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Review Article

Relationship between ferritin levels and the prognosis of COVID-19

Relação entre os níveis de ferritina e o prognóstico da COVID-19

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ABSTRACT: The high level of serum ferritin has been associated with severe COVID-19 due to its stimulation by cytokines related to the inflammatory process. Although this increase is expected, this review proposes to analyze how high ferritin can be related to this severeness. According to this premise, the hyperferritinemia on COVID-19 could be an important factor of prediction and another way to understand the complications of COVID-19 - coagulopathy, acute respiratory distress syndrome (ARDS). Furthermore, this co-relation has been seen as a possible fifth syndrome among the other "hyperferritinemic syndromes", which are all characterized by high serum ferritin; this is an pertinent comparison and analyzation in terms of treatments.

Keywords: Ferritin; COVID-19; Inflammation; Acute respiratory distress syndrome; Hyperferritinemia. Treatments.

RESUMO: O elevado nível de ferritina sérica tem sido associado à COVID-19 grave devido à sua estimulação por citocinas relacionadas com o processo inflamatório. Embora este aumento seja esperado, esta revisão propõe analisar o quão elevado o nível de ferritina pode estar relacionado com esta severidade. Nesta linha de pensamento, a hiperferritinemia na COVID-19 poderia ser um importante fator de previsão e outra forma de compreender as complicações da COVID-19 - coagulopatia, síndrome do desconforto respiratório agudo (SDRA). Além disso, esta correlação tem sido vista como uma possível quinta síndrome entre as outras "síndromes hiperferritinêmicas", todas caracterizadas por ferritina sérica elevada; esta é uma comparação e análise pertinente em termos de tratamentos.

Palavras-chave: Ferritina; COVID-19; Processo inflamatório; Síndrome do desconforto respiratório agudo; Hiperferritinemia; Tratamentos.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is an illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1], which has become a pandemic with a high number of deaths. In this sense, biological markers and predictors have become important for infectious conditions to be evaluated and to have the proper interventions. One of these markers is ferritin - iron storage protein, an acute phase protein of the immune response that can be a predictor of the patient's condition, since it is independently associated with poor prognosis in COVID-19[2,3]. Thus, ferritin may predict the development of acute respiratory distress syndrome (ARDS), as well as the severity of this condition[3]. In other words, it serves as another tool for health care professionals to evaluate the adoption of more incisive measures and medications.

Furthermore, it has been shown that ferritin may not only be a consequence of inflammation, but it may also play a role in it. In this vein, it is considered to stimulate the expression of interleukin (IL) mRNA - IL-1β, IL-6, IL-10, TNF-α, IL-12 - besides increasing some of these

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in the extracellular compartment[4]. Thus, since it has been seen that it is both stimulated during inflammation and can stimulate the production of pro-inflammatory cytokines, it is believed that it helps perpetuate the inflammatory cycle - like the cytokine storms, especially in severe COVID-19.

With this, it is possible to analyze the disease from two perspectives. In that we have ferritin as a consequence of the infection, it can be seen as a predictor and a biological marker. Thus, by noticing the characteristic elevation of serum ferritin in those infected with SARS-CoV-2, one can compare it with that of hyperferritinemic syndromes[5] - a set of four clinical conditions that have high ferritin levels as a common sign - and establish parameters and comparisons with effective therapies for these syndromes that may be relevant in the treatment of COVID-19. With regard to this protein as an inflammatory perpetuator, it is demonstrated how differences between this disease and its similar ones may exist. Coagulopathy problems in severe cases of COVID-19, for instance, are seenkk with an association between the D-dimer and ferritin - which may direct to the use of prophylactic anticoagulant therapies[6-8].

In this context, the main objective of this work was to review the main molecular and physiological aspects of ferritin that support its use as a prognostic marker in COVID-19, as well as to highlight the possibility of severe COVID-19 fitting in as a "hyperferritinemic syndrome" and also responding to treatments used in these syndromes.

METHODS

To construct this literature review, the following scientific databases were consulted between the months of June 2020 and May 2021: NCBI/PubMed (National Center for Biotechnology), ClinicalTrials.gov and Google Scholar, as well as NIH (National Institute of Health) guidelines. We used the following terms: "COVID-19" combined with "inflammation", "cytokine storm", "hematology", "IL-1" or "IL-6"; "ferritin" combined with "secretion", "regulation", "proinflammatory" or "COVID 19"; "NRLP3 inflamasome activation" and "ARDS". We included articles in Portuguese or English that addressed: molecular aspects of ferritin, such as function, structure, regulation; SARS-COV-2 and its pathological mechanisms, as well as clinical and laboratory manifestations of COVID-19; hyperferritinemic syndromes and their treatments. Articles that did not fit the scope and articles about other viral infections were excluded.

RESULTS

When searching for the construction of this narrative review, we obtained about 13833 papers, among which 69 were selected by reading the title and abstract. Among these, 24 were mainly addressed (Table 1) for meeting the search for the answer to the proposed objective.

Table 1 - Title and general characteristics of the main target articles present in the study

Title	Author/Year	Periodical	Main results
Iron regulatory proteins in pathobiology	Cairo G, Pietrangelo A. 2000	Biochem J	Iron regulatory proteins are a key part of iron homeostasis control, acting as sensors of cytoplasmic iron and controllers of ferritin and transferrin receptors - which causes elevation or decrease in ferritin translation. This happens not only in response to fluctuations in labile iron in the body, but also to factors such as oxidative stress.
Regulation of ferritin genes and protein	Torti FM, Torti SV. 2002	Blood	Cytokine storm influences ferritin production and secretion in direct and indirect ways respectively: cytokines per se stimulate the process; cytokines stimulate nitric oxide production which in turn induces ferritin production.
New functions for an iron storage protein: the role of ferritin in immunity and autoimmunity	Recalcati S, et al. 2008	J Autoimmun	Ferritin H has immunosuppressive effects - negative regulation of hematopoiesis - in humans due to inhibition of B cell maturation and suppression of T cell proliferation by a modulation of the cytokine-chemokine network. Thus, a complex formed between ferritin H and the chemokine receptor CXCR4 is demonstrated that prevents the activation of MAPK kinase, which is important in the process of cell proliferation, differentiation, and migration.
Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	Huang C, et al. 2020	Lancet	In the study, the new coronavirus was seen by its main symptoms as fever (98% of patients), cough (31%), dyspnea (55%), myalgia or fatigue (38%); less common symptoms were headache (8%) hemoptysis (5%) and diarrhea (3%), and criticality leading to admission to intensive care units (32%) with intervention or not of mechanical respirators. All 41 patients had pneumonia and abnormal findings on chest CT scan. In severe COVID-19, functional organ damage, acute respiratory distress syndrome, acute kidney damage, cardiac damage, liver dysfunction and susceptibility to opportunistic fungal and bacterial infections were noted. Elevated levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A and TNFalpha were seen in patients admitted to intensive care units when compared to those who did not require such hospitalization.

continue

Table 1 - Title and general characteristics of the main target articles present in the study *coninuation*

Title	Author/Year	Periodical	Main results
Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China	Qin C, et al. 2020	Clin Infect Dis	Most cases had low lymphocyte counts, high WBC counts and increased neutrophil to lymphocyte ratio, as well as low monocyte, eosinophil and basophil counts. In the most severe cases, high levels of inflammatory cytokines were found. Regarding T cells, a reduced number of T helper (Th) and memory cells were found, while the percentage of immature Th was high in severe patients.
The trinity of COVID-19: immunity, inflammation and intervention	Tay MZ, et al. 2020	Nature Rev Immunol	The cytokine storm in response to SARS-CoV-2 infection causes sepsis symptoms that generate uncontrolled inflammation, which is damaging to multiple organs and causes death in 28% of patients. This storm is, in the study, a vicious circle (loop): the virus causes cell death by pyroptosis due to damage; the release of cytokines and chemokines occurs due to damage-associated molecules and cell recognition patterns being released with the pyroptosis; the recruitment of white cells, such as macrophages, by the inflammation caused is further followed by the activation of the adaptive immune system; the feedback on the cytokine storm associated with the now activated immune system persists until the infection is cleared.
COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection	Al-Samkari H, et al. 2020	Blood	The incidence of confirmed venous thromboembolism was 4.8% - 3.1% in non-critical patients and 7.6% in critical patients. The incidence of arterial thrombosis was 2.8% - 1.2% in non-critical patients and 5.6% in critical patients. The incidence of thrombotic complications overall in the study was 9.5% - 4.7% in non-critical patients and 18.1% in critical patients. In the comparison of coagulation and inflammation parameters, patients who had thrombotic complications showed high counts of D-dimer, fibrinogen, ferritin, C-reactive protein and procalcitonin. In the study, these factors were understood as predictors of complications.
Iron enhances generation of fibrin fibers in human blood: implications for pathogenesis of stroke	Lipinski B, et al.. 2012	Microsc Res Techn	Divalent iron ions alter the fibrinogen molecule, which accelerates the polymerization of fibrin monomers - the modified fibrin becomes resistant to fibrinolytic degradation.
Mechanisms underlying FeCl3 - induced arterial thrombosis	Eckly A, et al. 2011	J Thromb Haemost	FeCl3 has been shown to pass through the vessel wall, which does not expose the innermost layers, but denudes the endothelial cells and allows contact between the components of the basement membrane and the circulating blood, and may initiate thrombogenesis.
Serum ferritin as an independent risk factor for severity in COVID-19 patients.	Lin Z, et al. 2020	J Infect	Meta-analysis indicated that high serum ferritin levels as an independent risk factor associated with the development of ARDS in patients with COVID-19.
C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis	Huang I, et al. 2020	Therap Adv Respir Dis	Demonstrated by meta-analysis that C-reactive protein (CRP), procalcitonin (PCT), d-dimer and ferritin are associated with poor prognosis of patients with COVID-19.
Immunosuppressive A ferritina H tem propriedades imunossupressoras, demonstrando inibir a resposta de linfócitos estimulados com anti-CD3. Effects of melanoma-derived heavy-chain ferritin are dependent on stimulation of IL-10 production	Christian P, et al. 2001	Int J Cancer	Ferritin H has immunosuppressive properties, shown to inhibit the response of anti-CD3-stimulated lymphocytes.
Ferritin functions as a proinflammatory cytokine via iron-independent protein kinase C zeta/nuclear factor kappaB-regulated signaling in rat hepatic stellate cells.	Ruddell RG, et al. 2009	Hepatology	This study defined the role of ferritin as a pro-inflammatory mediator of hepatic stellate cell biology acting through the NF-kappaB signaling pathway.
Pro-inflammatory properties of H-ferritin on human macrophages, ex vivo and in vitro observations	Ruscitti P, et al. 2020	Scient Rep	Shows the presence of FeH in bone marrow biopsies from patients with Adult-onset Still's disease (AOSD) complicated with macrophage activation syndrome (SAM), while FeL was the predominant form in the serum of these patients.

continue

Table 1 - Title and general characteristics of the main target articles present in the study *coninuation*

Title	Author/Year	Periodical	Main results
Characteristics of inflammatory factors and lymphocyte subsets in patients with severe COVID-19.	Ni M, et al. 2020	J Med Virol	A pro-inflammatory response, particularly at the level of IL - 2R, IL - 6, TNF - α and CRP, has been associated with severe cases of COVID-19. SARS - CoV - 2 infection primarily affects T lymphocytes, particularly CD8 + T cells.
The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome	Rosário C, et al. 2013	BMC Med.	Hyperferritinemic syndromes are four clinical conditions characterized by fever, elevated serum ferritin, hyperinflammatory activity, cytokine storm, with eventual outcome of multiple organ failure.
COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome?	Colafrancesco S, et al. 2020	Autoimmun Rev	The study analyzed similar characteristics of COVID-19 with hyperferritinemic syndromes, including: cytokine storm, lymphopenia, reduced number and activity of NK, abnormal liver function tests, coagulopathy, and hyperferritinemia. In addition, other similarities found were: fever, multiple organ involvement and ARDS.
Recovery of severely ill COVID-19 patients by intravenous immunoglobulin (IVIG) treatment: a case series	Mohtadi N, et al. 2020	Virology	Case series with 5 patients in the initial stage of clinical deterioration of the disease who received 0.3-0.5g/kg IVIg per day and had an improved outcome, without disease progression. Upon performing the intervention, it was observed an increase in $_{O2}$ saturation and recovery of the number of breaths to normal.
Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19	Xie Y, et al. 2020	J Infect	Retrospective study with 58 patients with severe COVID19 who received IVIg as adjuvant therapy. A correlation was observed in patients who received the intervention, within 48 hours of ICU admission, with reduced use of mechanical ventilation, shorter hospital stay, and reduced 28-day mortality.
Therapeutic plasma exchange in adults with severe COVID-19 infection	Khamis F, et al. 2020	Int J Infect Dis	In the case series, the use of plasma exchange therapy in patients with severe COVID-19 was associated with better outcomes, such as higher extubation rate, lower mortality at 28 and improvement of laboratory parameters, such as reduced levels of IL-6. CRP, D-dimer, and ferritin levels.
Interleukin-6 receptor Antagonists in critically ill patients with Covid-19	The REMAP-CAP Investigators 2021	N Engl J Med.	In this clinical trial, the use of IL-6 receptor antagonist monoclonal antibodies (tocilizumab or sarilumab) in critically ill patients with COVID-19 receiving ICU support improved their outcome, including survival.
Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial	Abani O, et al. 2021	Lancet	The tocilizumab intervention group was more likely to be discharged from the hospital within 28 days. Moreover, among the patients allocated to the intervention group, those who had not received invasive ventilation at the beginning of the study were less likely to receive invasive mechanical ventilation or die.
Anakinra for severe forms of COVID-19: a cohort study.	Huet T, et al 2020	Lancet Rheumatol.	In this retrospective cohort, anakinra reduced the need for invasive mechanical ventilation and mortality among patients with severe forms of COVID-19.
Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study	Cavalli G, et al. 2020	Lancet Rheumatol.	Retrospective cohort including patients with COVID-19, moderate to severe ARDS and hyperinflammation (ferritin ≥900 ng / mL, CRP≥100 mg / L or both) who were treated with non-invasive ventilation outside the ICU and who received standard treatment, the use of anakinra was associated with clinical improvement, with attenuation of systemic inflammation and progressive improvement of patients' respiratory function.

DISCUSSION

Ferritin- molecular aspects

Ferritin (FT) is a fundamental protein in iron storage - it stores up to 4500 ferric iron atoms - that macrophages, hepatocytes and Kupffer cells secrete, although its secretory pathway is still not completely clear1. It is composed of 24 subunits that are divided into two types: H (heavy) and L (light)[2–5]. The heavy chain is basic and has ferroxidase activity - necessary for iron uptake, it oxidizes Fe (II) to Fe (III)[2,3]; the light chain is slightly acidic and aids in hydrolysis and formation of the ferric core3. The proportion between these two types varies according to the tissue in which they are found and can be altered depending on the inflammatory or infectious stage, as well as other factors (xenobiotic and oxidative stress, for example). Being the ferritin H (FTH) that is mostly composed of the H subunit and ferritin L (FTL) that is predominantly composed of the L subunit[2-6]. In this respect, the L subunit is mainly present in the spleen, liver, and bone marrow, and the H subunit is

predominantly found in the heart, kidneys, placenta, and tumor tissue[3,7]. Furthermore, when compared to tissue FT, serum FT is low in iron, is constituted mostly by the L subunit, and its concentrations may change according to race, sex, and age. Acceptable normal values are between 30 to 300 ug/L in men and 15 to 200 ug/L in women[8-10].

Regulation

In the ferritin mRNA, on both the H and L chains, due to the iron responsive elements (IRE's) in the 5'-UTR region bind to iron regulatory proteins (IRP's) to regulate their translation. In this situation, when cellular labile iron levels are low, IRP's bind to the IRE's of FT and suppress their translation; when the labile iron pool is high, these proteins reduce their interference in the mRNA, which raises production[11]. In addition to iron, other factors can interfere with the ability of IRP's to bind to mRNA. Oxidative stress, for example, with the production of reactive oxygen species (ROS), is able to inhibit the activity of IRPs, which increases the production of FT[11]. As well, models in rodent macrophages show that nitric oxide (NO), especially in its oxidized form (NO+), decreases the binding of IRP-2 to the IRE, thereby also elevating translation[12,13]. But also, FT production and secretion can be increased by cytokines, such as interleukin-1-β (IL-1β), tumor necrosis factor-α (TNF-α), IL-1α and IL-66,14 (at transcriptional, post-transcriptional and translational levels). In addition, cytokines also induce NO production, which increases that of FT in an indirect way[6,11,12]. Such evidence demonstrates that inflammation pathways influence ferritin expression.

Ferritin and immunity/signaling

For the role of a signaling molecule, specific receptors are required. While several cell types, such as T and B lymphocytes, have receptors for ferritin H, only liver cells have, receptors for both chains[4].

Extracellular ferritin L is recognized by SCARA5, a scavenger receptor present on the surface of human kidney and spleen cells mainly. This interaction may contribute to obtaining iron by this cell, because this receptor acts by delivering iron to the cytoplasm, where IRE's are activated. Still, it is not resolved whether SCARA5 is a single ferritinemic receptor component or a common ferritin-scavenger interaction[15]. In another hand, only extracellular ferritin H was able to bind, in mice, to immunoglobulin and mucin domain 2 of the T-cell family (TIM-2), a receptor. This apparently does not have an orthologous gene in humans, despite this, the human TIM-1 gene shares some of the same functions as it[4,5].

Ferritin H can suppress the proliferation of T, and B cells, and also inhibit the differentiation, migration and also proliferation of myeloid cells. The mechanisms for these functions are not yet completely clear, but may participate in this process: signaling pathways for specific H-ferritin receptors (such as TIM-2), induction of IL-10 production (which will act by reducing T cell proliferation) or even by down regulation of CD2[4,5,16].

It is worth pointing out that immune cell migration and proliferation is driven by a cytokine-chemokine system and H-ferritin has a relevant role in this process, as it has been shown that it can bind to the chemokine receptor CXCR4, forming a complex that prevents the signaling and activation of MAPK, a family that plays an important role in cell proliferation, differentiation and migration[17].

COVID-19

The novel coronavirus, SARS-CoV-2, is part of the Betacoronavirus genus, as is SARS-COV (responsible for the SARS epidemic), with which it shares 79.6% identical genomic sequence[18,19] a large number of SARS-related coronaviruses (SARSr-CoVs. Like the latter, SARS-CoV-2 infects host cells through the transmembrane angiotensin-converting enzyme 2 (ACE 2), which functions as a target receptor for the virus spike protein[18] a large number of SARS-related coronaviruses (SARSr-CoVs. This binding, which has a higher affinity than SARS-CoV, generates a cascade of events that will culminate in endocytosis of the virus[18–20] a large number of SARS-related coronaviruses (SARSr-CoVs.

Upon entering the host cell, the pathogen replicates and as part of its cycle, causes damage and death to the infected cells. Apparently this death occurs by pyroptosis, a programmed inflammatory cell death, in which there is production of pro-inflammatory factors such as IL-1β and IL-18[20,21].

Then, with pyroptosis, the cell releases damage-associated molecules (DAMPs) and pathogen-associated molecular patterns (PAMP's), which will be recognized by local cells and culminate in the induction of inflammation, generating cytokines and chemokines[20]. Thus, consequently, the virus activates the innate immune system and there is the recruitment of macrophages and other white cells to contain the infection, moreover, the antigen-presenting cells (APCs) will activate the adaptive immune system. The actions of the immune cells, at the site of infection, will amplify the production of pro-inflammatory cytokines and chemokines, leading to an inflammatory loop of recruitment and pro-inflammation[20,22].

In most cases, the immune system is able to contain the infection and the inflammatory loop ceases, leading to recovery of the individual. However, in severe cases, where immune regulation fails and there is an imbalance of the immune system, this inflammatory loop can lead to a cytokine storm[20,23].

Inflammatory condition

Several clinical findings indicate the similarity between infections caused by the novel coronavirus and SARS-CoV and MERS-CoV, such as fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest

computed tomography (CT) scans. In addition, as in these other conditions, the serum level of pro-inflammatory cytokines is elevated[24].

Cytokines act in inflammatory responses and immune regulation, and are important in resolving and/or limiting the infectious process[25,26]. However, when there is an exacerbated response in this containment, the cytokine high can lead to more tissue damage than even resolution of the problem[25].

The cytokine storm would be this uncontrolled hyperinflammatory response, produced by the immune system[26]. The cytokines IL-1β, IL-1RA, IL-7, IL- 8, IL-9, IL-10, Granulocyte and Macrophage Colony Stimulating Factor (GM-CSF), IFNγ, the granulocyte colony-stimulating factor (G-CSF), IP10 (CXCL10), MCP1, MIP1A, and tumor necrosis factor (TNFα) had the increase, when compared to healthy adults, first detected in the plasmas of patients with COVID-19 by Huang et al.[24]. The same study demonstrated that the cytokines IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNFα were more prominent in ICU patients than in patients who did not require ICU[24]. Additionally, a retrospective study (n = 452) showed that the pro-inflammatory cytokines IL-1, IL-6, TNF-α, the chemokine IL-8, and the anti-inflammatory IL-10 have higher levels in patients with high severity than in those with mild disease[27].

Clinical predictive and inflammatory aspects of ferritin

Since ferritin, has its secretion stimulated by the presence of the inflammatory cytokines IL-1β, TNF-α, IL-1α and the IL-6[6,14]. As already described, IL-6, IL-1β, TNF-α are elevated in patients with COVID-19, especially in severe cases[24,27]. Thus, it is possible that ferritin is an indicator of severity of this pathology, being closely related to the cytokine storm. the hyperinflammation picture

In a meta-analysis of 25 retrospective observational studies (n = 5350)[28], it was shown that C-reactive protein (CRP), pro-calcitonin (PCT), d-dimer, and ferritin are associated with a worsening picture that includes mortality, severe COVID-19, ARDS, and need for ICU care in patients with COVID- 19. Ferritin is independently associated with poor prognosis ($p<0.0001$), ARDS, mortality ($p<0.00001$) and severe disease ($p<0.004$) in COVID-19[29]. Corroborating this idea, Zhi Lin et al.[29] also demonstrated in a retrospective study of 147 patients, that hyperferritinemia is an independent risk factor for severity in COVID-19, being positively correlated with CRP and inversely correlated with lymphocyte count.

This association with lymphopenia may be due to the immunosuppressive effects presented by ferritin, particularly Ferritin H (as already commented)[16]. It seems that this subunit may act on a specific receptor and also induce the production of the cytokine IL-10, which has immunosuppressive effects[16] and is shown to be high in patients with COVID-19, also increasing with disease severity[28], which corroborates a possible relationship between this protein and an immune dysregulation[24,27,30]. Additionally, a retrospective study of 27 patients (with a mean age of 60 years) diagnosed with severe COVID-19 was recorded that inflammatory factors such as ferritin, CRP and IL-2R were significantly elevated in all patients[31]. Moreover, lymphopenia was shown in 71.4% of men and 69.2% of women[31].

Feng Wang et al.[30] performed laboratory tests in patients with different severity levels of COVID-19 (mild, severe and extreme severe) and also reported the significant increase of ferritin in patients as the severity of disease ($p<0.01$), especially when comparing the mild group with the extreme severe group. In addition, CD4+ T cells, CD8+ T cells and B cells gradually decreased with disease severity, showing to be negatively correlated.

Furthermore, ferritin seems to have more than a role as an indicator or consequence of this inflammation, but also actively participates in this process. Ruddell et al. demonstrated in rat hepatic stellate cells (HSC) that ferritin, both H-chain rich (FTH) and L-chain rich (FTL), is more than a consequence of inflammation, but also a mediator of it, through a pathway independent of iron and the TIM-2 receptor[32]. Ferritin leads to an activation of nuclear factor kB (NF-kB), via a signaling cascade, in which phosphorylation of phosphatidylinositol 3-kinase (PI3K), activation of protein kinase zeta, MEK1/2, MAPK and IKK α/β occurs. This activating cascade leads to an induction of NFkB responsive genes, which culminates in increased IL-1β, inducible nitric oxide synthase (iNOS) and RANTES (Regulated by Activation, Normal T Expressed and Secreted, also known as CCL5), which have inflammatory and fibrogenic roles[32].

Soon, the increased synthesis of nitric oxide, due to the increased expression of iNOS and IL-1β, leads to a stimulus for the synthesis of more ferritin, which will act as a perpetuation of the positive feedback[6,12,13]. Although serum ferritin was not used in this study[32], it is likely that it also plays a role similar to that presented by tissue L ferritin and recombinant FT H and L, after all, serum ferritin is mainly composed of L subunits[8,32]. It is noteworthy to point out that ferritin may possess this inflammatory role in other organs that have cell types similar to HSCs, such as the heart, kidneys, pancreas, and even in the lungs[6,32].

Furthermore, Piero et al.[33] performed a work in which they also consider ferritin as a factor of inflammation and not only a consequence of this process. Human macrophages were treated with ferritin and increased expression of genes of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α was observed compared to untreated cells.

In FTH-treated cells, on the other hand, there was a significant increase in the mRNA expression of IL-1β, IL-6, IL-10, TNF-α, IL-12, and NLRP3. In addition, there was an increase in intracellular proteins NRLP3, IL-12 and

IL-1β in these (FTH-treated) macrophages[33]. The latter two also had a significant increase in their expression in the extracellular compartment. Thus, it demonstrated the role of ferritin in pro-inflammation, especially FTH, whereas, FTL was not shown to be effective in triggering the activation of these inflammatory factors[33].

It is worth noting regarding the increase in NLRP3, which is a signaling receptor of the innate immune system[33]. It is a pattern recognition receptor (PRR) that is activated upon recognition of DAMP's and PAMP's, and can undergo activation by a wide variety of stimuli such as fungal, bacterial and viral infections[34,35]. Activation will lead to the formation of the NRLP3 inflammasome, composed of the NRLP3 sensor, the ASC protein and procaspase-1. Thus, this inflammasome activates caspase-1 which will cleave pro-IL-1β and pro-IL-18, leading to the expression of the mature form of these, IL-1β and IL-18[33–35]. After, this there is the development of various inflammatory mechanisms, culminating in a pyroptotic death, like that seen in cytopathic viruses such as SARS-CoV-2[20,33].

Due to the large presence of macrophages in the infected region, and, these being one of the main secretors (sources) of ferritin1, it is likely that most of this protein comes from these cells. In another view, the cellular damage caused by the infectious process is a possible protagonist in the high levels of serum ferritin, which is consistent with its increase during inflammatory processes and with the poor prognosis of disease. This serum ferritin when leaving the damaged cell, releases part of its iron, in an unbound form, which is harmful to health[36].

Acute respiratory distress syndrome

Then, with this exaggerated increase in inflammatory mediators, more inflammatory cells will be recruited to the lungs, generating high infiltration and damage, which will hinder hematosis[25]. Commonly, the cytokine storm, in the alveolar environment, leads to the development of acute lung injury (ALI). After all, the following pro-inflammatory cytokines (IL-6, IL-8, IL-1 β, GM-CSF, ROS) as well as chemokines (such as CCL2, CCL3, CCL-5, IP-10) contribute to ARDS[25].

ALI is characterized by: bilateral pulmonary infiltrates, hypoxia, edema and intralveolar damage, and neutrophil and macrophage infiltration (mentioned above). This condition can progress to a more severe one (whose arterial partial pressure of oxygen/ fraction of inspired oxygen < 200, while for ALI < 300), called acute respiratory distress syndrome (ARDS)[26,37]. Ferritin may prove to be a useful predictor in the illness of ARDS, being elevated both in patients at risk of developing it and in patients with the injury already installed[38].

In an observational study with a group of 1099 hospitalized patients with COVID-19, ARDS was shown to be present in 15.6% of patients with severe disease[39]. So, the relationship between ferritin and ARDS was also shown to be true in patients with COVID-19, as ferritin was shown to be independently associated with acute respiratory distress syndrome[29].

COVID-19 and coagulopathy

Severe COVID-19 is associated with several complications, among these, coagulopathy. The host immune response is required to fight the pathogen, however, an exacerbation of this can lead to disseminated intravascular coagulopathy (DIC)[40]. D-dimer is related to coagulopathy in patients with COVID-19 and composes a significant association of worse prognosis and higher mortality in this pathology[28,41]. In addition to D-dimer, other inflammatory markers such as ferritin and CRP (C-reactive protein) have been shown to be significantly elevated in patients who had thrombotic complications compared to those who did not[42].

In a systematic review, it was reported that the risk of developing venous thromboembolism (VTE) in hospitalized patients with COVID-19 can range from 4.4 to 8.2%, and can be as high as 53.8% in ICU patients[43]. Although it is still unclear how SARS-CoV-2 develops coagulant states, it is more likely that this coagulation is triggered by the hyperinflammatory response, inducing an immunothrombosis, rather than by direct activation of the pathogen to the coagulation cascade[40,44].

Furthermore, high serum ferritin levels, in inflammatory conditions, seem to correlate with a state of hypercoagulation. One possible explanation, would be that during inflammation, the damaged cell releases its ferritin and this protein, in turn, ends up losing some of its iron during this process. This poorly bound iron acts in hypercoagulant states[36,45]. Lipinski et al.[46] demonstrated the role of divalent iron ions in the coagulation process and thrombus formation. According to the experiment, free iron decreased the coagulation time and accelerated the polymerization of fibrin monomers, making them more resistant to fibrinolytic degradation and inhibiting spontaneous fibrinolysis[46].

Furthermore, Ecly et al.[47] demonstrated that trivalent iron, in the form of FeCl3, causes damage to arterial walls, which can also lead to thrombus formation[47]. Thus, the use of iron chelating therapies may be a possible aid in reducing the coagulant state, as well as may also contribute to the reduction of viral replication and inflammatory state, even lowering the ferritin level in patients[48]. Thus, clinical trials are underway (NCT04333550 and NCT04389801) to evaluate the possible efficacy of iron chelators, such as Desferal, as adjunctive therapy in the treatment of COVID-19.

In addition, inflammation and coagulation are known to influence each other, after all, some inflammatory cytokines demonstrate the ability to be pro-coagulant. For example, TNF has a strong pro-coagulant effect, and IL-1 is shown to be an important agonist in tissue factor expression

(in vitro). Besides these, IL-6 shows a pro-coagulant role, even more than TNF[49]. As previously mentioned, these 3 cytokines are significantly elevated in COVID-19 and are also important in the regulation of ferritin.

Association with hyperferritinemic syndromes

Hyperferritinemic syndromes are the set of 4 clinical conditions that share similarities in symptoms, signs and laboratory parameters in common, among these similarities are high ferritin level, hypercytokinemia, fever, among others. The conditions are: Macrophage activation syndrome (MAS), Adult onset Still's disease (AOSD), Catastrophic phospholipid antibody syndrome (cAPS) and septic shock[3]. As with these syndromes, severe COVID-19 can trigger a hyperinflammatory reaction, with high levels of ferritin and cytokines and which can lead to multiple organ failure[3,50]. In addition to these features in common with hyperferritinemic syndromes, severe COVID-19 also has other similarities, such as lymphopenia, coagulopathy, reduced NK activity, fever, ARDS and irregular liver function tests[50].

In fact, severe COVID-19 leads to similar states or even to these syndromes themselves. Evangelos et al.[51] reported that in 28 patients with severe COVID-19 who developed systemic respiratory failure had MAS or immune dysregulation. In addition, the presence of antiphospholipid antibodies and coagulopathy, similar to the cAPS state, has been reported in critically ill patients[52]. Therefore, it is interesting to search and compare the results of therapies that have been shown to be effective in improving these syndromes, in order to analyze their efficacy against COVID-19.

Table 1 - Treatments for hyperferritinemic syndromes that have also been shown to be effective in severe COVID-19 (table modified from Rosario. C et al.[3])

	Corticosteroides	IVIg	Plasma exchange
Severe COVID-19	+++ [53]	++* [54–56]	++ [56–58]
MAS	+++	++	++
AOSD	+++	++	+
cAPS	+++	+++	+++
Septic shock	+/-	+/-	++

+++ first-line treatment recommended in international literature, ++ treatments recommended from case series, ++* case series showing positive effects of its application, but health guidelines not yet recommending it due to lack of information, + treatment used in clinical practice described in case reports, +/- controversial use in clinical practice

Corticoid therapy is used in order to decrease the hyperinflammation triggered by these pathologies. These drugs are able to decrease the migration of leukocytes to the inflamed areas, inhibit vasodilation and vascular permeability at these sites, and modulate T cells[59]. Most of these anti-inflammatory effects are believed to be due to suppression of the activity of pro-inflammatory genes, such as NF-Kb and AP-1[59]. The anti-inflammatory effects of corticosteroids are shown to be important allies in resolving the systemic hyperinflammatory response presented by patients with severe COVID-19, leading to the adoption of this therapy internationally[53].

IVIg consists of the infusion of a product, derived from plasma, rich in combined immunoglobulins from thousands of donors. It is used in the treatment of immunodeficiencies, autoimmune/inflammatory conditions and has also been reported to be used in human models to fight pathogens[54,60,61]. The justification for its use would be the reduction of the inflammatory state. Through a modulation of the immune response, IVIg blocks several pro-inflammatory cytokines, such as IL-6 (high in the pathology of COVID-19), neutralizes auto antibodies, besides being able to expand regulatory T cells[61].

In fact, a case series of 5 patients with severe COVID-19 who received 0.3-0.5g/kg IVIg per day showed improved O_2 saturation, lung lesions, and accelerated recovery from these, after using this therapy[55]. Corroborating the results of these cases, in a retrospective study, Yun Xie et al. reviewed 58 patients with severe or critical COVID-19 who received IVIg application as adjuvant therapy. In patients in whom IVIg was applied within 48 hours of ICU admission, the therapy was able to reduce mechanical ventilation use, decrease hospital length of stay, and even reduce 28-day mortality[54]. Despite these results, due to the paucity of better and larger studies, non-SARS-COV-2-specific IVIg infusion is still not recommended for the treatment of COVID-19 by the National Institutes of Health (NIH) guideline panel, except in clinical trials[53].

The techniques of extracorporeal blood purification are an alternative adjuvant therapy to reduce the hyperinflammatory state, and can act on different targets, such as the reduction of PAMP's, pro-inflammatory cytokines, activated lymphocytes and even toxins of pathogens[62]. Among these techniques is therapeutic plasma exchange (TPE). Khamis et al. reported, in patients with COVID-19, higher extubation rates, lower 28-day mortality, and improved ventilatory parameters

in those (n=11) in whom TPE was applied, compared to the control group (n=20), in which it was not. In addition, there was improvement in laboratory parameters, with a decrease in ferritin, IL-6, D-dimer, and CRP[57]. In fact, blood purification therapies, especially TPE, may be important allies for the improvement of hypercoagulant state, reduction of pro-inflammatory cytokines such as IL-1, IL-6, TNF, G-CSF, and even to reduce endothelial dysfunction, which can be caused by infection, by helping to stabilize endothelial membranes[55,57,58,63].

Because in AOSD there is an overproduction of pro-inflammatory cytokines, such as IL-1 and IL-6, monoclonal antibody drugs antagonistic to the receptors of these cytokines have been used in the treatment of this condition, such as, for example, anakinra and tocilizumab[64,65]. In parallel, COVID-19 also (as already mentioned) shows a significant increase in the level of these pro-inflammatory cytokines[24,27], which are also important for ferritin regulation, just as ferritin can increase the expression of these[32,33]. Therefore, clinical trials are being conducted with IL-1 and IL-6 receptor antagonist monoclonal antibodies (NCT04443881, NCT04603742, and NCT04330638) during the pathology of COVID-19 to evaluate their efficacy.

Among the randomized clinical trials (RCTs) with tocilizumab, most previously performed trials did not find positive results favoring the use of tocilizumab in patients with COVID-19, except the recent REMAP-CAP (n=353)[66], where it showed better outcomes critical adult patients with COVID-19. In that study, participants in the tocilizumab and sarilumab (another IL-6 monoclonal antibody) groups had more days free of organ support compared to the control group, in addition to improved survival in the secondary endpoint analysis[66]. Despite this positive result, the meta-analysis in the RECOVERY group study of these 8 previous RCTs showed no significant difference in 28-day mortality in patients treated with tocilizumab, even with the inclusion of REMAP-CAP.

However, more recently, in that same RECOVERY group study[66], 4116 patients (largest sample size of trials conducted with tocilizumab to date) adults with hypoxia and systemic inflammation were randomized, 82% of these patients were using systemic corticosteroids. In the group receiving tocilizumab, there was a significant reduction in 28-day death compared to the group receiving usual treatment alone (31% vs 35%; rate ratio 0.85; 95% confidence interval, 0.76-0.94; p=0.0028)[67]. In addition, tocilizumab also increased the probability of 28-day hospital discharge compared to the control group (57% vs 50%; rate ratio 1.22; 1.12-1.33; p<0.0001)[67].

Regarding IL-1 antagonists, anakinra (ANK) has been showing improvement in the status of severe patients with COVID-19 in several series, a retrospective cohort study[68] showed that in the group where anakinra was administered there was a significant decrease in the need for mechanical ventilation and mortality of severe patients with COVID-19. Indeed, ANK seems to be effective in improving respiratory function in patients with COVID-19 and reducing uncontrolled inflammation (being associated with reduced CRP levels)[68,69]. Therefore, randomized controlled trials to confirm this association and evaluate the use of this therapy are of interest.

FINAL CONSIDERATIONS

Therefore, it has become critical to use better clinical tools to treat and assess patients, assisting in decision making and reducing mortality. The source of the elevated ferritin levels during inflammation in COVID-19 is still not entirely clear. However, evidence suggests that this elevation originates from both the macrophages present in the region of inflammation/infection, and the cellular damage caused by these processes, which causes the cell to release its ferritin content, and the latter, release some of its iron. Therefore, given its ability to be regulated and also stimulate the production of pro-inflammatory cytokines, it is likely that the significant elevation of ferritin according to the severity of COVID-19 is not only a consequence of inflammation, but also a protagonist of the inflammatory process. Taking this into account, monoclonal antibody therapies antagonizing IL-1 and IL-6 receptors, the main pro-inflammatory cytokines elevated in COVID-19 and which also regulate and undergo stimulation by ferritin, deserve better attention. After all, the robust RCT (from the RECOVERY group) of tocilizumab has shown its efficacy in reducing mortality, which makes it an important therapeutic ally. As for anakinra, it is still necessary to be cautious and await the results of randomized controlled trials. Besides, the similarity of severe COVID-19 with hyperferritinemic syndromes and good response to therapies applied in these syndromes, may add possible strategies to improve severe patients and reduce hospitalization time. Finally, ferritin and its pro-inflammatory and immunomodulatory properties should be better studied, to improve the understanding of the consequences of its elevation and even for the development of protocols and possible therapeutic strategies.

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