (ACL) are of acidic origin derived from glycerol. These autoantibodies are typically present in individuals with tissue destruction and chronic diseases (TDCD), such as systemic lupus erythematosus (SLE), autoimmune placental infarction (API), and both primary and secondary antiphospholipid syndrome (APS). These conditions are often associated with habitual abortions, thrombocytopenia, and thrombosis as the final outcome [8]. ACL Abs. are induced via mimicry of antigen epitopes that of conserved for a virus. Therefore, immune cross-reactivity between viruses and autoantigens, immunological modulation of viral outer proteins, and molecular mimicry may occur between these antigens and abnormal T and B lymphocytes during autoimmune diseases particularly when the autoimmune condition affects a specific organ, such as in autoimmune pancreatitis. In such cases, anticardiolipin antibodies (ACL-Abs) are often highly detected and exhibit elevated levels even under otherwise normal conditions. Normally, the detection of ACL-IgM is rare and uncommon, and may occur merely by coincidence due to its initially hidden activity. However, its presence in the bloodstream before clinical detection can lead to severe consequences for the patient. Hence, by the time this occurs, ACL-G of IgG will begin to appear and be present in the circulatory system, striking every possible epitope that can match its template, such as the cardiovascular system, uterine tissue, kidneys, and lungs. etc., leading to miscarriage or abortion, myocardiopathy, renal impairment, pulmonary hemorrhagic alveolitis and even lymphatic fibrosis [10]. These catastrophic events took place while COVID–19 was having an impact patients suffering from chronic diseases, like autoimmune diseases, rendering them easy victims with complications during and after their supposed recovery; the consequences of COVID-19 affected those with rheumatoid and renal ailments, but patients with cardiac and pulmonary problems were the biggest sufferers, making them struggle for their life with support others and also their prayers [11].

2. Interleukins Profile

The host's response to infections, especially viral infections, involves several immunological components, primarily T lymphocytes, which regulate immune cytokines. T-helper 1 (Th1) cells secrete pro-inflammatory cytokines, while T-helper 2 (Th2) cells secrete cytokines that regulate the humoral immune response. Elevated levels of these cytokines are associated with the severity of infection, the progression of disease, and the type of causative agent.

The intense activity of cytokines in combating infections and mediating various immunological responses can, when dysregulated, result in excessive secretions, hemorrhagic strokes (HS), trauma, and sepsis. Such dysregulation may, as an adverse effect, contribute to the development of several diseases associated with this condition, including schizophrenia, Alzheimer's disease, major depression, and even certain cancers.

Over-secretion of cytokines can trigger the dangerous cytokine storm syndrome, which may cause severe adverse effects due to the extensive sources and potent triggers of cytokine release, especially against viral infections; which cause acute immunological response by all types of defense mechanisms that can respond toward; particularly IL-2 increases body temperature to induce fever "without mercy," aiming to inhibit viral motility and proliferation through the thermal destruction of infected cells. However, excessive IL-2 activity can cause thermal strokes, which may lead to the destruction of body tissues or even death if uncontrolled. In contrast, IL-6 is the fastest to rise in response to viral infection. in spite of its response against other microorganisms infections; especially systemic types of viruses, like COVID – 19 [14].

3. Interleukin-2 (IL-2)

Other members of the IL-2 family include IL-4, IL-7, IL-9, IL-15, and IL-21. These cytokines signal through their receptors to form a three-chain complex consisting of α = CD25, β = CD122, and γ = CD132. The γ-chain is shared by all members of the family, which makes the receptor highly active when the β and γ subunits bind together. This interaction can increase IL-2 receptor (IL-2R) expression by more than 100-fold above its normal plasma concentration. The dimeric IL-2R (CD122 + CD132), which has intermediate affinity, is expressed by natural killer cells (NKCs) and $CD8^+$ T cells. The trimeric form (CD25 + CD122 + CD132) is responsible for activating regulatory T cells.

IL-2 promotes the differentiation of T cells into effector T cells and memory T cells following the initial antigenic stimulation, thereby aiding in the body's defense against infections. These differentiated cells assist naïve $CD8^+$ T cells in developing into Th1 and Th2 lymphocytes, while also accelerating their differentiation into Th17 and follicular helper T lymphocytes. In addition, IL-2 enhances the cytotoxic ability and activity of innate immune components, including natural killer cells (NKCs) and $CD8^+$ T cells. This establishes its central role in cell-mediated immunity (CMI) by expanding selected T cell clones against specific antigens and generating memory immunological cells (MICs), particularly during systemic viral infections where speed and specificity are crucial—such as in COVID-19 [17].

During COVID-19, concern arose over hyperthermia caused by excessive IL-2 activity ("hyperfolding"), which could increase the risk of cytokine storm syndrome (CSS). This condition claimed many lives by sending incorrect recruitment signals to the immune system through dysregulated interleukin secretion from malfunctioning immune cells—sometimes even after patients had passed the most critical phase of their illness in intensive care [18–20].

4. Interleukin-4(IL-4)

IL-4 serves multiple biological functions, including promoting T cell proliferation and activating B cells, followed by their differentiation into plasma cells. It plays a key role in both humoral and adaptive immunity. IL-4 also acts as a regulator, switching B cells to the IgE class and enhancing the production of MHC class II molecules to improve antigen recognition. This, in turn, supports the generation of specific monoclonal antibodies against each epitope of the antigen. Additionally, IL-4 contributes to immune regulation by inhibiting Th1 cell responses, macrophages, dendritic cells, and interferon-gamma (IFN-γ) production, thereby directing the immune system towards active adaptive immunity [21].

Therefore, IL-4 plays a crucial role in preventing cytokine storm syndrome (CSS) and enhancing antigenic neutralization through its specific antibodies. 22 IL-4 is also a key contributor to the development of certain immune system disorders, particularly allergies and autoimmune diseases. In addition, through the activity of Th2 cytokines, IL-4 is involved in airway inflammation in asthma patients, which in some cases can lead to occlusion of the pulmonary airways by mucus as a reactive response to allergens, and may cause anaphylaxis under certain conditions. Th2 cytokines with a congestive role can have detrimental effects on the patient [23].

Furthermore, in systemic infections—especially viral pulmonary infections—disturbances in IL-4 secretion can lead to severe complications during the acute phase of the disease or even after recovery. This was evident in COVID-19 cases, where significant alterations in IL-4 levels were reported among ICU patients [23,24].

5. Interleukin - 6(IL-6)

Interleukin-6 (IL-6) is produced by immune system cells and most stromal cells, including mast cells, dendritic cells, and T and B lymphocytes. In addition, non-lymphocytic cells such as keratinocytes, endothelial cells, and fibroblasts also contribute to its production. IL-6 plays a central role in linking innate and adaptive immunity, and its dual function in mediating both pro-inflammatory and anti-inflammatory responses gives it a key role in the development of cytokine storm syndrome (CSS) [25,26]. Interleukin-6 (IL-6) exhibits highly complex activity and reactivity mechanisms in signaling to receptors through both trans-signaling and signal transduction. This process allows binding via either the classical or mediated pathway to cell surface receptors, such as the membrane-bound interleukin-6 receptor (mIL-6R). Following binding, the IL-6/mIL-6R complex interacts with the trans membrane glycoprotein 130 (gp130), enabling IL-6 to function in both membrane-bound and soluble forms. This dual capability grants IL-6 a high priority in generating intracellular and gene-expression signaling through its two functional morphemes. Additionally, IL-6 is present in the tunica media of arteries and veins [27]. It functions as a myosin by mediating the inhibition of tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), while activating interleukin-10 (IL-10) and its antagonist, interleukin-1 receptor antagonist (IL-1ra). This mediating activity is further linked to obesity, contributing to the development of asthma through impaired pulmonary function [28].

COVID-19 is associated with increased mortality, often correlated with acute pulmonary arrest (APA). Systemically elevated levels of interleukin-6 (IL-6) have been among the most significant laboratory findings recorded in severe cases of multiple organ failure integrated syndrome (MOFIS). Since COVID-19 primarily targets the lower respiratory tract, its signs and symptoms often resemble those of acute seasonal influenza. However, severe cases may progress to acute pneumonia due to the direct interaction with angiotensin-converting enzyme 2 (ACE2), which plays a key role in viral attachment and cellular entry. The lower expression of ACE2 in children, as well as the blocking of its binding sites, can hinder viral entry into host cells [29]. COVID-19 primarily affects the lower respiratory tract, producing signs and symptoms that often resemble those of acute seasonal influenza. In severe cases, however, the disease can progress to acute pneumonia due to its strong interaction with angiotensin-converting enzyme 2 (ACE2), a key receptor for viral attachment and entry into host cells. In children, the relatively low expression of ACE2, along with the blocking of its binding sites, may limit the virus's ability to penetrate cells [30]. Post-COVID-19 syndrome has been observed in individuals with otherwise good health, as well as in those with chronic health conditions and weakened immune systems who face ongoing challenges against various pathogens or diseases. In healthy individuals, complications can arise due to the activation of multiple lines of the defense system, leading to the release of large quantities of cytokines from different sources. This immune overactivation can progress to cytokine storm syndrome (CSS), resulting in multiple organ failure, thrombosis, embolism, or even death—particularly in those who do not receive medications to prevent coagulation events or manage angina [31].

6. Conclusions

High levels of many cytokines are observed in SARS-CoV-2 patients, which may be indicative of the disease progression and a potential target for treatment. Multiple organ dysfunction and subsequent infections can result from the unique immunological characteristics of SARS-CoV-2 infection. Thus, understanding how different cytokines contribute to infection and inflammation in COVID-19 patients may help develop more effective treatment plans. Furthermore, more research is needed into pharmaceuticals and treatments to develop methods to prevent the spread and replication of COVID-19 and mitigate its negative consequences.

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Declarations

Authors' contributions

Rana Talib Mohsen was responsible for conceptualization, data duration, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing the original draft, and writing—review and editing.

Ethical approval

The study was approved by the relevant ethics committee. Informed consent was obtained.

Data availability

The data supporting the findings of this study are available from the corresponding author upon request.

Conflict of interest

The authors declare no conflict of interest with other previous studies.

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