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REVIEW ARTICLE

The role of iron and ferritin in pathophysiology and as a laboratory marker in COVID-19

O papel do ferro e da ferritina na fisiopatologia e como marcador laboratorial na COVID-19

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ABSTRACT

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) emerged in China exponentially and is recognized as a multisystem disease that gradually elevates markers associated with iron metabolism as the infection becomes more intense, becoming a critical factor in the investigation of prognosis. We review the latest scientific findings on the behavior of iron and ferritin in pathophysiology and as laboratory markers in COVID-19 (Coronavirus Disease 2019). The findings showed that iron and ferritin play a key role in the pathogenesis of COVID-19, contributing to the worsening of the disease. Therefore, iron dysmetabolism, marked by hyperferritinemia, is associated with inflammatory states in SARS-CoV-2 infection, and ferritin measurement has been shown to be a useful laboratory marker with a clinical and discriminatory potential to define the severity and mortality during COVID-19.

PALAVRAS-CHAVE
Biomarcador
COVID-19
Ferritina
Ferro
Prognóstico
SARS-CoV-2

RESUMO

O SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus 2*) surgiu na China, de maneira exponencial e foi reconhecida como uma doença multissistêmica que eleva gradativamente marcadores associados ao metabolismo do ferro à medida que a infecção se torna mais intensa, sendo fator chave na investigação de prognóstico. Analisamos as últimas descobertas científicas sobre o comportamento do ferro e da ferritina na fisiopatologia e como marcador laboratorial na COVID-19 (*Coronavirus Disease 2019*). As descobertas evidenciaram que o ferro e a ferritina tem papel chave na patogênese da COVID-19 contribuindo para o agravamento da doença. Portanto, o dismetabolismo do ferro, marcado pela hiperferritinemia, está associado a estados inflamatórios na infecção por SARS-CoV-2 e a dosagem de ferritina mostrou ser um marcador laboratorial útil, com um potencial clínico e discriminatório para definir a gravidade e mortalidade durante o curso do COVID-19.

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INTRODUCTION

An infection of unknown origin has spread in Wuhan, China, since December 2019, and in April 2020, the number of infected people grew exponentially[1,2]. By inducing pneumonia similar to the SARS-CoV (*Severe Acute Respiratory Syndrome Coronavirus*), which caused the SARS epidemic in 2003, the new coronavirus was named by the World Health Organization (WHO) SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus-2*), which causes the disease COVID-19 (*Coronavirus Disease-2019*)[1]. Initial symptoms included signs of upper respiratory tract infection accompanied by fever, cough, and generalized weakness, in some cases progressing to pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and eventually multiple organ failure[3,4].

COVID-19 has recently been recognized as a multisystem disease caused by immunological, inflammatory, and coagulative cascades[3]. Identifying effective laboratory biomarkers capable of classifying patients based on their risk is essential to ensure prompt treatment. Patients with severe disease had reduced lymphocyte, platelet counts and other markers such as C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), interleukin (IL-6), D-dimer, troponin, creatine kinase (CK) and aspartate aminotransferase (AST) were significantly elevated[5].

Hemoglobin-associated markers, such as bilirubin and ferritin, gradually increase as the infection becomes more intense and may be critical factors in the investigation of prognosis and therapy[3]. Iron is an essential trace element for most organisms, and the balance between the host's defense system and viral proliferation plays a vital role in infectious conditions. Although the association of iron metabolism with the pathophysiology of COVID-19 remains poorly understood, it is known that the alteration of its regulation damages the ability of red blood cells to transport oxygen, acting on the tissue modification associated with the elevation of ferritin[6].

Additionally, persistent alterations in iron homeostasis were evidenced, correlating them with inflammatory anemia and pulmonary pathologies with hyperferritinemia present in about 38% of patients classified as severe or critical[6]. Since COVID-19 infection is widespread, the association of laboratory markers is essential to predict the clinical course of the disease, achieving a successful treatment of the patient. Several metabolic pathways that arise from hemoglobin denaturation and imbalance with iron metabolism should be highlighted for potential auxiliary therapeutic interventions[3]. Therefore, this narrative review aims is to provide a perspective beyond the usual markers available to predict the severity of COVID-19, estimating associations of iron metabolism parameters in the pathophysiology and ferritin as a possible prognostic marker of the disease.

IMPORTANCE OF IRON IN INFECTION

Iron is an essential mineral that participates in several stages of human metabolism, a functional component of many proteins, called hemoproteins, which are involved in vital functions such as oxygen transport and energy production, the main ones being hemoglobin, myoglobin, cytochrome P450, peroxidase, and catalase[7,8].

Iron is also essential for almost all microorganisms, plants and invertebrate animals, functioning as a catalytic component of enzymes that mediate many redox reactions crucial for energy production and intermediary metabolism[7,9,10]. In addition, it is required for viral replication and other host processes, including mitochondrial function, ATP generation, DNA/RNA synthesis and repair, and cellular ferroptosis[11].

The human body contains 3 to 4 g of iron, most of it intracellular, present in the hemoglobin of erythrocytes (about 2.5 g), in ferritin, an iron-storage protein present in hepatocytes and macrophages (about 1 g), and in myoglobin and enzymes (about 0.5 g). Major sources of iron include the recycling of iron from senescent erythrocytes by macrophages, intestinal absorption of iron, and release of stored iron from hepatocytes[12].

The relative stability of extracellular iron concentration results from regulation by the interaction of the iron-regulatory hormone hepcidin, together with transferrin, a carrier protein, and ferroportin, an iron export protein[12]. Approximately 95% of the plasma iron portion is transported as transferrin[7,9]. However, suppose the binding capacity of transferrin in the blood is exceeded. In that case, iron can be found in plasma as iron not bound to transferrin, changing to its redox-active form, called plasma labile iron, becoming toxic, damaging DNA, lipids and proteins, causing cells to undergo iron-mediated oxidative stress and programmed cell death[11,13].

According to Camaschella[14], iron is regulated at a cellular and systemic level, and hepcidin is responsible for its homeostasis in the systemic route. The regulation of hepcidin is performed by several factors, including inflammatory cytokines, iron storage in hepatocytes, anemia, and hypoxia[15].

Within hours of infection or other inflammatory stimuli, plasma iron concentrations decrease, often below 10 µM. This response is known as "hypoferremia of inflammation", an action induced by the increase of cytokines, mainly IL-6 (interleukin-6) that induces the transcription of the hepcidin gene through the activation of the JAK/STAT pathway (*Janus kinase/ signal transducer and activator of transcription*)[8,10]. The production of hepcidin induces endocytosis and proteolysis of ferroportin and increases intracellular ferritin that sequesters iron in enterocytes and macrophages. Thus, under the influence of increased concentrations of hepcidin and ferritin, recycled iron is retained in liver and spleen macrophages, and intestinal iron absorption is decreased[12,16](Figure 1).

In this context, erythropoiesis is inhibited when the iron concentration drops below 10 µM. Patients with infections or inflammatory disorders commonly develop normocytic normochromic anemia, called anemia of chronic disease. Inhibition of erythropoiesis by hypoferremia makes sense because it preserves iron for other metabolic uses during infection and may facilitate shunting in the bone marrow for the production of leukocytes important for host defense[12]. Thus, given the absolute dependence on exogenous iron for the survival

of most microorganisms, it is believed that inflammation triggers a defense mechanism by increasing ferritin, which stores iron adequately, depriving it of the pathogen[7,9,15]. Alternatively, this mechanism can also contribute to poor tissue oxygenation of the hosts.

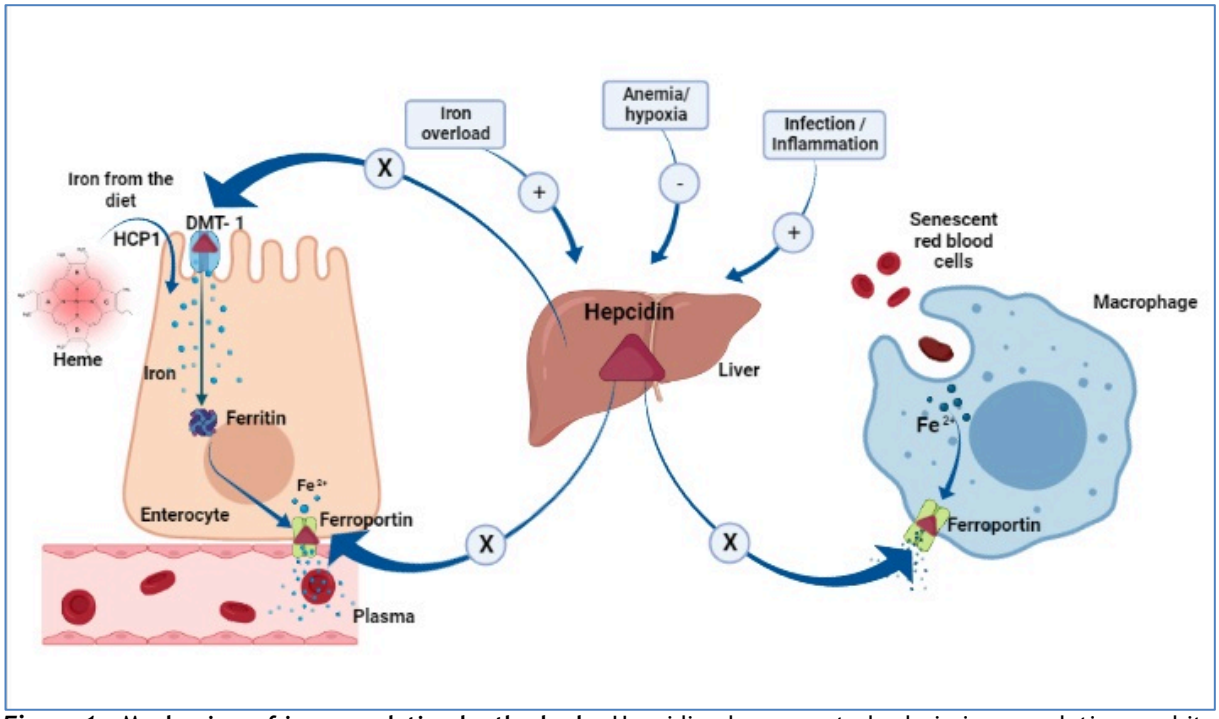

***Figure 1* - Mechanism of iron regulation by the body**. Hepcidin plays a central role in iron regulation, and its production is inhibited in anemia and hypoxia, while in infectious and inflammatory processes or when there is excess iron in the body, there is an increase in its release. Its action involves blocking the absorption and release of iron by inhibiting ferroportin and increasing intracellular ferritin that "sequesters" iron. Ferroportin is inhibited mainly in enterocytes responsible for obtaining iron through the diet (left figure) and in macrophages that recycle senescent red blood cells (right figure). Source: Authors.

IRON DYSMETABOLISM AS A PATHOPHYSIOLOGICAL MECHANISM OF COVID-19

Since the beginning of the pandemic, much has been learned about its clinical course, inflammatory markers, prognosis and complications of the disease. COVID-19 has three consecutive stages of increasing severity. The initial stage is characterized by SARS-CoV-2 infection. At this stage, flu-like symptoms may occur, mainly due to the viral infection itself. Later, patients develop viral pneumonia, requiring hospitalization or even invasive mechanical ventilation. The second stage is also characterized by pulmonary inflammation and coagulopathy, leading to multiple organ dysfunction, with acute pulmonary failure, acute liver failure, acute kidney injury, and cardiovascular disease. Additionally, it can also develop a broad spectrum of consecutive or often overlapping hematologic abnormalities and neurologic disorders. Finally, the third stage of the disease is characterized by pulmonary fibrosis, induced by the fibroproliferative state resulting from the excessive release of cytokines and neutrophil infiltration into the alveolar space, stimulated by opportunistic bacterial infections, leading to difficulty in lung expansion[17,18].

The SARS-CoV-2 has structural and biochemical characteristics that contribute to a significantly higher binding affinity with the angiotensin-converting enzyme 2 (ACE2) receptor when compared to SARS-CoV[19]. Cheng et al.[20] reported that ACE2 receptors are active in most tissues and widely distributed in the heart, kidneys, intestines, lungs and testis. They are present in large amounts in human alveolar epithelial cells and represent a crucial component of the Renin-Angiotensin System (RAS), considered a compensatory and "protective" axis that opposes the deleterious axis caused by the production of angiotensin 2 (Ang- II).

SARS-CoV-2 enters cells by interacting with the spike protein and the ACE2 receptor molecule. This interaction hampers the protective action of ACE2 on cells and causes organ damage due to the persistent level of Ang-II. The effects of Ang II range from increased oxidative stress to vasoconstriction, while ACE2's main pharmacological effect is to reduce blood pressure, catalyzing the cleavage of Ang I into Ang 1-9 and of Ang II into Ang 1-7 (vasodilatory, anti-inflammatory activity)[21]. Imai et al.[22] proposed that ACE2 reduction is related to acute lung injury because downregulation and its elimination can lead to RAS dysfunction and further increase inflammation, causing vascular permeability.

After the fusion phase, the virus replicates inside the host cells. With virus-cell interaction, antigen-presenting cells (APCs), including macrophages, present SARS-CoV-2 antigens to T cells[23]. This process leads to T

cell activation and cytokine production in various T cell subsets, particularly Th17, leading to massive cytokine release. In addition, SARS-CoV-2 infection causes a significantly amplified plasma levels of pro-inflammatory cytokines, including macrophage inflammatory protein 1-alpha (MIP1α), monocyte chemoattractant protein 1 (MCP1), Interleukin 1 beta (IL1- β), Interleukin 7 (IL7), Interleukin 8 (IL8), Interleukin 9 (IL9), interleukin 10 (IL10), platelet-derived growth factor B subunit (PDGFB), granulocyte-macrophage colony-stimulating factor (GM-CSF), Tumor Necrosis factor alpha (TNFα), Tumor Necrosis Factor gamma (IFNγ), among others[23,24].

This excessive release of cytokines results in the infiltration of activated neutrophils into the alveolar space and a fibroproliferative stage leading to interstitial fibrosis[11]. Thus, as the cytokine storm plays an essential role in worsening the disease, effectively suppressing it is a crucial way to prevent the deterioration of patients with COVID-19 infection[25].

Acute respiratory distress syndrome (ARDS) and multiorgan failure are the leading causes of mortality in patients with COVID-19, and excessive host inflammatory response or "cytokine storm" is part of the reason for an unfavorable clinical course[17] due to the associated systemic events such as hypercoagulability, oxidative stress, and altered iron metabolism[26].

Iron dysmetabolism, marked by hyperferritinemia, has been described as a characteristic associated with an increased risk of mortality in patients with COVID-19[26], plays an important role in the pathogenesis of the disease. Liu and Li[27] suggested that the key pathogenic molecular step of COVID-19 is caused by the viral protein that binds and attacks hemoglobin, more precisely the heme group, causing the dissociation of porphyrins from iron and releasing free iron into the circulation. According to Cavezzi et al.[3], the attack on the heme group of hemoglobin can cause hemolysis or the formation of dysfunctional hemoglobin with reduced oxygen displacement and hypoxia. The movement of free iron impairs endothelial cells in the same way that excessive ferritin accumulation contributes to endothelial inflammation, impairing alveolar-capillary permeability (Figure 2).

Excess intracellular iron interacts with molecular oxygen, generating reactive oxygen species (ROS), which can largely contribute to the oxidative damage of different organs[28]. Wenzhong and Hualan[29] adopted domain search techniques to analyze the SARS-CoV-2 E protein that was associated with viral infectivity and found that this protein can bind to iron from hemoglobin, forming a complex that synthesizes oxygen and water in ROS, causing damage to the host. This same complex could also reverse the ROS produced by the host's defense cells into oxygen and water, causing the virus to escape the immune system. Briefly, the virus can disrupt the immune system through “escape from ROS” and harm the immune system through “attack to ROS” (Figure 2).

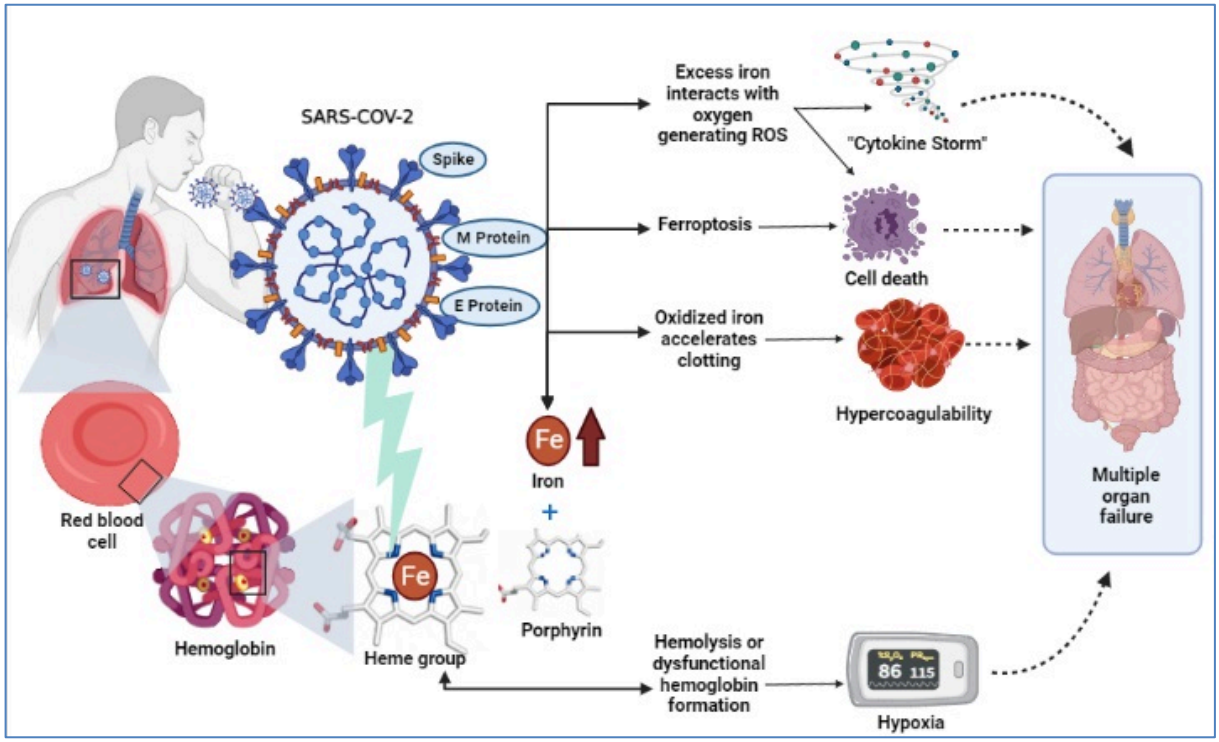

Figure 2 - **Role of iron and ferritin in the pathophysiology of COVID-19**. The SARS-COV-2 virus is capable of inducing several points of attack to the host. Intermediated by the viral protein that binds and attacks the heme group of hemoglobin, causing hemolysis or formation of dysfunctional hemoglobin. Excess intracellular iron interacts with molecular oxygen, generating reactive oxygen species (ROS) that contribute to the oxidative damage of different organs, in addition, oxidized iron accelerates coagulation by interacting with cascade proteins leading to hypercoagulability. Hyperferritinemia gives rise to ferroptosis, with high oxidative stress and lipid peroxidation, increasing mitophagy with apoptosis/necrosis and this set of factors may help to explain the cause of unexpected deterioration and multiple organ failure in COVID-19 patients. Source: Authors.

Furthermore, SARS-CoV-2 can mimic the action of hepcidin, further increasing circulating and tissue ferritin (affecting the liver, spleen, bone marrow, and muscles mainly), while inducing serum iron deficiency and, consequently, a decrease in hemoglobin. Hyperferritinemia leads to ferroptosis, with high oxidative stress and lipid peroxidation, increasing mitophagy with apoptosis/necrosis[3]. Recent studies have implied that ferroptosis, the process of programmed cell death mediated by non-dependent peroxidation mechanisms in inflammatory pathologies, involves multiple organs and may be linked to neurological disorders, including cognitive impairments, ageusia, and anosmia, which are common manifestations of COVID-19[30,31].

It has long been documented that coagulopathy is a hallmark of iron toxicity. Oxidized iron accelerates clotting by interacting with cascade proteins. Furthermore, the increase in iron and ferritin load leads to increased blood viscosity with diffuse and recurrent macro and microcirculatory thrombosis. This may explain the cause of unexpected deterioration and death in some COVID-19 cases[23,27].

High levels of free iron are harmful to tissues, especially through redox damage that can lead to fibrosis. Iron chelation represents a mainstay in treating iron overload and has shown antiviral and antifibrotic activity[11]. Several chelating agents are currently registered and routinely used in clinical practice. Deferoxamine (DFO) has a direct effect on ferritin since it promotes the degradation of ferritin in lysosomes by inducing autophagy, whereas deferiprone and deferasirox are likely to chelate cytosolic iron and iron that is extracted from ferritin before degradation of ferritin by proteasomes[32].

FERRITIN AS A LABORATORY MARKER IN COVID-19

Ferritin is classified as a cytosolic protein in most tissues, although a mitochondrial form also plays an essential role in cellular metabolism[33]. Ferritin also has the function of binding iron molecules and storing iron in a form that is biologically available for vital cellular processes, protecting proteins, lipids and DNA from the potential toxicity of this metallic element[11].

Iron indicators are directly associated with an acute inflammatory response, with serum ferritin being a good example of a protein that increases in acute inflammatory states[34]. The association between high levels of ferritin and more aggressive prognoses suggests a pathogenic role for this molecule. Additionally, its production by the liver and macrophages is potentiated by the inflammatory process since ferritin transcription is induced by IL-1B, IL-6 and IFN-Y[35].

Studies in COVID-19 patients have reported elevated levels of some inflammatory markers, such as procalcitonin, C-reactive protein, erythrocyte sedimentation rate, and serum amyloid A. However, little attention has been paid to ferritin, although hyperferritinemia is associated with complications in other viral diseases such as dengue[36]. Although ferritin is reported as an acute-phase protein, there is a lack of data in the literature reporting specific modified levels in some diseases. Recently, IL-6 has become a key marker in patients with COVID-19, and the link between IL-6 and iron metabolism is well known. Even so, in the most recent guidelines for COVID-19[37] there is no mention of ferritin, transferrin, or other iron parameters[38].

To assess whether ferritin can be used as a laboratory marker to predict severity and mortality in patients with COVID-19, 12 studies published in the years 2020 and 2021 analyzed the documented serum ferritin levels in patients with COVID-19 and correlated with several parameters. The analyzed data are summarized in Table 1.

Most studies have shown that high ferritin levels are correlated with increased severity in COVID-19 patients[6,39-45]. Dahan et al.[41] described a significant increase in ferritin levels in patients with severe COVID-19 (2,817.6 ng/ml) compared with those coded as non-severe (708.6 ng/ml). Hippchen et al.[42] verified in the multivariate analysis that low levels of serum iron and high levels of ferritin were predictors of severity in COVID-19.

Hyperferritinemia has also been evaluated as a promising predictor of mortality in patients with COVID-19[46-48]. In the work by Ahmed et al.[46], ferritin levels in non-survivors (1096.4 ng/mL) were significantly higher than those in survivors (548.9 ng/mL). Raman et al.[47] found that serum ferritin levels greater than 400 ng/mL predicted mortality with high sensitivity and specificity.

The increase in ferritin was also associated with the need for ICU admission[39], as this marker was closely associated with the difficulty in resolving pulmonary pathology and impaired physical performance[43].

Some authors have observed a difference in iron metabolism according to gender [42,43]. Sonnweber et al.[43] evaluated patients two months after COVID-19 infection and found that the persistence of hyperferritinemia was more frequent in men than in women. Hippchen et al.[42], in turn, observed a gender difference for ferritin and serum iron in all three patient cohorts, with men being more affected than women. In COVID-19, a gender difference in disease severity is well recognized, speculating that lower serum iron levels and higher ferritin levels in male patients may be associated with more severe COVID-19[42].

Another important aspect is that the inflammatory process appears differently in cases of common acute inflammation, such as surgeries or other diseases where ferritin values rise, but not excessively and rapidly as in patients with severe COVID-19. Banchini et al.[38] observed a significantly higher mean level of ferritin in patients with COVID-19 than in those who underwent surgery or who had leukocytosis, citing as an example a patient in the study who was hospitalized for acute peritonitis due to rectal perforation, with a leukocyte count of 27,000, a neutrophil count of 90%, a CRP of 36, and a ferritin level of 657, which is below the median value among discharged patients in the COVID group.

These findings reflect what has been previously reported about the prognostic role of this iron storage protein in other inflammatory diseases. Severe SARS-CoV-2 infection shares clinical and laboratory features with certain syndromes designated as hyperferritinemic, including Macrophage Activation Syndrome (MAS), Adult Still's Disease (ASD), Catastrophic Antiphospholipid

Table 1 — Articles that assess ferritin and other biomarkers as laboratory prognostic parameters in COVID-19.

Author	Year/ Country	Type of study	Subject	Study population	Results	Outcomes
Bolondi et al.[40]	2020 Italy	Observational Cohort Study	Assessment of iron metabolism and lymphocyte subtypes	31 patients admitted to the ICU diagnosed with COVID-19 by PCR	Ferritin was the first severely elevated biomarker together with lymphopenia in critically ill patients with values of 1470 (ug/L) between the 11th and 14th day of hospitalization.	Hyperferritinemia and lymphopenia were the first parameters to change in critically ill patients.
Dahan et al.[41]	2020 Israel	Cross-sectional study	Evaluation of the correlation between ferritin and disease severity	39 hospitalized patients diagnosed with COVID-19	Critically ill patients had significantly higher levels of ferritin (2,817.6 ng/ml) than non-critically ill patients (708.6 ng/ml).	Elevated ferritin levels correlated with severity in COVID-19.
Bellmann-Weiler et al.[39]	2020 Austry	Retrospective Study	Assessment of inflammatory anemia and changes in iron homeostasis	259 patients hospitalized with COVID-19	64 patients (24.7%) had anemia. And high ferritin levels were associated with longer hospital stays ($p < 0.001$) and higher risk of severity but were not associated with higher mortality.	Anemia and changes in iron homeostasis are prevalent in hospitalized patients with severe COVID-19.
Lv et al.[6]	2021 Wuhan	Retrospective cohort study	Association between iron status and risk of adverse outcomes in COVID-19	158 patients positive for COVID-19	Critically ill patients had a higher level of ferritin and lower serum levels of iron and transferrin than those in a non-severe condition. Iron metabolism parameters also differed in patients with or without multiple organ damage.	Elevated serum ferritin, reduced serum iron and transferrin have been associated with increased risk of severe COVID-19, ARDS, and multiple organ damage.
Sonnweber et al.[43]	2020 Austry	Prospective observational cohort study	Changes in iron homeostasis are prolonged in COVID-19 and are related to physical performance and lung pathologies	109 participants were evaluated two months after the onset of the first symptoms of COVID-19	Two months after COVID-19, 38% of individuals still had hyperferritinemia, being more frequent in men than women. High ferritin concentrations were associated with severe disease, lung disease, and decreased walking distance when compared to subjects with normal ferritin.	Hyperferritinemia can persist for up to two months and has been significantly associated with severe lung pathology, being more frequent in individuals who have had severe COVID-19.

Table 1 — Articles that assess ferritin and other biomarkers as laboratory prognostic parameters in COVID-19 (cont.).

Author	Year/ Country	Type of study	Subject	Study population	Results	Outcomes
Hippchen et al.[42]	2020 Germany	Retrospective Study	Iron metabolism markers in COVID-19 patients to predict severity	308 patients, being Cohort A (n = 204) outpatients, Cohort B (n=81) inpatients and Cohort C (n=23) outpatients who were hospitalized.	Iron metabolism was severely altered in cohort B and C patients (iron = 3.0 µmol/L and ferritin= 770ug/L) compared to cohort A (iron = 8.6 µmol/L and ferritin= 227ug/L). L). In the multivariate analysis, only low serum iron levels and high ferritin levels were predictors of severity.	Low serum iron levels as well as high ferritin levels have been associated with severe COVID-19.
Zhou et al.[45]	2020 Jiangsu, China	Retrospective Study	Ferritin and hepcidin as markers of severity in COVID-19	50 patients with COVID-19, being 12 with severe symptoms and 38 with mild symptoms, and a control group of 50 healthy people.	Hepcidin and serum ferritin levels were higher in patients with severe COVID-19 when compared to mild patients and healthy controls ($p < 0.001$). The severity of COVID-19 was predicted when serum ferritin was greater than 162 ng/mL, with hepcidin greater than 32.7 ng/mL.	The combination of serum hepcidin and ferritin tests proved to be good markers of severity in COVID-19.
Tojo et al.[44]	2021 Yokohama	Retrospective and prospective observational study from two centers	Severity-related iron metabolism markers in COVID-19	136 adult patients hospitalized with COVID-19, divided into patients with severe respiratory failure (RF), with moderate RF and without RF.	Ferritin levels increased significantly in patients with RF compared with patients without RF. Serum iron levels were significantly lower in the moderate RF group than in the no RF group.	Ferritin levels increased in patients with severe RF, regardless of iron metabolism.
Ahmed et al.[46]	2021 Paquistan	Retrospective observational study	Ferritin assessment for predicting mortality and severity in COVID-19	157 patients with COVID-19 who were divided into two groups: survivor (n=129)/ non-survivor (n=28)/ and severe (n=86)/ non-severe (n=71)	Mean ferritin levels were significantly higher in the severe group (828.5 ng/mL) when compared to non-severe group (357.5 ng/mL). Likewise, ferritin levels in non-survivors (1096.4 ng/mL) were significantly higher compared to survivors (548.9 ng/mL).	Serum ferritin concentration is a promising predictor of mortality in COVID-19.
Raman et al.[47]	2021 India	Retrospective cohort study	Ferritin and hemoglobin as predictors of mortality in COVID-19	210 hospitalized patients diagnosed with COVID-19	Mean serum ferritin levels (640.00 ng/mL vs 220.00 ng mL) were significantly higher among non-survivors, while hemoglobin levels were significantly lower (12.12 g/dl vs 13.73 g/mL). dl). Serum ferritin levels greater than 400ng/mL predicted mortality with high sensitivity and specificity.	The ferritin-hemoglobin ratio (FHR), which encompasses high ferritin levels and anemia severity, functions as an independent risk and prognostic marker for mortality in COVID-19.

Table 1 — Articles that assess ferritin and other biomarkers as laboratory prognostic parameters in COVID-19 (cont.).

Author	Year/ Country	Type of study	Subject	Study population	Results	Outcomes
Yağcı et al.[48]	2021 Istanbul	Cross-sectional study	Relationship of biochemical markers and severity of COVID-19	59 COVID-19 patients admitted to ICU and wards and 19 healthy volunteers.	Serum ferritin levels were higher in deceased patients than in survivors (P = 0.003) and higher in intubated patients (1205 ug/L) than in non-intubated patients (595 ug/L) (P = 0.005)	Ferritin level is a crucial parameter in terms of prognosis and mortality in COVID-19.
Banchini et al.[38]	2021 Italy	Retrospective observational study	Comparison of serum ferritin in patients with COVID-19 and patients with acute inflammation	17 patients hospitalized with COVID-19 (group A), 30 patients admitted for acute surgical disease, without COVID-19 (group B), and a subgroup of patients with leukocytosis, without COVID-19	Group A had a significantly higher mean ferritin level (674 ng/ml) compared to the entire group B (231 ng/ml), and the leukocytosis subgroup (149 ng/ml) (p < 0.0014).	In acute inflammation, changes in iron metabolism appear to be limited and ferritin can be used as a biomarker in COVID-19.

Syndrome (CAS) and septic shock. All exhibit excessively high serum ferritin levels associated with a hyperinflammatory cytokine storm and multiorgan failure. The similarities between severe COVID-19 and hyperferritinemic syndromes suggest that severe COVID-19 is a fifth member of this spectrum of hyperferritinemic inflammatory diseases[49,50].

According to this hypothesis, elevated ferritin is just the tip of the iceberg of a possible underlying dysregulated hyperimmune response. In this subgroup of critically ill patients, the inflammatory response escalates out of control, leading to lung disease and life-threatening systemic involvement[41]. To identify these patients early, we believe that all COVID-19 patients should be screened for hyperferritinemia.

Finally, the studies' results significantly supported ferritin's usefulness as a promising and robust clinical biomarker[6,39,40,43,45,46]. Thus, as expected, ferritin can predict clinical progression and mortality in hospitalized patients with COVID-19, also serving to assess severity during hyperinflammation.

CONCLUSION

The findings found in this review showed that iron and ferritin play a key role in the pathogenesis of COVID-19, involving the attack on hemoglobin, causing hypoxia, production of reactive oxygen species, ferroptosis, and hypercoagulability that cause cellular damage, and development of a wide spectrum of abnormalities that contribute to the worsening of the disease. Iron dysmetabolism, marked by hyperferritinemia, is associated with inflammatory states in SARS-CoV-2 infection, and the inflammatory process in this disease seems to differ from other acute inflammations by being more exacerbated. Therefore, ferritin dosage proved to be a laboratory marker with clinical and discriminatory potential to define severity and mortality during COVID-19, in addition to the usual markers available.

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