Ferritin as a Marker of Severity in COVID-19 Patients: A Fatal Correlation

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ABSTRACT **Background:** Ferritin, the cellular protein storage for iron, has emerged as a key molecule in the immune system, orchestrating the cellular defense against inflammation. At the end of 2019, the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) rapidly spread throughout China and other countries around the world, resulting in a viral pandemic.

Objectives: To evaluate the correlation between ferritin and disease severity in coronavirus disease-2019 (COVID-19).

Methods: In this cross-sectional study, we obtained clinical and laboratory data regarding 39 hospitalized patients with confirmed COVID-19 from two hospitals in Israel.

Results: A significant increase in ferritin levels was demonstrated in patients with moderate and severe disease, compared to patients with mild disease (P = 0.006 and 0.005, respectively). Severe patients had significantly higher levels of ferritin (2817.6 ng/ml) than non-severe patients (708.6 ng/ml) P = 0.02.

Conclusions: In this preliminary cross-sectional study, elevated ferritin levels were shown to correlate with disease severity in 39 patients from Israel with confirmed COVID-19 infection. Our results further strengthen the hypothesis that severe COVID-19 disease might be due to an underlying dysregulated hyperimmune response. In order to identify these patients early and prioritized resources, we believe that all patients with COVID-19 should be screened for hyperferritinemia.

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Ferritin, a ubiquitous and highly conserved iron-binding protein, was first isolated from horse spleens in 1937 [1]. The quantification of serum ferritin in human was documented only in 1972, with the development of sensitive immunoassay techniques [2]. Since then, measuring serum ferritin has become a useful and convenient method to assess the status of intracellular iron [3]. In the last few decades, ferritin has emerged as a key molecule in the immune system, and its role as an acute phase reactant has been revealed and extensively reviewed [4-7].

At the end of 2019, a novel enveloped RNA coronavirus emerged as the cause of a cluster of pneumonia cases in Wuhan city, the capital of Hubei province in China [8]. It quickly spread throughout China and to other countries around the world, resulting in a viral pandemic. The virus was isolated from human airway epithelial cells by Zhu and colleagues [8] and named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), previously referred to as 2019-nCoV. In February 2020, the World Health Organization (WHO) declared coronavirus disease-2019 (COVID-19) as a public health emergency [9].

Understanding of COVID-19 epidemiology, clinical and laboratory features, as well as diagnosis and treatment, is still evolving. The disease caused by SARS-CoV-2 is known to cause varying degrees of illness [10]. Severity ranges from asymptomatic infection or mild disease characterized by dry cough, fever, dyspnea, and fatigue, to critical illness with respiratory failure, acute respiratory distress syndrome (ARDS), and death.

Retrospective studies from China have described several risk factors for severe disease and death, including older age, male gender, and certain co-morbidities [11,12]. In addition, some laboratory features, particularly lymphopenia and elevated D-dimer, have been shown to correlate with a deleterious outcome [13]. Recent data on the immunological features of COVID-19 underlined the importance of subpopulations of T lymphocytes in the different stages of the disease [14]. The cytokine milieu belonging to the IL-1 and IL-6 family was associated with more severe disease [15,16]. The potential role of anti-inflammatory drugs in the treatment of critical COVID-19 patients was noted [17].

In light of these new findings, and considering the pivotal role of ferritin in infection and inflammation, we aimed to evaluate the correlation between ferritin and disease severity in COVID-19, hoping to find a novel prognostic marker that would predict the clinical outcomes in ill patients. Such an endeavor may help with rapid diagnosis and timely treatment for patients at the onset of their clinical symptoms.

PATIENTS AND METHODS

STUDY OVERSIGHT

The study was approved by the institutional review boards of Assuta Ashdod Medical Center and of Sheba Medical Center. It was performed in accordance with the ethics standards laid down in the 1964 Declaration of Helsinki and its later amendments. Data were analyzed and interpreted by the authors. All of the authors reviewed the manuscript and confirmed the accuracy and completeness of the data.

DATA COLLECTION

In this cross-sectional study, we obtained data regarding 39 patients with confirmed COVID-19 from two hospitals in Israel: Assuta Ashdod and Sheba medical centers. We reviewed the medical records and compiled data for hospitalized patients between 21 February 2020 and 30 March 2020. Clinical outcomes were followed until 31 March 2020. COVID-19 was diagnosed on the basis of the interim guidance issued by the WHO [18]. Confirmed cases of COVID-19 were defined as a positive result on polymerase-chain-reaction (PCR) assay of nasal and pharyngeal swab specimens. One patient was diagnosed using sputum sample. Only PCR confirmed cases were included in the analysis. Laboratory findings were obtained from electronic medical records. All laboratory tests were performed according to the clinical care needs of the patient. Laboratory assessments consisted of a complete blood count, blood chemical analysis including liver and renal function, electrolytes, C-reactive protein (CRP), lactate dehydrogenase, creatine kinase, and ferritin. Chest X-rays were reviewed by the authors who extracted the data. Data were entered into a computerized database and checked by two physicians. If data were missing from the records or clarification was needed, we obtained data by direct communication with attending doctors and other healthcare providers.

STUDY DEFINITIONS

We defined the degree of severity of COVID-19 at the time of admission using the Report of the WHO-China Joint Mission on COVID-19 [19].

- Mild disease included non-pneumonia and pneumonia cases
- Moderate disease was defined as dyspnea, respiratory frequency ≥ 30/minute, blood oxygen saturation ≤ 93%, PaO2/FiO2 ratio < 300, and/or lung infiltrates > 50% of the lung field within 24–48 hours
- Severe or critical disease was defined as respiratory failure, septic shock, and/or multiple organ dysfunction/failure

STATISTICAL ANALYSIS

Variables were initially compared using the non-parametric Kruskal–Wallis H because of a non-normal distribution. Sequential Mann-Whitney tests were used for further investigation. Descriptive statistics, comparison, and graph plotting were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 for Macintosh (SPSS, IBM Corp, Armonk, NY, USA).

CHARACTERISTICS AND DEMOGRAPHICS OF THE STUDY POPULATION

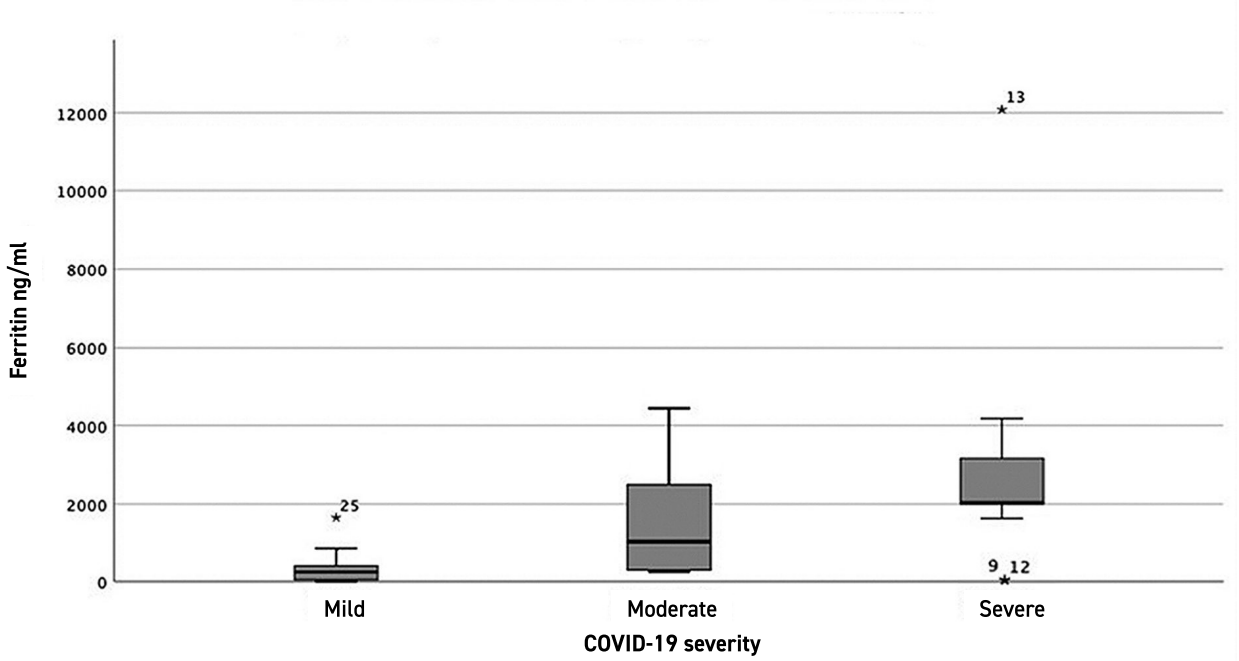
A total of 39 participants were enrolled in an attempt to recognize a simple yet efficient bio-marker for COVID-19 severity. Patient ages ranged from 19 to 82 years (mean 52.46 ± 2.76 years), which distributed unevenly and not normally across different age groups. Male gender was more frequent (n=23, 59%) than female gender (n=16, 41%). One-fifth of the cohort were smokers (n=8, 20.5%) , yet fewer than half of the patients were considered healthy without any history of chronic disease, (n=17, 43.6%) [Table 1].

Table 1. Characteristics and demographics of the study population

Variable	Statistic	
Age (years)	**Frequency**	**Percent**
≤ 19	1	2.6%
20–29	4	10.3%
30–39	6	15.4%
40–49	3	7.7%
50–59	10	25.6%
60–69	8	20.5%
	Mean (Std. error)	Range (Min–Max)
Total	52.46 (2.76)	63 (19–82)
Gender		
Female	16	41%
Male	23	59%
Smoking		
Non-smoker	31	79.5%
Smoker	8	20.5%
Hospital		
Assuta Ashdod	17	43.6%
Sheba (Tel Hashomer)	22	56.4%
Co-morbidities		
Healthy	17	43.6%
Non-healthy	22	56.4%

Std. error = standard error, Min = minimum, Max = maximum
Co-morbidities include a prior diagnosis of at least one condition: chronic obstructive pulmonary disease, diabetes mellitus, dyslipidemia, hypertension, inflammatory bowel disease, ischemic heart disease, multiple myeloma, lymphoma, rheumatoid arthritis, scleroderma, scleroderma

Figure 1. Ferritin levels by COVID-19 severity. Simple boxplot of ferritin ng/mg by COVID-19 severity
Comparing ferritin levels across different disease severity using the Kruskal–Wallis H test revealed a significant difference ($P = 0.003$). Further comparisons using the Mann-Whitney procedure reveled significant increase in ferritin levels, for both the moderate and severe disease severity groups, in comparison to the mildly ill group ($P = 0.006$ and 0.005, respectively). We did not find a significant difference between the moderate and severe disease groups ferritin levels ($P = 0.513$ and $P = 0.101$ after excluding extremely deviant cases)



RESULTS

COVID-19 SEVERITY AND THERAPY CHARACTERISTICS

In our study, 51.3% (n=20) of the patients were considered to have a mild COVID-19, 21.3% (n=9) were considered to have moderate disease, and the remaining 25.6% (n=10) presented with severe disease, which required invasive ventilation. Plain chest X-rays were normal in 41% (n=16), while abnormal X-rays, unilateral or bilateral infiltrates, were demonstrated in 15.4% (n=6) and 43.6% (n=17), respectively. Only 15.4% of the patients required vasopressor support. [Table 2].

FERRITIN LEVELS BY COVID-19 SEVERITY

The mean ferritin level of the entire study sample was 1249.37 ng/ml (SD-2176.34), with a range of 12709, starting from 6 ng/ml and toping at 12085 ng/ml. Patients with mild disease had the lowest ferritin level with a mean of 327.27 ng/ml, followed by patients in the moderate group with a mean of 1555 ng/ml. The severe group had a mean ferritin level of 2817.6 ng/ml. Comparing ferritin levels across different disease severity using the Kruskal–Wallis H test revealed a significant difference ($P = 0.003$). Further comparisons using the Mann-Whitney procedure reveled significant increase in ferritin levels, for both the moderate and severe disease groups, in comparison to the mildly ill group ($P = 0.006$ and 0.005, respectively). Last, we did not find a significant difference between the moderate and severe disease groups ferritin levels ($P = 0.513$ and $P = 0.101$, respectively) after excluding extremely deviant cases. When classifying patients by disease severity into severe and non-severe groups, we found that severe patients had significantly higher levels of ferritin, 2817.6 ng/ml compared to 708.6 ng/ml in non-severe patients ($P = 0.02$). [Table 3, Figure 1, Figure 2].

DISCUSSION

At present, the pathophysiology, disease evolution, prognosis, and immune status of patients with COVID-19 are still unclear. Our study is a retrospective cohort study describing the epidemiological and clinical characteristics of COVID-19 patients in Israel. In this study, ferritin levels were shown to correlate with illness severity in 39 patients with confirmed COVID-19 disease [Table 3, Figure 1]. Severe patients had significantly higher levels of ferritin (2817.6 ng/ml) compared to non-severe patients (708.6 ng/ml) $P = 0.02$.

Ferritin is a large protein (440 kDa) present within the cytosol, or less often, within the mitochondria of the cell, and it

Table 2. COVID-19 severity and therapy characteristics

Variable	Statistic	
COVID-19 severity	**Frequency**	**Percent**
Mild	20	51.3%
Moderate	9	23.1%
Severe	10	25.6%
Chest X-ray		
Normal	16	41%
Unilateral infiltrate	6	15.4%
Bi-lateral infiltrate	17	43.6%
Vasopressors support		
Not needed	33	84.6%
Required	6	15.4%

COVID-19 = coronavirus disease-2019

Table 3. Ferritin levels by COVID-19 severity

Variable	Ferritin			
COVID-19 severity	**N**	**Mean (SD)**	**Range (Min-Max)**	***P* value**
Mild	20	327.72 (401.19)	1650 (6–1656)	Ref
Moderate	9	1555 (1578.06)	4188 (247–4435)	0.006
Severe	10	2817.6 (3457.85)	12048 (37–12085)	0.005
Non-severe	29	708.6 (1074.53)	4429 (6–4435)	Ref
Severe	10	2817.6 (3457.85)	12048 (37–12085)	0.02
Total	**39**	**1249.37 (2176.34)**	**12079 (6–12085)**	**-**

P value represent Mann-Whitney Tests

COVID-19 = coronavirus disease-2019; N = number; SD = standard deviation; Min = minimum; Max = maximum, Ref = reference

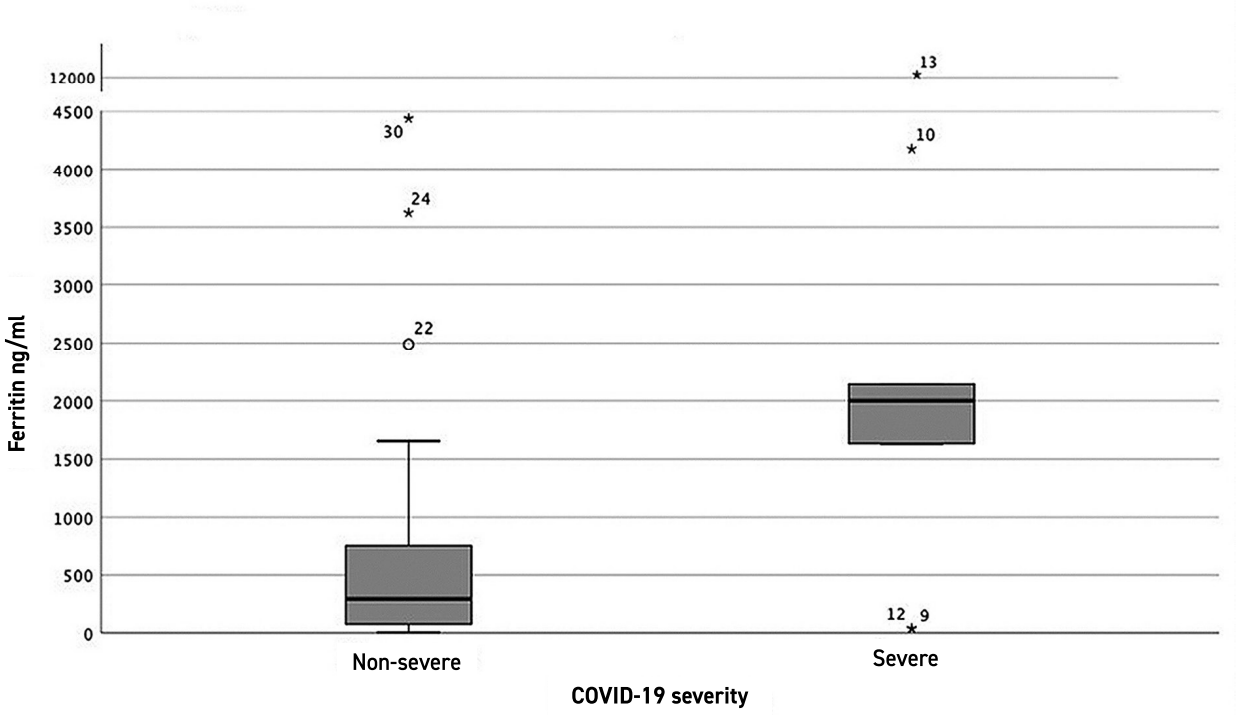
can sequester up to approximately 4500 atoms of iron [20]. Cytosolic ferritin is composed of a light (L ferritin) and heavy (H ferritin) subunits [21]. Twenty four subunits assemble into a structure designed to contain such large amounts of iron in a compact and bioavailable form [22]. The ratio of H to L subunits varies depending on the tissue type and the developmental stage of the cell, and can be modified in inflammatory and infectious conditions, as well as in response to xenobiotic stress [21]. In plasma, ferritin circulates as apoferritin, a non-iron containing molecule. The plasma level generally reflects overall iron storage, with 1 ng of ferritin per ml indicating approximately 10 mg of total iron stores [23].

Due to its crucial role in cellular iron homeostasis, it is not surprising that ferritin synthesis is tightly regulated [24]. This control includes different levels: from DNA regulation via the promoter, to interactions with numerous iron regulatory proteins in the process of mRNA translation [25]; and finally to a diverse set of signaling pathways that affect ferritin content within cells. Of note, pathways related to inflammation and autoimmunity impacted ferritin regulation. Among these pathways, several pro-inflammatory cytokines, including tumor necrosis factor-α (TNFα), interleukin 1 (IL-1), interleukin 6 (IL-6) and interferon γ, have been shown to transcriptionally induce the H chain of ferritin in different cell types [21,26-29]. Cytokines also regulate ferritin synthesis post-transcriptionally [30], alter ferritin levels indirectly through increasing nitric oxide [31] and stimulated the secretion of ferritin from hepatocytes [32].

It has been well-established that elevated serum ferritin levels may suggest not only the presence of an iron overload state, but is also a marker of inflammatory, autoimmune, infectious or malignant conditions [5,33,34]. Extremely high levels can be found in patients with macrophage activation syndrome (MAS) [35], adult-onset still disease (AOSD) (36), catastrophic anti-phospholipid syndrome (cAPS) and sepsis [5]. These four conditions were identified by Shoenfeld et al., and coined under the term 'hyperferritinemic syndrome' [7,37-39].

The pathogenicity of the novel SARS-CoV-2 and its effects on the immune system has yet not been completely understood. However, accumulating evidence suggest that severe progressive COVID-19 disease is associated with uncontrolled inflammation and massive cytokine release, a condition very similar to secondary hemophagocytic lymphohistiocytosis (HLH) or MAS [10,40,41]. MAS is an aggressive and life-threatening syndrome of excessive immune activation, most commonly triggered by viral infections [42]. It is associated with immunological abnormalities, including cytokine storm and hyperferritinemia [42]. A cytokine profile resembling MAS, characterized by elevated levels of IL-1, IL-2, IL-6, IL-7, IL-8, and TNFα, has been reported in patients with severe COVID-19 disease requiring intensive care unit (ICU) admission [43]. In concert with our findings, a recent retrospective, multicenter study identified elevated levels of ferritin (mean 1297·6 ng/ml in non-survivors vs 614·0 ng/ml in survivors; $P < 0{\cdot}001$) and IL-6 ($P < 0{\cdot}0001$) as predictors of mortality among 150 confirmed COVID-19 cases [44]. Ferritin levels were also elevated in severe compared to moderate cases in a smaller retrospective study of 21 patients with COVID-19 conducted in China [16].

Figure 2. Ferritin levels: Severe vs. non-severe patients. Simple boxplot of ferritin levels by COVID-19 dichotomous severity
Severe patients had significantly higher levels of ferritin (2817.6 ng/ml) compared to non-severe patients (708.6 ng/ml) *P* = 0.02



In light of this data, we postulate that severe COVID-19 disease may represent another condition belonging to the hyperferritinaemic syndromes, sharing a common pathophysiology with MAS [45,46]. According to this hypothesis, elevated ferritin is only the tip of the iceberg of a possible underlying dysregulated hyper-immune response. In this subgroup of critically ill patients, the inflammatory response flares out of control, leading to pulmonary and systemic life-threatening involvement. In order to identify these patients early and prioritized resources, we believe that all patients with COVID-19 should be screened for hyperferritinemia.

The hypothesis of hyper-inflammation as a possible pathogenic mechanism in COVID-19 raises an important question regarding the use of immunosuppression. Corticosteroids inhibit the host inflammatory response, but may also lead to severe infections and delay viral clearance [47]. Lessons can be learned from previous epidemics with the two betacoronaviruses, severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS- CoV). Current evidence in patients with SARS-CoV [48] and MERS- CoV [49] show that adjunctive glucocorticoids therapy did not have a beneficial effect on mortality. Therefore, according to the current WHO interim guidance, glucocorticoids should not be used routinely in all COVID-19 patients, unless there are other evidence-based indications [50]. However, steroids use in the management of critically ill patients with COVID-19-related ARDS is currently controversial. Several observational studies, as well as animal experiments, have demonstrated that corticosteroids might ameliorate acute lung injury in SARS-CoV patients, by induction of T-regulatory cells, promoting the differentiation of macrophage type 2 (M2) and reducing the burden of pro-inflammatory cytokines [51,52]. An ongoing randomized controlled trial by Zhou et al. [53] is evaluating intravenous methylprednisolone versus a control group in patients with severe COVID-19 disease, in hope to discover evidence either supporting or opposing this approach. As summarized recently by Ferro and co-authors [54], other options in the growing therapeutic armamentarium of the disease include intravenous immunoglobulin (IVIG), small molecules and antibodies with selective cytokine blockade (e.g., anakinra or tocilizumab) and JAK inhibition. Further studies are urgently needed to better define the subgroup of patients that will benefit a more aggressive intervention with immunomodulatory drugs.

LIMITATIONS

Our study has some limitations. First, our sample size was small. We describe a modest-sized case series of hospitalized patients. In order to better define the clinical course of the disease, natural history, and risk factors for mortality, collection of data for a larger cohort would be needed. Second, this is a cross-sectional study, with ferritin levels taken on admission. It would be relevant to investigate the change of ferritin levels over time to con-

firm its correlation with prognosis. In addition, we lack data regarding the total body iron storage in these patients. This could affect our results, since ferritin levels are expected to be lower in patients with iron deficiency anemia, even if they have severe COVID-19 disease. Last, we collected and analyzed data from only hospitalized patients. Outpatients with mild symptoms or patients under home observation were not included in this study. As a consequence, mild patients consisted only 51% of the cases in our cohort, compared to the general population where most infections (about 80%) are mild [55]. This may result in a selection bias in our results and in our general understanding of the disease. At the same time, since we did find a significant different in ferritin levels when using mild hospitalized patients as a reference, it further strengthens our results. Further studies in the outpatient settings are required to get a complete picture of the spectrum of illness severity.

CONCLUSIONS

In the new era of COVID-19, extensive and rapid research is important to help guide clinical practices and public health policies. In this preliminary cross-sectional study, elevated ferritin levels were shown to correlate with disease severity in 39 patients from Israel with confirmed COVID-19 infection. Our results further strengthen the hypothesis that severe COVID-19 disease might be due to a host immune system that gone awry, leaving ferritin behind as a remnant of this cytokine storm.

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References

1. Laufberger V. Sur la cristallisation de la ferritine. (On the crystallization of ferritin). *Soc Chim Biol* 1937; 19: 1575-82. [French].
2. Addison GM, Beamish MR, Hales CN, Hodgkins M, Jacobs A, Llewellin P. An immunoradiometric assay for ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. *J Clin Pathol* 1972; 25 (4): 326-9.
3. Jacobs A, Worwood M. Ferritin in serum: clinical and biochemical implications. *N Engl J Med* 1975; 292 (18): 951-6.
4. Sharif K, Vieira Borba V, Zandman-Goddard G, Shoenfeld Y. *Eppur Si Muove*: ferritin is essential in modulating inflammation. *Clin Exp Immunol* 2018; 191 (2): 149-50.
5. Agmon-Levin N, Rosário C, Katz BP, et al. Ferritin in the antiphospholipid syndrome and its catastrophic variant (cAPS). *Lupus* 2013; 22 (13): 1327-35.
6. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: past, present and future. *Biochim Biophys Acta BBA-Gen Subj* 2010; 1800 (8): 760-9.
7. Rosário C, Zandman-Goddard G, Meyron-Holtz EG, D'Cruz DP, Shoenfeld Y. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. *BMC Med* 2013; 11 (1): 185.
8. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382 (8): 727-33.
9. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. [Available from https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020]. [Accessed March 2020].
10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395 (10223): 497-506.
11. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 382 (18): 1708-20.
12. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; 323 (11): 1061-9.
13. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in *Lancet* 2020; 395 (10229): 1038]. *Lancet* 2020; 395 (10229): 1054-62.
14. Wang F, Nie J, Wang H, et al. Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia. *J Infect Dis* 2020; 221 (11): 1762-9.
15. Sarzi-Puttini P, Giorgi V, Sirotti S, et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin Exp Rheumatol* 2020; 38: 337-42.
16. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J Clin Invest* 2020; 130 (5): 2620-9.
17. Pires da RG, Ferreira E. Therapies used in rheumatology with relevance to coronavirus disease 2019. *Clin Exp Rheumatol* 2020; 38 (2): 370.
18. World Health Organization. Novel coronavirus (2019-nCoV) technical guidance: laboratory testing for 2019-nCoV in humans. [Available from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance]. [Accessed March 2020].
19. McIntosh K, Hirsch MS, Bloom A. Coronavirus disease 2019 (COVID-19). UpToDate Hirsch MS Bloom Eds [Available from https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-epidemiology-virology-clinical-features-diagnosis-and-prevention]. [Accessed March 2020].
20. Harrison PM, Arosio P. The ferritins: molecular properties, iron storage function and cellular regulation. *Biochim Biophys Acta BBA-Bioenerg* 1996; 1275 (3): 161-203.
21. Torti FM, Torti SV. Regulation of ferritin genes and protein. *Blood J Am Soc Hematol* 2002; 99 (10): 3505-16.
22. Arosio P, Levi S. Cytosolic and mitochondrial ferritins in the regulation of cellular iron homeostasis and oxidative damage. *Biochim Biophys Acta BBA-Gen Subj* 2010; 1800 (8): 783-92.
23. Finch CA, Stray S, Huebers HA, et al. Plasma ferritin determination as a diagnostic tool. *West J Med* 1986; 145 (5): 657.
24. Hintze KJ, Theil EC. DNA and mRNA elements with complementary responses to hemin, antioxidant inducers, and iron control ferritin-L expression. *Proc Natl Acad Sci* 2005; 102 (42): 15048-52.
25. Hentze MW, Muckenthaler MU, Andrews NC. Balancing acts: molecular control of mammalian iron metabolism. *Cell* 2004; 117 (3): 285-97.
26. Smirnov IM, Bailey K, Flowers CH, Garrigues NW, Wesselius LJ. Effects of TNF-α and IL-1β on iron metabolism by A549 cells and influence on cytotoxicity. *Am J Physiol-Lung Cell Mol Physiol* 1999; 277 (2): L257-63.
27. Wei Y, Miller SC, Tsuji Y, Torti SV, Torti FM. Interleukin 1 induces ferritin heavy chain in human muscle cells. *Biochem Biophys Res Commun* 1990; 169 (1): 289-96.
28. Fahmy M, Young SP. Modulation of iron metabolism in monocyte cell line U937 by inflammatory cytokines: changes in transferrin uptake, iron handling and ferritin mRNA. *Biochem J* 1993; 296 (1): 175-81.
29. Hirayama M, Kohgo Y, Kondo H, et al. Regulation of iron metabolism in HepG2 cells: a possible role for cytokines in the hepatic deposition of iron. *Hepatology* 1993; 18 (4): 874-80.
30. Konijn AM, Carmel N, Levy R, Hershko C. Ferritin synthesis in inflammation: II. Mechanism of increased ferritin synthesis. *Br J Haematol* 1981; 49 (3): 361-70.
31. Weiss G, Goossen B, Doppler W, et al. Translational regulation via iron-responsive elements by the nitric oxide/NO-synthase pathway. *EMBO J* 1993; 12 (9): 3651-7.
32. Muntané-Relat J, Ourlin J-C, Domergue J, Maurel P. Differential effects of cytokines on the inducible expression of CYP1A1, CYP1A2, and CYP3A4 in human hepatocytes in primary culture. *Hepatology* 1995; 22 (4): 1143-53.
33. Zandman-Goddard G, Shoenfeld Y. Ferritin in autoimmune diseases. *Autoimmun Rev* 2007; 6 (7): 457-63.
34. Orbach H, Zandman-Goddard G, Amital H, et al. Novel biomarkers in autoimmune diseases: prolactin, ferritin, vitamin D, and TPA levels in autoimmune diseases. *Ann N Y Acad Sci* 2007; 1109 (1): 385-400.

35. Trottestam H, Horne A, Arico M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood J Am Soc Hematol* 2011; 118 (17): 4577-84.
36. Bishara R, Braun-Moscovici Y, Dagan A, et al. Severe hyperferritinemia-a clue for severe hepatitis in a patient with adult-onset Still's disease. *Clin Rheumatol* 2016; 35 (3): 795-800.
37. Zandman-Goddard G, Shoenfeld Y. Hyperferritinemia in autoimmunity. *IMAJ* 2008; 10 (1): 83.
38. Rosário C, Shoenfeld Y. The hyperferritinemic syndrome. *IMAJ* 2014; 16 (10): 664-5.
39. Colafrancesco S, Priori R, Alessandri C, et al. The hyperferritinemic syndromes and CD163: a marker of macrophage activation. *IMAJ* 2014; 16 (10): 662-3.
40. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: faraway, so close! *Autoimmun Rev* 2020; 19 (5): 102523.
41. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; 395 (10229): 1033-4.
42. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet* 2014; 383 (9927): 1503-16.
43. Wan S, Yi Q, Fan S, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv 2020.02.10.20021832.
44. Ruan Q, Yang K, Wang W, Jiang L, Song J. *Intensive Care Med* 2020; 46 (5): 846-8.
45. Ruscitti P, Berardicurti O, Cipriani P, Iagnocco A, Shoenfeld YJ, Giacomelli R. Severe COVID-19, another piece in the puzzle of the hyperferritinaemic syndrome. An immunomodulatory perspective to alleviate the storm. *Front Immunol* 2020; 11: 1130.
46. Kanduc D, Shoenfeld Y. On the molecular determinants the SARS-CoV-2 attack. *Clin Immunol* 2020; 215: 108426.
47. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020; 395 (10223): 473-5.
48. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006; 3 (9): e343.
49. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med* 2018; 197 (6): 757-67.
50. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. [Available from https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf].
51. Tu G, Shi Y, Zheng Y, et al. Glucocorticoid attenuates acute lung injury through induction of type 2 macrophage. *J Transl Med* 2017; 15 (1): 181.
52. Sung JJY, Wu A, Joynt GM, et al. Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax* 2004; 59 (5): 414-20.
53. Qin YY, Zhou YH, Lu YQ, et al. Effectiveness of glucocorticoid therapy in patients with severe coronavirus disease 2019: protocol of a randomized controlled trial. *Chin Med J (Engl)* 2020; 133 (9): 1080-6.
54. Ferro F, Elefante E, Baldini C, et al. COVID-19: the new challenge for rheumatologists. *Clin Exp Rheumatol* 2020; 38 (2): 175-80.
55. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; 10.1001/jama.2020.2648.

Capsule

SARS-CoV-2 spike protein, elaborated

Vaccine development for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is focused on the trimeric spike protein that initiates infection. Each protomer in the trimeric spike has 22 glycosylation sites. How these sites are glycosylated may affect which cells the virus can infect and could shield some epitopes from antibody neutralization. **Watanabe** et al. expressed and purified recombinant glycosylated spike trimers, proteolysed them to yield glycopeptides containing a single glycan, and determined the composition of the glycan sites by mass spectrometry. The analysis provides a benchmark that can be used to measure antigen quality as vaccines and antibody tests are developed.

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Capsule

Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19

Juno et al. characterized humoral and circulating follicular helper T cell (cTFH) immunity against spike in recovered patients with coronavirus disease-2019 (COVID-19). The authors found that S-specific antibodies, memory B cells and cTFH, are consistently elicited after severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, demarking robust humoral immunity and positively associated with plasma neutralizing activity. Comparatively low frequencies of B cells or cTFH specific for the receptor binding domain of S were elicited. Notably, the phenotype of S-specific cTFH differentiated subjects with potent neutralizing responses, providing a potential biomarker of potency for S-based vaccines entering the clinic. Overall, although patients who recovered from COVID-19 displayed multiple hallmarks of effective immune recognition of S, the wide spectrum of neutralizing activity observed suggests that vaccines might require strategies to selectively target the most potent neutralizing epitopes

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