SERUM FERRITIN LEVEL AS PROGNOSTIC BIOMARKERS IN PATIENTS WITH CONFIRMED COVID19 IN NORTHERN BORDERS PROVINCE

Muneera Abdullah Alnajdy
Medical Technologist at Ministry of National Guard Health Affairs

Jawahir Ali Y Sama
Laboratory Technician – NGHA

Mohammed Farhan Alenazi
Medical Technologist

Rakan Mohammed Bannunah
Imamm Abdulrahman Al-faisal, Medical Technologist II

Ahmed Zayed Almutairi
Home Care, Al Medina

Abdulelah Zayed Almutairi
King Salman Medical City

Nouf Qasem Mohammed Albulayhishi
King Salman Medical City

Essa Minaallah Al Mutairi
King Salman Medical City

Mona Eid Al enazi
King Salman Medical City

Abdulkarim Misfer Al Jabari
King Salman Medical City

Wijdan Nasser Salem Al Ahmadi
King Salman Medical City

Fahad Ismail Al Moteri
Regional Blood Bank Al Medina

Ahmed M Aljohani
Nojod Medical Center, Al Medina

Abdulelah S Almoteri
Ohud Hospital, Al Medina

Gland Surg 2024; *VOL:9 (2)*
ISSN:2227-684XE-ISSN:2227-8575

Abstract

Background

Some COVID-19 patients have higher mortality and the responsible factors for this unfavorable outcome are still not well understood. Ferritin is a known inflammatory biomarker in COVID-19. However, many factors and co-morbidities can confound the level of serum ferritin.

Objective

To study the association between ferritin levels at admission, representing an inflammatory state, and hospital mortality in COVID-19 patients.

Methods

From January through March 2022, COVID-19 positive patients with moderate to severe clinical symptoms were evaluated at admission, regarding clinical and laboratory data on hematologic parameters, C-reactive protein (8-10 mg/L), D-dimer (<500 µg/L), and cytomegalovirus co-infection. Patients were stratified based on ferritin levels (ferritin levels 24-336µg/L).

Results

A total of 506 patients were included; mean age = 46.56±16.15 years, 355 (70.15%) were male, and 151(29.85%) were female. Age, ferritin, C-reactive protein, and D-dimer were significantly associated with mortality. The magnitude of inflammation presents at the admission of COVID-19 patients, represented by high ferritin levels, is independently predictive of in-hospital mortality.

Keywords: COVID-19; Ferritin; mortality. Introduction

By the end of 2019, a novel viral infection emerged. The microbial agent that caused the w pandemic was named the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and showed human-to-human transmission. The clinical syndrome is named COVID-19 (Coronavirus Dieses 2019), which is characterized by severe acute respiratory distress and is highly infectious. It has only been discovered recently and spreads between individuals through close contact and respiratory droplets when an infected person sneezes, talks, or coughs (WHO, 2020). According to the Johns Hopkins University and medicine resource center, the world had recorded more than 420 million cases and over 5 million deaths from COVID-19 by the end of February 2022 worldwide. In Saudi Arabia, COVID-19 infected more than 737 thousand causing 8,978 death cases till the end of February 2022 (WHO, 2020)

SARS-cov2 is one of the Coronaviruses that belong to the family Coronaviridae and Coronovirinae subfamily. genetically, there are 4 categories of the subfamily Coronovirinae, alpha (α), beta (β), gamma (γ), and delta (δ). Alpha and beta coronaviruses are the most clinically important in humans (Payne, 2017; Pal *et al*., 2020). The virus is positive single-strand RNA, it belongs to the beta-coronaviruses. It has some similarities to SARS and MERS viruses. But it is much closer to two bat coronaviruses (Perlman *et al*., 2020). Both SARS-COV and SARS-cov2 use human angiotensin-converting enzyme 2(AC2) receptors to get access to the cell helped by the receptor-binding domain of its spike protein (Zhou *et al.,* 2020; Hoffmann *et al*., 2020). SARS-cov2 emerged over time because of mutations that do not affect the virus function but may give rise to more transmission and affect clinical severity and manifestations (Lai *et al*., 2019). Those of concern are Omicron, Delta, Beta, Gamma, and alpha (Figure 1) (WHO, 2022).

More than 30 mutations occurred in the spike protein of coronavirus resulting in the Omicron (B.1.1.529 lineage) with more transmission ability and decreased response to neutralizing antibodies. the mutated one emerged by the end of 2021(CDC, 2022). Although it

ISSN:2227-684XE-ISSN:2227-8575

causes a less severe clinical disease, it could evade the humoral immune response induced by the COVID-19 vaccine and has a higher infectivity rate. Viral transmission occurs directly from person -person through the respiratory droplets, especially with a close-range distance of about 2 meters. the virus comes out in the respiratory secretions during coughing or sneezing. indirect transmission occurs when the hands of a person get in touch with contaminated surfaces and then touch the nose, eye, or other mucous membranes (Huang *et al*., 2019). The incubation period ranges from 2 to 5 days and infectivity starts with the onset of clinical symptoms. The virus could be detected up to 12 days after the appearance of symptoms (Rothe *et al*., 2020).

There is no specific finding in laboratory testing for covid -19, however, lymphopenia, leucopenia, elevated liver enzymes, D-dimer, PT, PTT and inflammatory markers including CRP, ESR, LDH and cytokines could be detected. Elevated liver enzyme and bilirubin were found in some patients. High blood glucose and impaired kidney function are another abnormality. Serum ferritin was found to be elevated an inconsiderable number of patients especially those with cytokine storm. Laboratory parameters are more important in patient follow up and picking those who will benefit from anti-interleukin therapy (Zhou *et al.,* 2020; Chen T *et al.,* 2020).

Ferritin, a globular protein in nanocells, has 24 subunits. It is found not only in numerous tissues and cells but also in skeletal fluids, including plasma and serum (Kell and Pretorius, 2014). Depending on the type and body structure of the molecule or tissue, the proportions of H and L subunits in 24-mer proteins may also additionally differ, possibly reflecting useful differences. The L subunit predominates in liver and spleen ferritin, while the H subunit predominates in the brain, kidney, and cardiac ferritin. Serum ferritin is composed primarily of L subunits, indicating that it is liver-derived and glycosylated (Cragg *et al*. 1981). Intracellular iron must be converted to Fe3+ before it can be transported outside the cell. The process is facilitated by either hephaestin or ceruloplasmin, both of which have ferroxidase activity (Fe2+ + Fe3+). Both proteins are active in the intestine, while ceruloplasmin is the primary worker in the liver (a major storage site for iron). After loading iron onto transferrin, the primary transporter of iron in the circulation is released. As a result of binding to transferrin, Fe3+ is soluble and nonreactive, allowing it to enter the circulatory system (Knovich *et al*., 2009).

As a result of the oxidation of Fe (II) to Fe (III), cells are capped towards Fe (II), which in turn enables the conversion of hydrogen peroxide, a product of mitochondria. Fe (II) is converted to Fe (III) by the ferroxidase of the H subunit, while the L subunit assists in the incorporation of Fe (III) into ferritin. The iron response element/iron regulatory protein tightly controls ferritin expression, demonstrating the importance of ferritin in iron metabolism. These processes are dependent on translation. The heavy chain of ferritin (FTH) and the light chain of ferritin (FLC) incorporate human ferritin. The peroxidase contained in the chain converts Fe2+ to Fe3+. When Fe3+ reaches the nucleation point, iron oxidation and nucleation occur simultaneously (Kuhn, 2015).

The ferritin gadgets are in inner cells with an outer diameter of 12 nanometers and an inner diameter of eight nanometers. These nanocells (pH 3-9) separate the iron inside the center from the external environment and protect the framework from the harmful effects of additional, unbound iron. Ferritin can contain up to 5000 iron atoms in a single molecule. Oxidizing marketers and antioxidants, including nitrous oxide, glutathione, and other "reactive oxygen species," affect ferritin production (Kaushal *et al*., 2022). Inflammation affects the expression of individual genes. FTL mRNA is translated by transcriptional repression using iron regulatory proteins 1 and 2. These proteins interact with regulatory regions of mRNA that are known as “iron-sensitive elements" located in the "5'-untranslated region” (Wang *et al*., 2021).

ISSN:2227-684XE-ISSN:2227-8575

In addition to continuous inflammatory responses, serum ferritin also shows acute inflammatory responses. Hyperferritinemia can be both a cause and a consequence of inflammation. An increase in ferritin levels indicates brisk monocyte-macrophage activity (Edeas *et al*., 2020). Changes in cytokine repletion in monocytes and macrophages affect both transcription and translation of ferritin. Macrophages respond to immunological stimuli by polarizing toward M1 or M2, thereby regulating the body's inflammatory state. There is also evidence that there is a direct link between ferritin and lymphocyte properties (Wang *et al*., 2021).

COVID-19 is considered one of the systemic inflammatory disorders with the release of pro-inflammatory proteins and cytokines such as IL-6, and TNF-alpha (Mulchandani *et al*., 2021). Markedly elevated level of the cytokines has been encountered in patients with severe disease-causing the well-known cytokine storm. The release of cytokines by the immune cells. cellular impairment and damage, developed metabolic acidosis, and generation of oxidant may be the mechanism by which ferritin is elevated in COVID-19 patients. Ferritin is a common acute phase inflammatory biomarker. Some studies reported that in patients with COVID-19, serum ferritin correlates with disease severity and the follow up of its serum level could estimate clinical progression (Lin *et al*., 2020)

Ferritin is one of the serum biomarkers indicating the extent of the inflammatory process in COVID-19. Ferritin has a role in minimizing the intracellular oxidative stress and intake of cytosolic iron thus modifying the host response to infection as in malaria, sepsis, and some viral infection (Chiou and Connor, 2018).

Mild to moderate elevation of serum ferritin may be indicative of a healthy host response to acute infectious process as in COVID-19. This may occur through the activation of useful defensive pathways. however, marked elevation of serum ferritin beyond a certain limit will lead to more deleterious effects and worsen patient outcomes through immune dysregulation and cytokine storm. The extent of serum ferritin elevation may reflect the balance between regulated beneficial and dysregulated harmful immune responses in patients with COVID-19 pneumonia (Kooistra *et al,.*2020).

In the usual inflammatory disorders, systemic inflammation occur then impaired iron metabolism happen latter, however In COVID-19 impaired iron metabolism occur early in the disease followed later by systemic inflammation and organ damage suggesting the role of iron dysregulation in covid-19 patients' outcome (Banchini *et al*., 2021). Some recent studies consider s hyperferritinemic syndrome is considered one of the major modifiers in SARS-COV2 infection (Fisler *et al*., 2020), which make the evaluation of ferritin levels a parameter of infection. Presently, excluding reviews and metanalysis, only ten papers have been published on the contemporary topic of “ferritin” and “COVID” (Gandini *et al*.,2020)

Covid -19 is has very complex pathogenesis, hypoxemic respiratory failure, and severe acute respiratory syndrome are life-threatening complications that could develop in absence of cytokine storm (Zhou *et al.,* 2020). In this clinical situation serum ferritin was found to be excessively high Which suggest the use of serum ferritin as predictor of mortality. These findings support the suggestion that COVID-19 is a member of hyperferrinemia syndrome.

ISSN:2227-684XE-ISSN:2227-8575

Table 1. Demographic data of the studied COVID-19 patients

Parameters	N	Percentage
Total patients' number	506	100%
Mean of age (Mean, SD)	46.56±16.15 years	--
Female	151	29.85%
Male	355	70.15%
Saudi	233	46.05%
Non-Saudi	273	53.95%

Aim of the study

This study aimed at:

- Estimation of the level of the serum ferritin biomarker in patients with COVID-19.
- Study the impact of serum ferritin level on COVID-19 patient's outcome.

Study design and samples collection

The medical records of 508 confirmed COVID-19 patients were analyzed for demographic data, clinical data, and patient's outcome. Those patients were selected from the North Medical Tower, Arar, Saudi Arabia from January 2022 to March 2022.

- patients with confirmed covid -19 test results at the time of diagnosis Covid-19 patients were involved in the study.
- Patients with viral respiratory infections other than Coronaviru were excluded from the study. Blood samples were obtained from North Medical Tower in Arar hospitalized COVID-19 patients, from January 2022 to March 2022.

Studied subjects were COVID-19 patients admitted to the ICU, in the wards, and in recovery. The patient's files were reviewed for the demographic data, clinical data, laboratory test results, and patient outcomes. The study was approved by the ministry of health .

Statistical analysis

Analysis of the data collected data was performed using Statistical Package for Social Sciences version 20 (SSPS20) computer program and Microsoft Excel 2010. the mean±SD or median as appropriate was used. Qualitative data were presented as frequency and percentages were used for Qualitative information. Comparison between the two groups was conducted by using for all comparisons, the p-value was set at 0.05 and was considered significant and highly significant. Results with a probability value less than 0.05 were deemed statistically significant.

Result

Basic data of the studied patients

A total of 506 confirmed patients with COVID-19 were analyzed. An average age of 46.56±16.15 years was observed, with 355 (90.75%) males and 151 (29.85%) females. Saudis represented 46.05 % of the survey participants, while non-Saudis made up 53.95 %. The severity of the case dictated whether the patient was admitted to the emergency room, an infectious disease unit, or an intensive care unit. The main symptoms observed upon hospital admission were fever, cough, sore throat, sneezing, loss of taste, and abdominal pain. A blood test was done within the first 24 hours after hospitalization to determine the laboratory result (Table 1).

As a result of severity, 407 (80.43%) of them were discharged home, 69 (13.64%) were in the intensive care unit, and 30 (5.93%) died (Table 2).

ISSN:2227-684XE-ISSN:2227-8575

Table 2. Mortality distribution		
Patients Mortality	Number (506)	100%
Recovery	407	80.43%
ICU	69	13.64%
Death	30	5.93%

Age affects ferritin levels in COVID-19 patients

Age and risk markers were interrelated, with a significant relationship between ferritin and age (mean±SD, 738.4±21.28; p<0.001; 95% CI, 696.7 to 780.2) ((Figure 5). There were no significant differences between age, mortality risk (death), ICU, or discharge to home (p=0.723, p=0.422, p=1.42; respectively) (Table 3).

Table 3. age group distribution						
	Under 18 (n=4)	18-35 (n=122)	35-50 (n=177)	50-70 (n=150)	70+ (n=53)	*P*- value
Recovery	4	120	163	103	17	0.236
ICU	0	0	9	34	27	1.652
Death	0	2	5	13	9	1.322

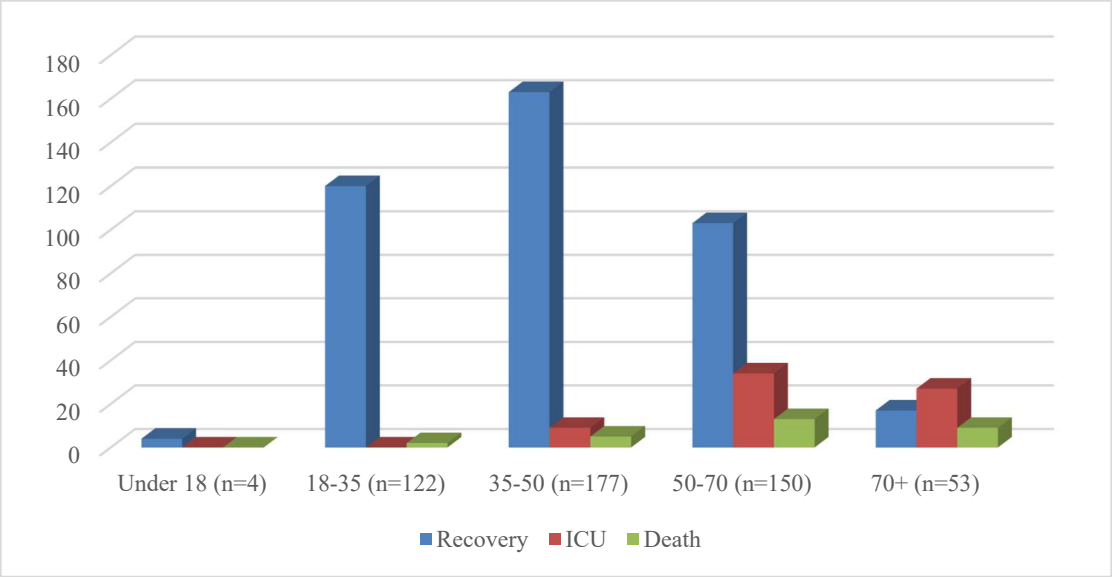

Figure 1. age group distribution in recovery, ICU, and death

Hospitalized COVID-19 patients' laboratory parameters

There are two different laboratory tests, both measuring plasma D-Dimer (P=0.0029). A significant correlation was found between ICU admission and patients' mortality and serum ferritin on admission (P<0.0001). Between the different patient categories, there was no statistically significant difference in PT, PTT, or CRP levels (Table 4, Figure 6).

ISSN:2227-684XE-ISSN:2227-8575

Table 4. Laboratory parameters of COVID-19 hospitalized patients				
Parameters	**Death (n=30)**	**Recovery (n=407)**	**ICU(n=69)**	***P*-value**
	Mean± SD			
Age	59.37±16.15	42.88±13.69	64.33±13.38	<0.001*
Serum ferritin	807.9±388.7	762.5±477.4	927.2±506.0	0.0294*
D-dimer	1086±1328	742.5±517.2	928.0±1223	0.0098*
PT	12.15±1.818	11.80±0.9755	11.83±0.7182	0.1713
PTT	35.81±4.753	34.65±2.994	35.18±3.087	0.0817
CRP	75.12±49.75	60.24±39.58	54.95±35.45	0.0732
***Significant *P*<0.05**				

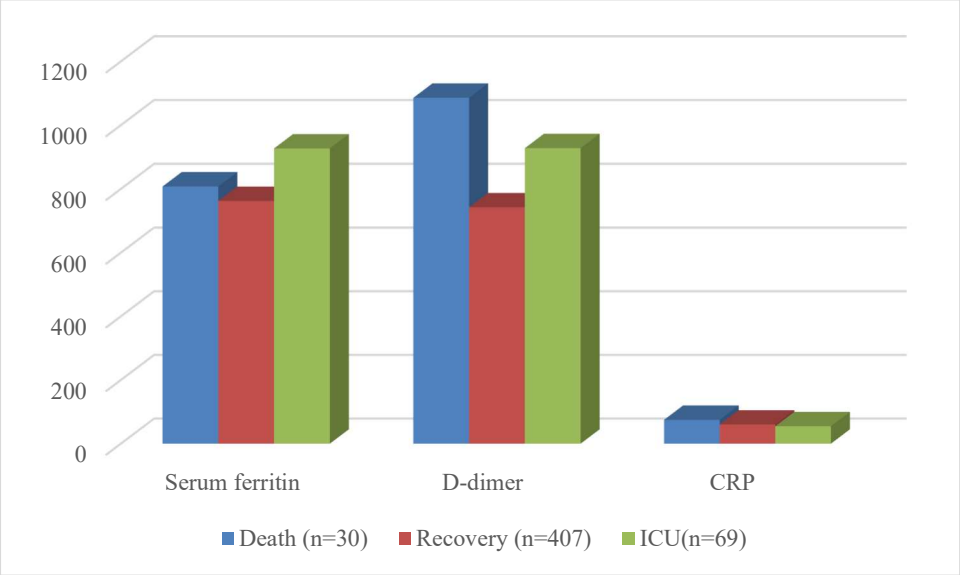

Figure 2. correlation between Serum ferritin, D-dimer, and CRP in mean of Death, ICU, and recovery patients.

Relationship between ferritin serum levels and other laboratory parameters.

Comparison of laboratory parameters between patients whose ferritin levels are > 336µg/L abnormal and those whose ferritin levels are 24-336µg/L normal. The CRP and D-dimer levels were significantly higher in patients with ferritin levels >336 µg/L when compared with those with ferritin levels 24-336µg/L (63.37±37.44, p=0.0011; 816.9±792.7, p=0.0312, respectively) (Table 5 and Table 6).

Table 5. Serum Ferritin Level in Covid-19 patients.						
Parameters		N=506	%	Mean	SD	P value
Serum Ferritin	Abnormal	413	81.62%	787.6	±479.1	<0.0001*
	Normal	93	18.73%			
***Significant *P*<0.05**						

ISSN:2227-684XE-ISSN:2227-8575

Table 6. Laboratory findings of COVID-19 patients grouped by ferritin level (µg/L)			
(Mean±SD)	**Abnormal (336µg/L)**	**Normal (24-336µg/L)**	***P*-value**
Serum Ferritin	892.8±465.5	11.72±6.581	0.0003*
D-dimer	816.9±792.7	666.8±229.6	0.0312*
PT	11.82±0.9627	11.90±1.760	0.6809
PTT	34.86±3.193	32.53±2.179	0.1787
CRP	63.37±37.44	26.59±22.33	0.0011*
Lymphocytes count	4.987±53.13	1.737±0.5581	0.8710
***Significant *P*<0.05**			

Serum Ferritin and COVID-19 Mortality

Patients in the ICU had a serum ferritin value of 927.2 (SD, 506.0) ng/ml, and those who were dead had a value of 807.9 (SD, 388.7) ng/ml, and those who had a value of 927.2 (SD, 506.0) ng/ml. In the study, the difference between Serum Ferritin levels in ICU and dead patients was 119.2±103.7 µg/ml (95% confidence interval CI, -86.51 to 325.0). There was a significant increase in Serum Ferritin levels in the ICU and in dead patients. In addition, the difference in the mean value of Serum Ferritin between the dead and the recovered patients was 164.7±62.70 µg/ml (95 % confidence interval, 41.51 to 287.9), indicating that the level of Serum Ferritin was significantly higher in the dead patients than in the recovered patients.

Discussion

New coronaviruses have been detected in China for the first time in December 2019, and they were later dubbed SARS-CoV-2 (Cruickshank *et al.,* 2020). In March 2020, the World Health Organization (WHO) declared COVID-19, the viral illness associated with the virus, an international public health emergency (Cucinotta *et al*., 2020). Based on reverse transcription real-time PCR, scientists developed specific diagnostic tests for this virus through genome sequencing (Henter *et al*., 2007). Acute respiratory distress syndrome and multisystemic inflammation may result in organ failure in patients with severe disease. Thus, it is mandatory to do good patient evaluations upon admission and investigate possible biomarkers to take fast and correct clinical decisions.

Ferritin has been identified as an inflammatory marker in pneumonia that may be associated with disease progression and severity. Hyperferrinemia, a key mediator of immunologic response, could be associated with the severe inflammatory condition (Slaats *et al.*, 2016). It has been found that hyperferritinaemia is a useful inflammatory biomarker among rheumatologic disorders, some cancers, and diseases with inflammatory backgrounds (Kernan and Carcillo,2017). It has been proposed by Edeas M *et al*., that hyperferritinemia is caused by leakage from damaged intracellular stores. Ferritin loses its inner iron content after being released from tissue stores, resulting in excess free iron. Some clinically important viruses grow more rapidly in the presence of excess iron or iron repletion (Colafrancesco *et al*., 2020; Edeas M *et al*., 2020).

It was observed that serum ferritin is generally elevated in most of the COVID-19 patients, higher levels were found in patients admitted to the ICU and non-survivors. This study examined 506 confirmed COVID-19 patients with regard to serum ferritin levels on admission, and its

ISSN:2227-684XE-ISSN:2227-8575

relationship to other biomarkers such as CRP, D-dimer, PT, and PTT (Drakesmith and Prentice,2008).

Serum ferritin was strongly correlated with overall survival, regardless of age. In accordance with Cheng *et al*., who reported higher serum ferritin levels in severe covid-19 patients and confirmed that their level was correlated with mortality. In contrast to other patients with acute surgical disorders, Banchini *et al*. reported elevated serum ferritin levels in COVID-19 patients (Cheng *et al.,* 2020; Banchini *et al.,* 2021).

Coronavirus disease is a multisystemic inflammatory disorder characterized by elevated pro-inflammatory markers and cytokines such as CRP, IL-6, TNF-alpha, etc., especially in patients with clinically severe disease (Mulchandani *et al.*, 2021). The release of IL-6, IL-1B, and TNF-alpha, associated ROS production, metabolic acidosis, and secondary tissue damage are proposed mechanisms of high ferritin levels associated with COVID-19. Studies have shown that high serum ferritin correlates with disease severity, outcome, and other inflammatory markers like CRP (Lin *et al.* ,2020).

Ferritin levels in the blood may not only reflect acute phase responses but may also play a critical role in inflammation. Serum ferritin levels are a non-specific indication of the acute phase response for most doctors dealing with inflammatory disorders, and they are frequently overlooked or not evaluated while the patient is acutely unwell (Torti, 2020). Ferritin levels can be exceedingly high in some conditions, and while not specific, these excessively high levels can assist identify people who are at risk. Ferritin levels were shown to be higher in elderly and/or hypertensive participants in prior investigations, which was linked to an increased risk of death (Rosario *et al*., 2013).

High levels of serum ferritin in the first seven days of hospitalization were found to be a predictor for the cytokine storm syndrome in a study of COVID-19 patients, and serum ferritin was also found to be a biomarker for potential progression to critical illness in a meta-analysis of 21 studies (3377 patients and 33 laboratory parameters) (Taneri *et al*., 2020). However, new research has shown that anti-inflammatory biomarkers can also be upregulated during the acute phase of COVID-19. This emphasizes the necessity of future research focused on the balance of pro- and anti-inflammatory mediators, as well as how this may affect disease development (Caricchio *et al*., 2020).

In this study age showed a negative impact on disease severity and mortality, whereas patients with more advanced age showed more ICU admission and higher mortality in COVID-19 patients, this was also reported by Omotade *et al*., 2022.

Conclusion

. When compared to other severity markers in COVID-19, ferritin may serve as an easy-to-use predictor for risk stratification of covid-19 disorder. This study concluded that elevated serum ferritin level was frequently found in those with more severe disease and non-survivors of COVID-19. Thus, serum ferritin level on admission could serve as an important risk stratification biomarker in COVID-19 management. However, serum ferritin level needs to be interpreted cautiously in presence of another comorbid disease.

References

Banchini, Filippo & Cattaneo, Gaetano & Capelli, Patrizio. (2021). Serum ferritin levels in inflammation: a retrospective comparative analysis between COVID-19 and emergency

surgical non-COVID-19 patients. World Journal of Emergency Surgery. 16. 10.1186/s13017-021-00354-3.
C. Rosario, G. Zandman-Goddard, E.G. Meyron-Holtz, D.P. D'Cruz, Y. Shoenfeld. (2013). The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophicantiphospholipid syndrome. BMC Med, 11 (2013), pp. 185
CDC, 2022. https://covid.cdc.gov/covid-data-tracker/#variant-proportions (Accessed on December 24, 2021).
Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. (2020). Epidemiolog- ical and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223):507–13.
Chen, T., et al., 2020. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ (clinical research ed.), 368, m1091.
Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. (2020). Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. J Clin Lab Anal. 2020;34: e23618. https://doi.org/10.1002/jcla.23618.
Chiou B, Connor JR. (2018). Emerging and dynamic biomedical uses of ferritin. Pharmaceuticals (Basel). 2018;11 (4): E124. doi:10.3390/ph11040124
Colafrancesco, S., et al., 2020. COVID-19 gone bad: a new character in the spectrum of the hyperferritinemic syndrome? Autoimmunity Reviews, 19 (7), 102573.
Cragg, S., Wagstaff, M., and Worwood, M., 1981. Detection of a glycosy- lated subunit in human serum ferritin. Biochemical journal, 199 (3), 565–571.
Cucinotta, D., & Vanelli, M. (2020). WHO Declares COVID-19 a Pandemic. *Acta bio-medica : Atenei Parmensis*, *91*(1), 157–160. https://doi.org/10.23750/abm.v91i1.9397
Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Spijker R, Taylor-Phillips S, et al. (2020). Antibody tests for identification of current and past infection with SARS-CoV-2. Cochrane Database Syst Rev;(6):Art. No.: CD013652. https://doi.org/10.1002/14651858.CD013652. Accessed 16 Jul 2020.
Drakesmith H, Prentice A. (2008). Viral infection and iron metabolism. Nat Rev Microbiol. 2008;6:541–52. https://doi.org/10.1038/nrmicro1930.
E. Taneri, S.A. Gomez-Ochoa, E. Llanaj, *et al*. (2020). Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Eur J Epidemiol, 35, pp. 763-773
Edeas M, Saleh J, Peyssonnaux C. (2020). Iron: innocent bystander or vicious culprit in COVID-19 pathogenesis? Int J Infect Dis. 2020. https://doi.org/10.1016/j.ijid.2020. 05.110
F.M. Torti, S.V. Torti. (2002). Regulation of ferritin genes and protein. Blood, 99, pp. 3505-3516
Fisler G, Haimed A, Levy CF, Stiles J, Capone CA, Fish JD, Brochstein JA, Taylor MD. (2020). Severe coronavirus disease 2019 infection in an adolescent patient after hematopoietic stem cell transplantation. Chest. 2020;158(4): e139–42. https://doi.org/10.1016/j.chest.2020.05.579.
Gandini O, Criniti A, Ballesio L, Giglio S, Galardo G, Gianni W, Santoro L, Angeloni A, Lubrano C. (2020). Serum ferritin is an independent risk factor for acute respiratory distress syndrome in COVID-19. J Infect. 2020;15:S0163- 4453(20)30617-4. https://doi.org/10.1016/j.jinf.2020.09.006.
Hoffmann M, Kleine-Weber H, Schroeder S, et al. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020; 181:271.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu y, et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.Lancet2020DOI: 10.1016/S0140-6736(20)30183-5

I Omotade, M Bennett, S Chitson, F Asiedu, B Harrington, M Patel. (2022). 670 FACTORS ASSOCIATED WITH MORTALITY IN MULTI-ETHNIC HOSPITALISED COVID PATIENTS. Age and Ageing, Volume 51, Issue Supplement_1, March 2022, afac037.670, https://doi.org/10.1093/ageing/afac037.670

J.I. Henter, A. Horne, M. Arico, *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer, 48 (2007), pp. 124-131

John Hopkins hospital and data center https://coronavirus.jhu.edu/map.html

Kaushal, K., Kaur, H., Sarma, P., Bhattacharyya, A., Sharma, D. J., Prajapat, M., Pathak, M., Kothari, A., Kumar, S., Rana, S., Kaur, M., Prakash, A., Mirza, A. A., Panda, P. K., Vivekanandan, S., Omar, B. J., Medhi, B., & Naithani, M. (2022). Serum ferritin as a predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis. Journal of critical care, 67, 172–181. https://doi.org/10.1016/j.jcrc.2021.09.023

Kell, D.B. and Pretorius, E., 2014. Serum ferritin is an important inflamma- tory disease marker, as it is mainly a leakage product from damaged cells. Metallomics: integrated biometal science, 6 (4), 748–773.

Kelly-Cirino C, Mazzola LT, Chua A, Oxenford CJ, Van Kerkhove MD. (2019). An updated roadmap for MERS-CoV research and product development: focus on diagnostics. BMJ Glob Health. 2019;4:e001105.

Kernan K.F., Carcillo J.A. (2017). Hyperferritinemia and inflammation. Int Immunol. 2017;29:401–409. doi: 10.1093/intimm/dxx031.

Knovich, M. A., Storey, J. A., Coffman, L. G., Torti, S. V., & Torti, F. M. (2009). Ferritin for the clinician. Blood reviews, 23(3), 95–104. https://doi.org/10.1016/j.blre.2008.08.001

Kooistra EJ, Waalders NJB, Grondman I, et al; (2020). RCI-COVID-19 Study Group. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. Crit Care. 2020;24(1):688. doi:10.1186/s13054-020-03364-w

Kuhn, L.C., 2015. Iron regulatory proteins and their role in controlling iron metabolism. Metallomics, 7, 232–243.

Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J. & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int. J. Antimicrob. Agents* **55**, 105924.

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia.N Engl J Med2020DOI: 10.1056/NEJMoa200131

Lin Z, Long F, Yang Y, Chen X, Xu L, Yang M. (2020). Serum ferritin as an independent risk factor for severity in COVID-19 patients. J Infect. 2020; 81:647–79. https://doi.org/ 10.1016/j.jinf.2020.06.053

Mulchandani R., Lyngdoh T., Kakkar A.K. (2021). Deciphering the COVID-19 cytokine storm: systematic review and meta-analysis. Eur J Clin Invest. 2021;51 doi: 10.1111/eci.13429.

Pal, M.; Berhanu, G.; Desalegn, C.; Kandi, V. (2020). Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus 2020, 12, e7423.

Payne, S. (2017). Family Coronaviridae. Viruses 2017, 149, 149–158.

Perlman S. (2020). Another decade, another coronavirus.N Engl J Med2020DOI: 10.1056/NEJMe2001126
Plays M., Müller S., Rodriguez R. (2020) Chemistry and biology of ferritin. Metallomics. mfab021. doi: 10.1093/mtomcs/mfab021.
R. Caricchio, M. Gallucci, C. Dass, *et al*. (2020). Preliminary predictive criteria for COVID-19 cytokine storm. Ann Rheum Dis.
Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. (2020). Transmission of 2019-nCoV infection from an asymptomatic contact in Germany.N Engl J Med2020DOI: 10.1056/NEJMc2001468
Slaats J, Ten Oever J, van de Veerdonk FL, Netea MG. (2016). IL-1beta/IL-6/CRP and IL-18/ferritin: Distinct Inflammatory Programs in Infections. PLoS Pathog. 2016; 12: e1005973.
Taiwan Centers for Disease ControlSevere Special Infectious PneumoniaAvailable at https://www.cdc.gov.tw/Disease/SubIndex/N6XvFa1YP9CXYdB0kNSA9A. Accessed February 7, 2020
Wang B., Thompson M.S., Adkins K.M. (2021). Characteristics of the iron-responsive element (IRE) stems in the untranslated regions of animal mRNAs. Open Biochem J. 2021;15 doi: 10.2174/1874091X02115010026.
Wang W, Tang J, Wei F. (2020). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China.J Med Virol2020DOI: 10.1002/jmv.25689
World Health Organization. Coronavirus disease 2019 (COVID-19) (2021) Situation Report-55. World Health Organization. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
Wu, Yi-Chia; Chen, Ching-Sunga; Chan, Yu-Jiuna,b,c,*(2020). The outbreak of COVID-19: An overview, Journal of the Chinese Medical Association: Volume 83 - Issue 3 - p 217-220 doi: 10.1097/JCMA.0000000000000270
Zhou F, Yu T, Du R, et al.(2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet ;395:1054-1062.

References

Banchini, Filippo & Cattaneo, Gaetano & Capelli, Patrizio. (2021). Serum ferritin levels in inflammation: a retrospective comparative analysis between COVID-19 and emergency surgical non-COVID-19 patients. World Journal of Emergency Surgery. 16. 10.1186/s13017-021-00354-3.
C. Rosario, G. Zandman-Goddard, E.G. Meyron-Holtz, D.P. D'Cruz, Y. Shoenfeld. (2013). The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophicantiphospholipid syndrome. BMC Med, 11 (2013), pp. 185
CDC, 2022. https://covid.cdc.gov/covid-data-tracker/#variant-proportions (Accessed on December 24, 2021).
Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. (2020). Epidemiolog- ical and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223):507–13.
Chen, T., et al., 2020. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ (clinical research ed.), 368, m1091.

Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. (2020). Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. J Clin Lab Anal. 2020;34: e23618. https://doi.org/10.1002/jcla.23618.

Chiou B, Connor JR. (2018). Emerging and dynamic biomedical uses of ferritin. Pharmaceuticals (Basel). 2018;11 (4): E124. doi:10.3390/ph11040124

Colafrancesco, S., et al., 2020. COVID-19 gone bad: a new character in the spectrum of the hyperferritinemic syndrome? Autoimmunity Reviews, 19 (7), 102573.

Cragg, S., Wagstaff, M., and Worwood, M., 1981. Detection of a glycosy- lated subunit in human serum ferritin. Biochemical journal, 199 (3), 565–571.

Cucinotta, D., & Vanelli, M. (2020). WHO Declares COVID-19 a Pandemic. *Acta bio-medica : Atenei Parmensis*, *91*(1), 157–160. https://doi.org/10.23750/abm.v91i1.9397

Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Spijker R, Taylor-Phillips S, et al. (2020). Antibody tests for identification of current and past infection with SARS-CoV-2. Cochrane Database Syst Rev;(6):Art. No.: CD013652. https://doi.org/10.1002/14651858.CD013652. Accessed 16 Jul 2020.

Drakesmith H, Prentice A. (2008). Viral infection and iron metabolism. Nat Rev Microbiol. 2008;6:541–52. https://doi.org/10.1038/nrmicro1930.

E. Taneri, S.A. Gomez-Ochoa, E. Llanaj, *et al*. (2020). Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Eur J Epidemiol, 35, pp. 763-773

Edeas M, Saleh J, Peyssonnaux C. (2020). Iron: innocent bystander or vicious culprit in COVID-19 pathogenesis? Int J Infect Dis. 2020. https://doi.org/10.1016/j.ijid.2020. 05.110

F.M. Torti, S.V. Torti. (2002). Regulation of ferritin genes and protein. Blood, 99, pp. 3505-3516

Fisler G, Haimed A, Levy CF, Stiles J, Capone CA, Fish JD, Brochstein JA, Taylor MD. (2020). Severe coronavirus disease 2019 infection in an adolescent patient after hematopoietic stem cell transplantation. Chest. 2020;158(4): e139–42. https://doi.org/10.1016/j.chest.2020.05.579.

Gandini O, Criniti A, Ballesio L, Giglio S, Galardo G, Gianni W, Santoro L, Angeloni A, Lubrano C. (2020). Serum ferritin is an independent risk factor for acute respiratory distress syndrome in COVID-19. J Infect. 2020;15:S0163- 4453(20)30617-4. https://doi.org/10.1016/j.jinf.2020.09.006.

Hoffmann M, Kleine-Weber H, Schroeder S, et al. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020; 181:271.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu y, et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.Lancet2020DOI: 10.1016/S0140-6736(20)30183-5

I Omotade, M Bennett, S Chitson, F Asiedu, B Harrington, M Patel. (2022). 670 FACTORS ASSOCIATED WITH MORTALITY IN MULTI-ETHNIC HOSPITALISED COVID PATIENTS. Age and Ageing, Volume 51, Issue Supplement_1, March 2022, afac037.670, https://doi.org/10.1093/ageing/afac037.670

J.I. Henter, A. Horne, M. Arico, *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer, 48 (2007), pp. 124-131

John Hopkins hospital and data center https://coronavirus.jhu.edu/map.html

Kaushal, K., Kaur, H., Sarma, P., Bhattacharyya, A., Sharma, D. J., Prajapat, M., Pathak, M., Kothari, A., Kumar, S., Rana, S., Kaur, M., Prakash, A., Mirza, A. A., Panda, P. K., Vivekanandan, S., Omar, B. J., Medhi, B., & Naithani, M. (2022). Serum ferritin as a

predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis. Journal of critical care, 67, 172–181. https://doi.org/10.1016/j.jcrc.2021.09.023

Kell, D.B. and Pretorius, E., 2014. Serum ferritin is an important inflamma- tory disease marker, as it is mainly a leakage product from damaged cells. Metallomics: integrated biometal science, 6 (4), 748–773.

Kelly-Cirino C, Mazzola LT, Chua A, Oxenford CJ, Van Kerkhove MD. (2019). An updated roadmap for MERS-CoV research and product development: focus on diagnostics. BMJ Glob Health. 2019;4:e001105.

Kernan K.F., Carcillo J.A. (2017). Hyperferritinemia and inflammation. Int Immunol. 2017;29:401–409. doi: 10.1093/intimm/dxx031.

Knovich, M. A., Storey, J. A., Coffman, L. G., Torti, S. V., & Torti, F. M. (2009). Ferritin for the clinician. Blood reviews, 23(3), 95–104. https://doi.org/10.1016/j.blre.2008.08.001

Kooistra EJ, Waalders NJB, Grondman I, et al; (2020). RCI-COVID-19 Study Group. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. Crit Care. 2020;24(1):688. doi:10.1186/s13054-020-03364-w

Kuhn, L.C., 2015. Iron regulatory proteins and their role in controlling iron metabolism. Metallomics, 7, 232–243.

Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J. & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int. J. Antimicrob. Agents* **55**, 105924.

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia.N Engl J Med2020DOI: 10.1056/NEJMoa200131

Lin Z, Long F, Yang Y, Chen X, Xu L, Yang M. (2020). Serum ferritin as an independent risk factor for severity in COVID-19 patients. J Infect. 2020; 81:647–79. https://doi.org/ 10.1016/j.jinf.2020.06.053

Mulchandani R., Lyngdoh T., Kakkar A.K. (2021). Deciphering the COVID-19 cytokine storm: systematic review and meta-analysis. Eur J Clin Invest. 2021;51 doi: 10.1111/eci.13429.

Pal, M.; Berhanu, G.; Desalegn, C.; Kandi, V. (2020). Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus 2020, 12, e7423.

Payne, S. (2017). Family Coronaviridae. Viruses 2017, 149, 149–158.

Perlman S. (2020). Another decade, another coronavirus.N Engl J Med2020DOI: 10.1056/NEJMe2001126

Plays M., Müller S., Rodriguez R. (2020) Chemistry and biology of ferritin. Metallomics. mfab021. doi: 10.1093/mtomcs/mfab021.

R. Caricchio, M. Gallucci, C. Dass, *et al*. (2020). Preliminary predictive criteria for COVID-19 cytokine storm. Ann Rheum Dis.

Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. (2020). Transmission of 2019-nCoV infection from an asymptomatic contact in Germany.N Engl J Med2020DOI: 10.1056/NEJMc2001468

Slaats J, Ten Oever J, van de Veerdonk FL, Netea MG. (2016). IL-1beta/IL-6/CRP and IL-18/ferritin: Distinct Inflammatory Programs in Infections. PLoS Pathog. 2016; 12: e1005973.

Taiwan Centers for Disease ControlSevere Special Infectious PneumoniaAvailable at https://www.cdc.gov.tw/Disease/SubIndex/N6XvFa1YP9CXYdB0kNSA9A. Accessed February 7, 2020

Wang B., Thompson M.S., Adkins K.M. (2021). Characteristics of the iron-responsive element (IRE) stems in the untranslated regions of animal mRNAs. Open Biochem J. 2021;15 doi: 10.2174/1874091X02115010026.

Wang W, Tang J, Wei F. (2020). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China.J Med Virol2020DOI: 10.1002/jmv.25689

World Health Organization. Coronavirus disease 2019 (COVID-19) (2021) Situation Report-55. World Health Organization. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

Wu, Yi-Chia; Chen, Ching-Sunga; Chan, Yu-Jiuna,b,c,*(2020). The outbreak of COVID-19: An overview, Journal of the Chinese Medical Association: Volume 83 - Issue 3 - p 217-220 doi: 10.1097/JCMA.0000000000000270

Zhou F, Yu T, Du R, et al.(2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet ;395:1054-1062.