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REVIEW ARTICLE

Serum Ferritin and its Importance for SARS-CoV-2-Infected Patients

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SUMMARY

Background: **Serum ferritin is an acute-phase protein whose level is increased in several inflammatory diseases. This review describes the structure and function of ferritin as well as its association with the prognosis of patients with COVID-19.**
Methods: **We searched MEDLINE/PubMed databases, Scopus, and Web of Science for prospective and review articles that examined ferritin and its association with COVID-19 severity. Based on all these articles and clinical experience, a review was constructed and full texts of the articles that were retrieved were accessed.**
Results: **All COVID-19 related studies conducted in 2020, which performed serum ferritin testing, clearly showed ferritin as a biomarker of COVID-19 severity in hospitalized patients. Ferritin levels in severe patients were significantly increased relative to those in non-severe patients ($p < 0.001$). Non-survivors had significantly higher ferritin levels than the survivors ($p < 0.001$).**
Conclusions: **Determination of ferritin levels was specific and sensitive for early disease severity prediction in patients with COVID-19. Serum ferritin can also be used for predicting the response to COVID-19 vaccines.**
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INTRODUCTION

A new RNA coronavirus was detected in the city of Wuhan, the capital of the Hubei province, China, in early December 2019 as the cause of a cluster of pneumonia cases [1]. The disease spread widely throughout China and across the world, leading to a viral pandemic. Zhu et al. isolated the virus from human epithelial airway cells and designated it as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), previously known as 2019-nCoV [1]. Subsequently, the World Health Organization (WHO) announced coronavirus disease 2019 (COVID-19) as a global health emergency in February 2020 [2].
Most patients infected with SARS-CoV-2 show a mild disease and typical symptoms including dry cough and

high fever. Other symptoms include shivering with chills, diarrhea, hemoptysis, sore throat, headache, loss of taste, loss of smell, and muscle pain [3]. A small percentage of the patients develop severe acute respiratory distress syndrome, and some show multiple organ failure in a short period and death, especially elderly patients with comorbidities [4]. Early identification of severe COVID-19 is thus important for the timely triage of patients [5].

In the ongoing global pandemic, COVID-19 needs to be classified based on the clinical and laboratory indicators of disease development as severe and fatal types. These predictors can promote risk stratification, direct intervention to concentrate on patients at risk of developing severe disease, and to improve allocation of the available technological and human resources. Furthermore, laboratory criteria can differentiate if a patient is a severe case and determine the mortality risk, which will increase the clinical situation awareness [6].

Ferritin, a ubiquitous iron-binding protein, is an immune dysregulation mediator that exerts direct immunosuppressive and pro-inflammatory effects on the cytokine storm under excessive hyperferritinemia [7]. In 1937, ferritin was first isolated from horse spleens, where it is stored in high amounts [8]. Evaluation of human serum ferritin was achieved in 1972 with the improvement of delicate immunoassay methods [9]. Since then, the serum ferritin test has become a useful and easy means of evaluating intracellular iron levels [10]. Techniques that can predict the progression of severe disease are of great benefit for the treatment and prognosis of SARS-CoV-2 infection. Development of these techniques depends on the understanding of disease pathogenesis. They may also help to develop vaccination methods and to identify potential therapeutic targets [11]. Therefore, in this study, we briefly reviewed the publications supporting the hypothesis that ferritin levels may be associated with the severity of COVID-19 and attempted to examine its role as a novel prognostic marker that could improve the clinical outcomes of patients. Such efforts can help speed up the diagnosis and early treatment of patients at the early in their clinical symptoms.

Ferritin structure and function

Ferritin is a spherical nanocage protein composed of two subunits, H and L; in various tissue types, 24 of these subunits are assembled in a characteristic manner to form apoferritin (the iron-free form of ferritin; the term ferritin or holoferritin indicates iron-containing apoferritin), which is found in body fluids, particularly in blood plasma and serum [12,13]. Ferritin is found in the blood and within cells and functions as an iron-binding protein [14]. Apoferritin acts as a vehicle for ferric iron and stores it as a ferrihydrite mineral; it has a characteristic shape forming a roughly spherical shape, as shown in Figure 1 [15]. The outside components of apoferritin are composed of 24 H and L subunits. The ratio of these subunits differs based on the tissue type and can be changed under inflammatory and infectious conditions. In H-subunit rich tissues (mainly the heart and kidney), the ratio of the H subunit to the L subunit increases, whereas it decreases in L-subunit rich tissues (predominantly the liver and spleen) [16]. Each molecule of the apoprotein is approximately 450,000 Da. The L monomer has 174 amino acids with a molecular weight of 18,500 Da; the H monomer features 182 amino acids with a molecular weight of 21,000 Da.

Iron homeostasis is critical for the well-being of cells and tissues, and ferritin is a major iron regulator, as shown in Figure 2 [16]. Iron sequestration occurs due to the action of the enzyme ferroxidase. Ferritin can act as a ferroxidase and function as an iron sequestrator, leading to the conversion of Fe(II) to Fe(III), as iron is internalized and sequestered in the binding sites of ferritin, thus preventing the generation of reactive oxygen species that are harmful to cellular systems, which can be induced by the ferric Fe(II) iron state [16].

Oxidation of Fe(II) to Fe(III) protects cells from hydroxyl free radicals by the utilization of Fe(II) and catalyzing the conversion of hydrogen peroxide (a product of mitochondrial oxidative respiration), which prevents the production of the highly toxic hydroxyl free radicals in the Fenton reaction. Cellular ferritin also serves as a store of iron ions, as oxidation of Fe(II) to Fe(III), leads to its deposition in the ferritin cavity in a mineral form [17]. Overall, the oxidation of Fe(II) to Fe(III) is catalyzed by the ferroxidase activity of the H-subunit, whereas the L-subunit contributes to Fe(III) incorporation into the ferritin core [18].

Iron toxicity and reactive oxygen species generation are decreased due to ferritin-mediated capture and buffering. The intracellular iron pool prevents damage to the cellular system, thereby allowing organism survival. For instance, a homozygous mutation in ferritin H in a murine knockout resulted in a lethal phenotype.

Extracellular ferritin is found in the serum and it acts as a significant diagnostic marker for monitoring and assessment of iron levels. However, despite its routine use in clinical medicine, the exact source of serum ferritin is yet to be identified. The preponderance of serum ferritin is immunologically related to ferritin L. A mutation in the ferritin L gene results in increased serum ferritin levels, or hyperferritinemia. Increases in the serum levels of H-type ferritin have also been found in some pathophysiological settings [19].

Iron levels in the body can be assessed using serum ferritin concentrations; for instance, low ferritin concentrations indicate iron deficiency, whereas high ferritin concentrations indicate iron overload [12,20]. Thus, serum ferritin is used as a clinical biomarker to assess the depletion or overload of iron stores. However, ferritin is also influenced by acute-phase reactants; it thus represents an acute phase protein that is upregulated in both infectious and non-infectious inflammation [21]. Thus, iron status assessment based on serum ferritin concentration is confounded in the setting of inflammation [20]. Therefore, in addition to biomarkers of inflamma-

tion such as CRP biomarkers, soluble transferrin receptor or transferrin saturation are important because they are influenced by inflammation to a lesser degree compared to serum ferritin [20,22].

Ferritin concentration during inflammation following COVID-19

The cause of elevation in serum ferritin concentration and the potential role of this protein in inflammation following the development of COVID-19 remain unclear. The level of certain inflammatory markers such as procalcitonin, C-reactive protein, erythrocyte sedimentation rate and serum amyloid A have been identified in a study with COVID-19 patients. Over the last few decades, ferritin has emerged as a vital molecule in the immune system, and its function as an acute phase reactant has been described and thoroughly reviewed [23]. However, despite the fact that hyperferritinemia has been linked to complications in other viral diseases like dengue fever, ferritin has received little recognition [24]. In addition, higher levels of ferritin are associated with the development of macrophage activation syndrome (MAS) in adult-onset Still's disease (AOSD), the most frequent life-threatening complication for these patients [25]. Furthermore, elevated levels of ferritin are correlated with mortality in MAS patients [26]. Likewise, in sepsis, elevated levels of ferritin are associated with more severe patients at high risk with poor prognosis [27]. This link between elevated levels of ferritin and a more aggressive subset of these diseases indicates the potential pathogenic function of this molecule as suggested in hyperferritinemic syndrome [28]. Hyperferritinemic syndrome comprises four inflammatory diseases - AOSD, MAS, sepsis, and catastrophic anti-phospholipid syndrome - and studies on this syndrome have suggested that ferritin could be a pathogenic mediator enhancing the inflammatory process [28].

Numerous studies have shown that increased levels of serum proinflammatory cytokines are correlated with pulmonary inflammation and severe lung damage in SARS and Middle East Respiratory Syndrome coronavirus (MERS-CoV) and recently COVID-19 infections [29-31]. Patients infected with the novel coronavirus, defined as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), establish COVID-19 disease, which can potentially cause pneumonia and damage to the lung, heart and kidneys. Inflammatory cytokine storms have been identified as the primary cause of death, which is defined by the excessive and unregulated release of pro-inflammatory cytokines, as documented in other infections caused by pathogenic coronaviruses [32]. For instance, inflammatory cytokines released by macrophages (IL-6, IL-10, and TNF) increase in patients with extreme COVID-19 disease, resulting in lung and another organ damage [31].

However, more studies are required to ascertain the cause of increased plasma ferritin concentration and the possible function of this protein in inflammation following the development of COVID-19 disease. Active ferritin formation can occur during inflammatory diseases (Figure 3) [21-23]. Macrophages that generate cytokines and account for the majority of immune cells in the lung parenchyma may be responsible for serum ferritin secretion [23].

In addition, ferritin synthesis may be induced by many inflammatory agents, including cytokines such as IL-6. Interestingly, elevated concentrations of IL-6 in COVID-19 patients were associated with disease severity [33]. So, as ferritin can be deliberately secreted at the site of infection, it is likely that ferritin may have other roles aside from its classical role as an iron storage protein. Accumulated results included the role of ferritin as a signaling molecule and as a direct mediator of the immune system [23]. Since cytokines may induce ferritin expression and ferritin can induce the expression of pro- and anti-inflammatory cytokines, complex feedback pathways between ferritin and cytokines in the regulation of pro-inflammatory and anti-inflammatory mediators can occur, as presented in Figure 3 [23]. There is controversy between various schools of thought on the pathogenic effect of ferritin in inflammation. The composition of plasma ferritin in COVID-19 patients will be a promising field for future study [21]. Ferritin consists of two distinct subunits, H and L. Several studies have indicated that inflammatory stimuli drive H subunit expression and that H-ferritin can act as an immunomodulatory molecule with both pro-inflammatory and immunosuppressive properties [21-23].

Finally, if ferritin is implicated as a pathogenic mediator in COVID-19, strategies such as therapeutic plasma exchange can be useful for patients afflicted with SARS-CoV-2, as it will reduce ferritin and cytokine levels.

Role of ferritin in COVID-19

Several retrospective studies have shown that inflammatory characteristics are biomarkers in SARS-CoV-2-infected patients (Table 1). Ferritin concentrations recorded for patients with COVID-19 upon hospital admission indicate average concentrations within the normal range (30 - 400 µg/L) in non-severe patients. However, patients with severe disease on admission showed hyperferritinemia (ferritin level > 400 µg/L) [34] with average ferritin concentrations greater than 800 µg/L. Furthermore, in patients who were diagnosed as critically ill, the admission levels of ferritin were between 1.5 and 5.3 times higher than those in patients with a lower severity of COVID-19 [35,36].

Studies comparing the admission levels of ferritin among patients with COVID-19 who did not survive and patients who had been discharged following successful treatment are presented in Table 1. These studies reported that the ferritin levels on admission in non-surviving patients were approximately 1,400 µg/L, which were 3 - 4 times higher than those in the survivors.

Table 1. Ferritin levels in patients with non-severe and severe COVID-19.

Disease	Study	Set-ting	Sample Size	Non-Severe disease			Severe disease			p- value	Comments
				n	Avg. age (years)	Avg. ferritin (µg/L)	n	Avg. age	Avg. ferritin (µg/L)		
Covid-19 diagnosis by RT-PCR assay for respire-tory specimens	Zhou et al. 2020 Ref. [37]	China	50	38	41.7	135.6	12	48.2	207.8	< 0.001	Serum ferritin levels can be measured and used as clinical markers for predicting disease severity in patients diagnosed with COVID-19
	Chen et al. 2020 Ref. [31]	China	21	10	52	337.4	11	61	1,598.2	0.049	Higher ferritin values in severe cases suggest an increased level of systemic inflammation in these patients and correlate with disease severity
	Wang et al. 2020 Ref. [11]	China	65	30	52.2	821.1	35	62	1,368	< 0.01	Ferritin correlation with disease severity. Ferritin levels could clearly distinguish between mild and extremely severe disease groups
	Qin et al. 2020 Ref. [32]	China	49	34	38	318.1	15	57	907.4	< 0.001	Ferritin > 400 µg/L acts as a risk factor for progression to severe disease
	Liu et al. 2020 Ref. [33]	China	80	11	31	155.7	69	56	827.2	< 0.001	The level of IL-6, CRP, LDH, and ferritin was closely related to the severity of COVID-19. CRP and ESR were higher in patients with severe disease. IL-6 correlated with lung damage, body temperature, CRP, and ferritin. With the remission of disease, ferritin, CRP, and IL-6 levels were decreased
	Zhou et al. 2020 Ref. [38]	China	191 patients, 137 survivors, 54 non-survivors	137	52	503.2	54	69	1,435.3	< 0.001	Ferritin was clearly elevated in non-survivors compared with that in survivors on admission as well as throughout the clinical course, and was increased with illness deterioration. In univariate analyses, higher levels of ferritin were associated with higher odds of death
	Bai et al. 2020 Ref. [39]	China	127 patients, 91 survivors, 36 non-survivors	91	50	500	36	67	1,900	< 0.001	Non-survivors had higher CRP and IL-6 levels on admission, but not ESR (which was high in both groups)

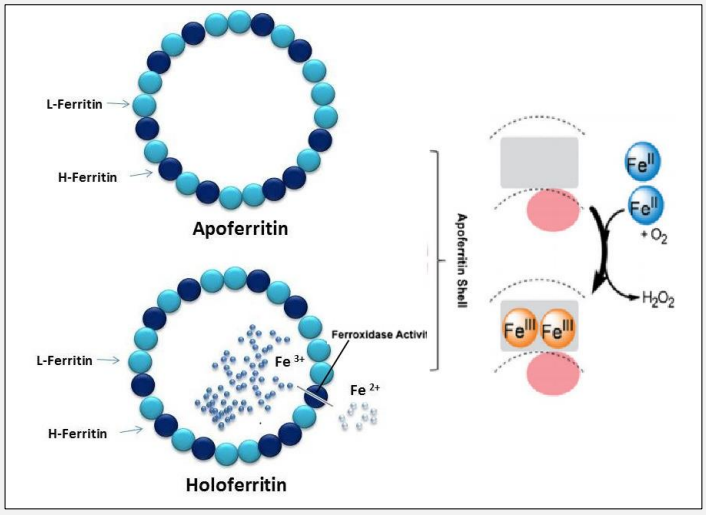

Figure 1. Ferritin Structure: Apoferritin forms a roughly spherical container within which ferric iron is stored as a ferrihydrite mineral.

Apoferritin describes the iron-free form of the protein, whereas the iron-containing form is termed as holoferritin or simply, ferritin [15]. The apoferritin shell is composed of 24 subunits of two types, termed H and L, the ratio of which varies widely depending on the tissue type and inflammation. One O_2 molecule is consumed for the simultaneous oxidation of two Fe(II) ions (blue spheres) in the ferroxidase center to form an intermediate peroxodiferric species, which subsequently decays to Fe(III) and hydrogen peroxide. Iron is toxic in cellular systems because of its capacity to generate reactive species (shown as yellow spheres) which can directly damage DNA and proteins [15,16].

The impact of COVID-19 severity on serum ferritin levels

Zhou et al. examined the association of COVID-19 prognosis with iron homeostasis [37] and found that iron homeostasis was closely correlated with the incidence of severe COVID-19; it was specific and sensitive for the early prediction of the disease severity and was therefore clinically useful. According to their findings, hepcidin and serum ferritin levels were higher in patients diagnosed with extreme COVID-19 than in the other groups ($p < 0.001$). Combined tests for hepcidin and serum ferritin offered the best specificity and sensitivity for predicting COVID-19 prognosis. They found that tandem tests of hepcidin and serum ferritin predicted COVID-19 intensity with 94.6% precision, whereas parallel tests of hepcidin and serum ferritin had 95.7% sensitivity [37].

In a retrospective analysis examining the clinical, immunological, and laboratory characteristics of 21 patients diagnosed with COVID-19 by Chen et al., results in agreement with the above findings were obtained [31]. The patients were graded as extreme and moderate based on the guidelines issued by the National Health Commission of China (11 and 10 cases, respectively). Of these, 12 patients had serum ferritin values > 800 μg/L (normal range: 30 - 400 μg/L, including nine patients classified as extreme and three patients classified as moderate. Overall, the median values in patients identified as extreme were 4.7-fold higher ($p = 0.049$). Furthermore, the blood levels of additional inflammatory biomarkers, including high-sensitivity CRP (hsCRP, median: 6.3-fold higher; $p = 0.003$), IL-6 (median: 2.7-fold higher; $p = 0.040$), and procalcitonin (median: 3.6-fold higher; $p = 0.059$) also appeared to be higher in severe cases than in mild cases. These findings indicate a relatively higher degree of systemic inflammation in COVID-19, and suggest that higher inflammatory biomarkers correlate with disease severity [31,37].

In a study by Wang et al., a total of 65 SARS-CoV-2-positive patients were graded as mild, severe, and ex-

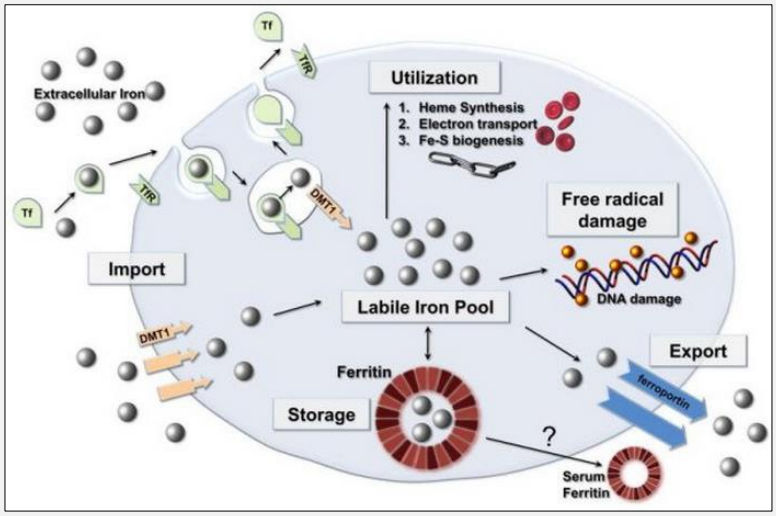

Figure 2. Intracellular Iron Homeostasis: Ferritin functions as a ferroxidase, converting Fe (II) to Fe (III) as iron is internalized and sequestered in the ferritin mineral core.

Reactive species (shown as yellow spheres) can directly damage DNA and proteins. DMT1 - divalent metal ion transporter 1, Tf - transferrin, TfR - transferrin receptor [16].

tremely severe (n = 30, 20, and 15, respectively) [11]. The levels of a few typical markers including lactate dehydrogenase, D-dimer, and ferritin were increased in extreme and highly serious patients. With increased disease incidence, the absolute numbers of CD4+ T cells, CD8+ T cells, and B cells steadily decreased. Furthermore, in a retrospective study of clinical mortality predictors in 49 patients, higher levels of ferritin were associated with the occurrence of fatal diseases relative to patients who were discharged [32]. Liu et al. found that the baseline levels of IL-6, CRP, LDH, and ferritin were closely related to the severity of COVID-19, and the elevated IL-6 level was significantly related to the clinical manifestations of patients with severe disease. Reduction in IL-6 was closely linked with treatment efficacy, whereas an increase in IL-6 showed an aggravation of the illness. This complex variance in IL-6 levels can be used collectively for disease monitoring in patients with extreme COVID-19 [33]. According to a large retrospective study by Zhou et al., the levels of d-dimer, high-sensitivity cardiac troponin I, serum ferritin, lactate dehydrogenase, and IL-6 were clearly elevated in non-survivors compared with those in survivors throughout the clinical course. In addition, they were further increased with illness deterioration, showing a significant difference between the two groups ($p < 0.0001$) [38]. Bai T et al. also noted that inflammatory biomarkers such as C-reactive protein, ferritin, procalcitonin, and interleukin-6 levels, in patients who had died were significantly elevated on admission compared to those in the cured patients ($p < 0.001$ for all) [39]. However, no significant changes were observed in the erythrocyte sedimentation rates recorded at admission [39].

DISCUSSION

The role of systemic hyperinflammation as a major cause of death has recently been highlighted in coronavirus disease-2019 (COVID-19) [40]. An inflammatory response is elicited in patients with COVID-19 by repeated replication of the virus, cellular destruction, and multi-organ damage. Overwhelming systemic inflammation is accompanied with a virus-induced cytokine storm, and this affects a subgroup of patients with severe COVID-19, leading to pulmonary inflammation

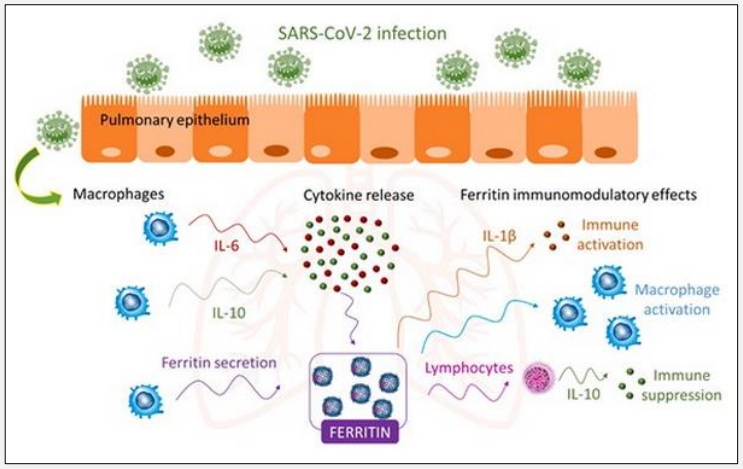

Figure 3. Potential role of ferritin during inflammation following COVID-19 infection.

Active ferritin production by macrophages and cytokines may lead to hyperferritinemia, which, in turn, might promote the production of several pro-inflammatory (IL-1β) and anti-inflammatory cytokines (IL-10) [21,23].

and severe lung damage; these patients are characterized by elevated ferritin levels [40,41]. In patients with extreme COVID-19 (2,817.6 ng/mL), a marked increase in ferritin levels was observed relative to those in patients with non-severe disease (708.6 ng/mL) [37]. These results confirm what is already known regarding the prognostic significance of this iron storage protein in other inflammatory diseases [25].

The connection between COVID-19 severity and the degree of inflammatory response has been identified in several studies [42,43]. Of the reported biomarkers, ferritin appears to have the potential to determine the disease severity in patients with COVID-19 patients; however, it is also detected in other infectious and non-infectious diseases [44,45]. In this review, we compared the pathological changes in serum ferritin and its potential as a biomarker in various diseases, especially COVID-19.

Ferritin is a protein that stores iron; its serum level represents the natural level of iron and helps detect iron deficiency anemia. During viral infections, circulating ferritin levels increase, and may be a marker of viral replication [46]. Increased ferritin levels have also been reported in patients with severe COVID-19 due to cytokine storm and secondary hemophagocytic lymphohistiocytosis (sHLH) [47]. Many inflammatory cytokines such as IL-6, TNF-α, IL-1β, IL-12, and IFN-γ, which trigger hepatocytes, Kupffer cells, and macrophages to secrete ferritin, are rapidly generated during the cytokine storm in COVID-19 [14]. The unregulated and dysfunctional immune response associated with macrophage activation, hyperferritinemia, and thrombotic storm eventually result in multiple organ destruction. Ferritin is not only an outcome of uncontrolled inflammation but also plays a pathogenic role in the inflammatory pathway by binding to the T-cell immunoglobulin and mucin domain 2 (TIM-2) and inducing the expression of multiple downstream pro-inflammatory mediators. In addition, some reports have shown that macrophages are triggered by the H chain of ferritin to secrete inflammatory cytokines [21].

Serum ferritin is usually used to evaluate iron metabolism or to diagnose a patient with anemia; further, it is an acute-phase protein in both infectious and non-infectious inflammatory diseases [20-22]. Ferritin is found to be extremely increased in patients with critical conditions, either due to macrophage activation syndrome or sHLH [23]. As it is related to the disease severity, it can be helpful as a biomarker for both macrophage activation syndrome and sHLH; it can also provide an estimate of treatment effectiveness [48].

Indeed, its levels in the liver and macrophages are increased by the inflammatory process, as ferritin transcription is affected by IL-1β, IL-6, and IFN-γ, which

upregulate ferritin gene transcription by increasing the binding of nuclear factor-KB to FER2 upstream of the iron-responsive element and coding region [23,44]. Ferritin can then promote intracellular inflammatory pathways, regardless of its iron content, leading to the activation of NF-κB. Ultimately, ferritin stimulation results in increased expression of pro-inflammatory mediators such as IL-1β and inducible nitric oxide synthase [49]. In this review, we determined the effectiveness of serum ferritin as an inflammatory marker for COVID-19. An increase in serum ferritin was observed in patients who did not survive treatment compared to that in patients who recovered from COVID-19. This increase can be associated with secondary bacterial infection, leading to the exacerbation of COVID-19 [50]. Usually, an increase in serum ferritin occurs due to viral or bacterial infection, hemochromatosis, or long-term blood transfusion. Studies have also shown that a microbial infection secondary to a pre-existing viral infection also causes increases serum ferritin levels [51].

Finally, in SARS-CoV-2 affected patients, treatments such as therapeutic plasma exchange could be useful if ferritin is involved in COVID-19 as a pathogenic mediator, as this would decrease the ferritin and cytokine levels. Plasma exchange is an automatic procedure by which the plasma of the recipient is replaced with donor plasma; this strategy has been shown to be very beneficial in certain diseases. Notably, most studies included in this review were performed in Wuhan during the early phase of the outbreak. The patients included in these were thus at the frontline of the pandemic; further, SARS-CoV-2 itself may have undergone improvement in virulence during human-to-human transmission. Therefore, multi-center trials with larger sample sizes and in different countries are required to examine hyperferritinemia in patients with COVID-19. Based on the abovementioned findings, we suggest that longitudinal ferritin monitoring during hospitalization could help distinguish critical patients and determine the progression of COVID-19 towards a worse clinical prognosis.

Serum ferritin thus appears to have a strong value for assessing patients with COVID-19, even though a complete understanding the disease remains elusive. Further, the relevance of serum ferritin levels in asymptomatic patients or in patients with mild COVID-19 remains unknown. Therefore, even though serum ferritin is effective as a marker for COVID-19 progression to critical disease, its use as a reliable marker to determine treatment effectiveness remains uncertain. Additional in-depth studies are thus needed to clarify whether serum ferritin plays a crucial role as a biomarker of disease prognosis in patients with COVID-19 patients. Furthermore, based on reviews of influenza vaccination studies, serum ferritin could also be used as a predictive biomarker for predicting the response to SARS-CoV-2 vaccines [52,53].

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