ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 6, Issue – 2, April - 2023, Page No. : 241 - 250

Association of inflammatory biomarkers with ferritin levels in covid19 patients

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How to citation this article: Dr. N. Sanjana, Dr. Archana. A. Dharwadkar, Dr. Bindupavani, Dr. S. Praveena, Dr. Zarin Kauser, "Association of inflammatory biomarkers with ferritin levels in covid19 patients", IJMACR- April - 2023, Volume – 6, Issue - 2, P. No. 241 – 250.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Introduction: Covid-19 is mainly hypothesized to be caused by cytokine storm. Increased levels of inflammatory biomarkers including ferritin, crp have been found in covid-19 patients, and is associated with increased risk of severe form of covid-19 infection.

Aim objectives: To determine levels of procalcitonin (pct), c-reactive protein(CRP), lymphocyte count in patients with high-ferritin & low-ferritin levels.

Materials &methods: This is an observational study which included 109confirmed covid-19 patients attending our hospital& divided them into high(>500ng/ml) and low-ferritin(<500ng/ml). serum ferritin cut-off value of 500ng/ml is derived from hlh-2004 criterion(hemophagocytic lympho-histiocytosis-hlh).in both the groups we have estimated crp, pct and lymphocyte count.

Results: The mean & sd values of ferritin in low-ferritin group (223.78 and 151.86), in high-ferritin group (1006.98 and 351.57), with p value of (0.000) which is statistically significant. The mean and sd values of pct in low-ferritin group (1.025 and 0.5), in high-ferritin group (3.22 and 1.2),with p value (< 0.001) which is statistically significant. The mean &sd values of lymphocyte count in low-ferritin group (16.95 and 9.79), in high-ferritin group (8.90 and 5.27), with p value (0.0002) which is statistically significant. The mean and sd values of crp in low-ferritin group (19.29 and 15.7),in high-ferritin group (24.68and 17.56),with p value (0.096),which is not statistically significant.

Conclusion: This observational study demonstrated that serum ferritin can be taken as independent risk factor in segregation of patients in to high and low risk groups. This finding has been reflected by lymphopenia and increased procalcitonin levels in high ferritin groups which is due to altered immune response causing susceptible to bacterial infections. Hence assessing serum ferritin levels may be important to recognize high-risk individuals with severe covid-19.

Keywords: Covid -19, SARS, WHO.

Introduction

Since December 2019, the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-cov-2) has rapidly developed into a global outbreak characterized by a human-to-human transmission [1].

World Health Organization (WHO) named the disease as “Coronavirus disease 2019” (COVID-19) and declared it as a public health emergency of international concern on January 30, 2020.[2] On March 11, 2020, WHO declared the COVID-19 a pandemic [2].

Globally, as of 6:19pm CET, 13 February 2023, there have been 755,703,002 confirmed cases of COVID-19, including 6,836,825 deaths, reported to WHO [3].

In India, from 3 January 2020 to 6:19pm CET, 13 February 2023, there have been 44,684,197 confirmed cases of COVID-19 with 530,750 deaths, reported to WHO [3].

Patients with comorbidities such as diabetes, cardiovascular disease, underlying respiratory diseases and cancer are at high risk of severe complications and even death [4].

Although most patients have mild symptoms and good prognosis, patients with critically severe disease are at high risk of mortality. Therefore, it is urgent to find appropriate indicators to discriminate the severity and improve the progress to reduce the mortality rate of patients with COVID-19[5].

COVID-19 is accompanied by cytokine storm which results in significant elevation of cytokines and biomarkers such as Ferritin, C-reactive protein, Lymphocyte count, Procalcitonin ultimately having fatal outcome. The levels of these inflammatory markers help the clinician to plan therapeutic intervention [6].

Ferritin is a key mediator of immune dysregulation, especially under extreme hyperserotonemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm [7].

CRP predicts the possibility of aggravation of non-severe COVID-19 infection in patients, which can help health care workers identify those patients at an early stage for early treatment [8].

Lymphocyte reduction is due to lymphocytic infiltration, sequestration in the lung and git. Other mechanisms like lymphocyte expression of ace2 receptor and increase of

pro-inflammatory cytokines could also induce further lymphocyte reduction [9].

Procalcitonin test does not appear substantially altered in patients with covid-19 at admission, but the progressive increase of its value seemingly mirrors the severity of the disease with poor prognosis. Serum procalcitonin levels are typically normal in patients with viral infections (or viral sepsis), whilst its gradual increase probably mirrors bacterial superinfection, which may then contribute to drive the clinical course towards unfavorable progression [10].

The laboratory tests combined with the clinical evaluation can allow a rapid assessment of the patient's condition to guide clinicians in finding the optimal approach and priority in these covid-19 patients. Serum ferritin is particularly interesting due to its potential diagnostic and prognostic role. The present study conducted to determine the potential relationship of ferritin with other inflammatory biomarkers like of c-reactive protein (crp), lymphocyte count, procalcitonin (pct)of covid-19 patients.

Aim: To study the association of c-reactive protein (crp), lymphocyte count, procalcitonin (pct) with ferritin levels in covid 19 patients.

Materials &methods: This is an observational study carried in the department of biochemistry from august 2020 to February 2021 at Kamineni academy medical sciences and research Centre& hospital, lb Nagar, Hyderabad. Study included 109 confirmed covid-19 patients who are tested positive for rt-pcr. Study subjects were divided into two groups. Group1(<500ng/ml) and group 2(>500ng/ml). Serum ferritin cut-off value of 500ng/ml is derived from hlh-2004 criterion (hemophagocytic lymph histiocytosis-hlh). In both the groups we have compared and correlated crp, lymphocyte count, and pct.

Inclusion criteria: all the patients who are tested positive for covid-19 with rt-pcr and age group between 20-80 are included in this study.

Methods

1. ferritin: chemiluminescence immunoassay method in beckman coulter immunoassay.
2. C-reactive protein: latex agglutination manual method.
3. Procalcitonin: time resolved fluorescence method in aqt90 radiometer.
4. Lymphocyte count: flowcytometry method in cell counter.

Reference ranges

1.ferritin: 11.0 -306.8ng/ml

2.C-reactive protein: <6mg/l

3. Procalcitonin: 0-0.5ng/ml

4. Lymphocyte count: X 10^3/µL

Results

This is an observational study carried out in the Department of Biochemistry from August 2020 to February 2021 at Kamineni Academy Medical Sciences and Research Centre& Hospital, LB Nagar, Hyderabad. Study included 109 confirmed covid-19 patients who are tested positive for RT-PCR. Thestudy subjects were divided into 2 groups i.e., group 1 (<500ng/ml) and group 2(>500ng/ml) and their CRP, lymphocyte count, PCT were compared among both groups.

The present study statistical analysis was done with the SPSS version 20 software.

Figure-1: **Mean age (yrs.) among Group 1&Group 2with COVID 19.**

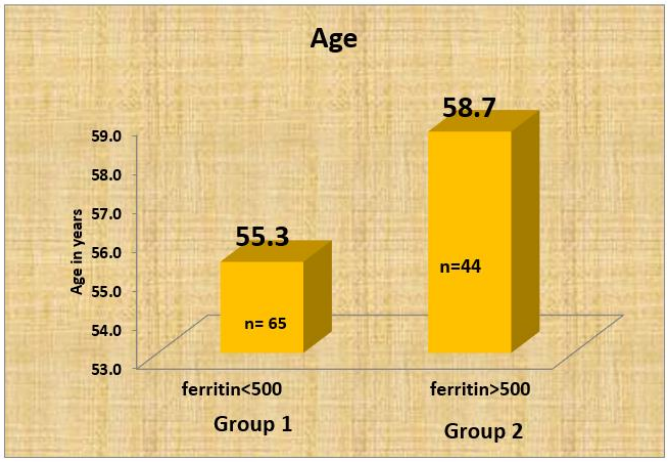
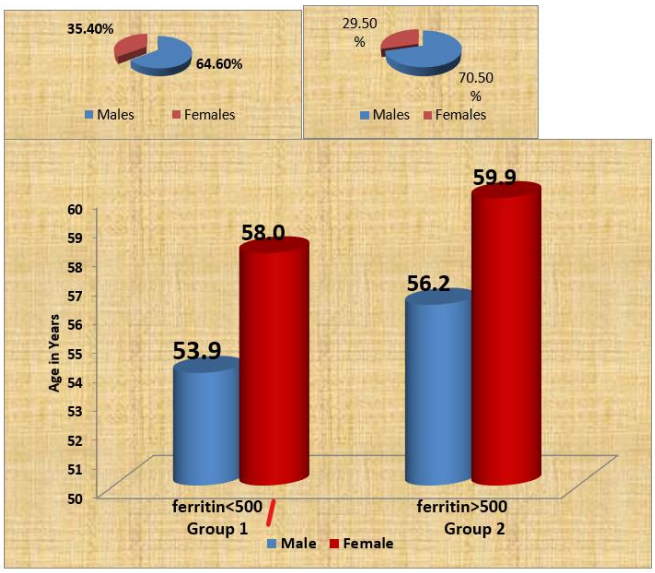


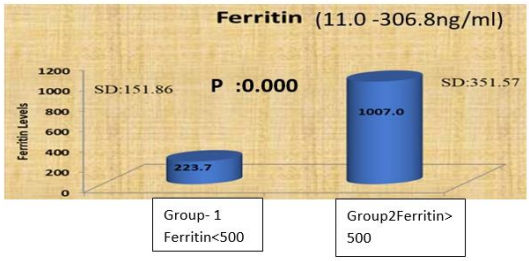
Figure-2: **Mean age (yrs.) of Males & Females among Group 1&Group 2 with COVID 19**



Total number of covid patients in group 1 (ferritin <500ng/ml) are 65 with Mean age -55.33yr (Males-53.9yr; Females 58yr)

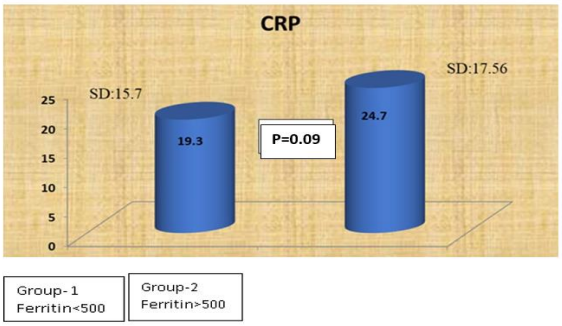
Total number of covid patients in group 2 (ferritin >500ng/ml) are 44 with Mean age - 58.68yr, (Males-56.2yr Females 59.9yr.)

Figure -3: **Mean±SD of Ferritin among males and females in group 1 and group 2**



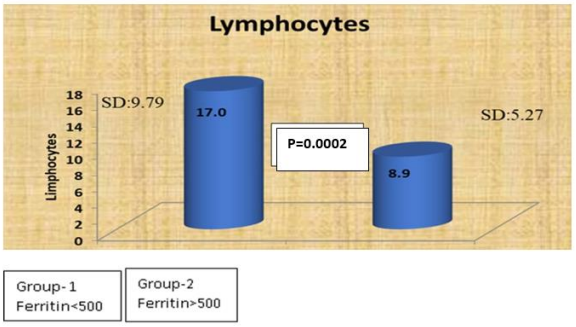
This figure shows increased ferritin levels in group 2 (1007.0±351.7) when compared with group 1 (223.7±151.86). P value is statistically significant.

Figure-4: **Mean±SD of CRP among males and females in group 1 and group 2**



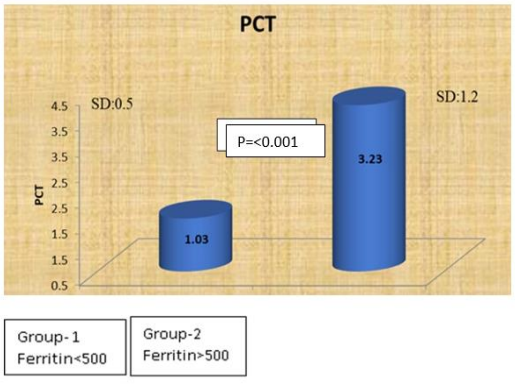
This figure shows mild increase of CRP levels in group2 (24.7±17.56) when compared with group 1 (19.3±15.7). P value is 0.09.

Figure-5: **Mean±SD of Lymphocytes among males and females in group1 and group 2**



This figure shows increased Lymphocyteslevels in group 1 (17.0±9.79) when compared with group 2 (8.9±5.27). P value is statistically significant.

Figure-6: **Mean±SD of PCT among males and females in group 1 and group 2**



This figure shows increased PCT levels in group 2(3.23±1.2) when compared with group 1(1.03±0.5). P value is statistically significant.

Table 1: Correlation of ferritin with CRP, lymphocytes, PCT in Group-1.

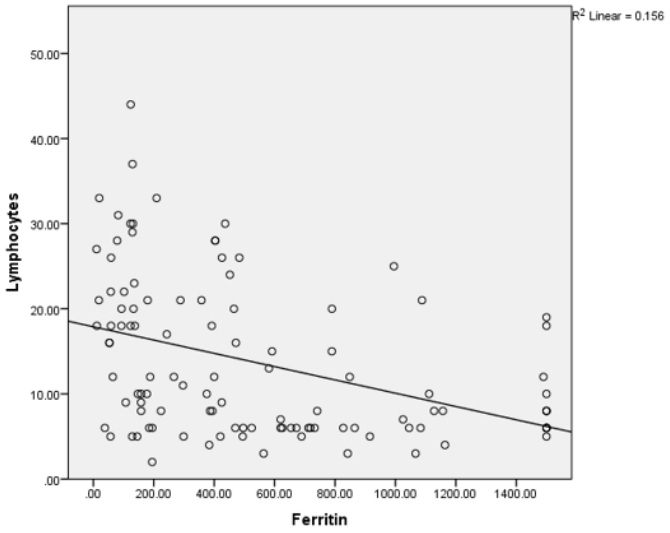
Group 1		CRP	Lymphocytes	PCT
Ferritin (<500 ng/ml)	Pearson Correlation	.211	-.200	.058
	P Value	.091	.110	.645
	N	65	65	65

Table 1: shows that the significant correlation of Ferritin with CRP, lymphocytes and PCT ingroup 1

Table 2: Corerelation of ferritin with CRP, lymphocytes, PCT in Group 2

Group 2		**CRP**	**Lymphocytes**	**PCT**
Ferritin (>500ng/ml)	Pearson Correlation	.018	-.063	.111
	P Value	.906	.686	.474
	N	44	44	44

Figure 7: correlation of Ferritin with lymphocytesin both groups-1 and 2



As ferritin levels are decreasing lymphocytes levels are increasing. (GROUP-1)

As ferritin levels are increasing lymphocytes levels are decreasing. (GROUP-2)

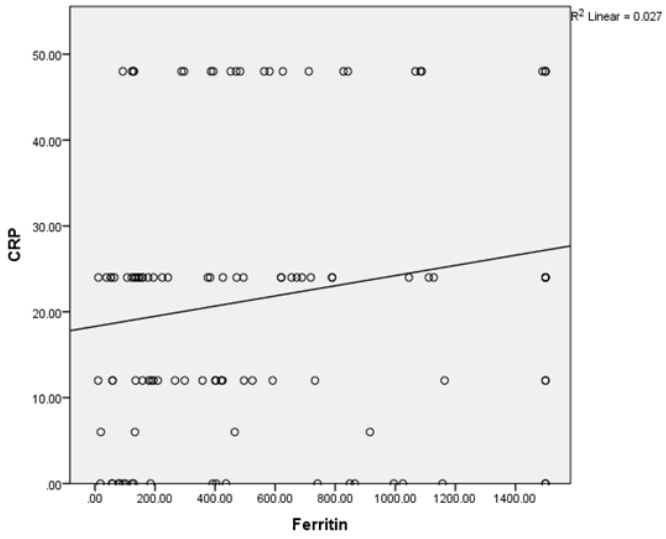


Figure 8: Correlation of Ferritin with CRP.

As ferritin levels decrease, CRP levels also decrease.

As ferritin levels increase, CRP levels also increase.

Discussion

Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm. It has been reported that fatal outcomes by covid-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome. Many individuals with diabetes exhibit elevated serum ferritin levels, and it is known that they face a higher probability to experience serious complications from covid-19. On this basis, we briefly review evidence supporting the hypothesis that ferritin levels might be a crucial factor influencing the severity of covid-19 [7].

In the systemic hyper inflammation phase of covid-19 proposed by siddiqi and mehra,[11] there is a significant elevation of inflammatory cytokines and biomarkers, such as interleukin (il)-2, il-6, il-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-

α, tumor necrosis factor-α (tnf-α), crp, ferritin, pct, and d-dimer. This stage consists of the most severe manifestation of the cytokine storm, in which excessive hyperinflammation may lead to cardiopulmonary collapse and multi-organ failure [11,12].

Crp is an acute phase inflammatory protein produced by the liver that may be elevated in several conditions, such as inflammation, cardiovascular disease, and infection. Despite its value in predicting a poor outcome in covid-19, it should be noted that various factors could affect serum crp levels, including age, gender, smoking status, weight, lipid levels, blood pressure, and liver injury [13]. These factors should be taken into account while interpreting the serum crp level. In addition, recent evidence has shown that serum crp level could also be used in monitoring the progression and improvement of patients with covid-19 [14].

A peptide precursor of the hormone calcitonin, pct, has been widely investigated as a promising biomarker for the initial investigation of a bacterial infection [15].an elevated serum pct is often found in patients with sepsis and septic shock[16]. While it is still controversial whether pct can accurately distinguish bacterial or viral pneumonia,[17] it was found that pct-guided therapy in acute respiratory infections reduces the antibiotic exposure and side effects, and improves the survival rate [18]. Bacterial infections trigger extra thyroidal synthesis of pct, which is actively maintained by elevated values of il-6, il-1β, and tnf-α, while viral infections hinder pct production due to interferon-γ [19]. This explains why serum pct concentrations remain normal in uncomplicated cases of covid-19 and inflated values may indicate bacterial co-infection in severe cases [10].

In a study by jian bo xu et al, it was found that baseline levels of pct (≥ 0.10 ng/ml) and crp (≥ 52.14 mg/l) have been addressed as independent predictors of survival in patients with covid-19 [5].

In a study by rui hu et al, demonstrates that pct may be an indicator of disease severity and may contribute to determining the severity of patients with covid-19. In addition, serial pct measurements may be useful in predicting the prognosis of covid-19 [20].

According to a study by zachary illg et al, absolute lymphocyte count can be used as a marker of disease severity in patients with covid-19 [21]

In a study done by dominic stringer et al, a crp of >40 mg/l on admission to hospital should be seen as a reliable indicator of disease severity and increased risk of death. Crp can be used as a prognostic indicator [22].

In a meta-analysis by ian huang et al, they found that an elevated serum pct was associated with mortality and severe covid-19. Sroc analysis showed the diagnostic value of serum pct ⩾0.5 mg/l for a composite poor outcome in covid-19 (88% sensitivity, 68% specificity, lr +2.7 and lr -0.2) [23].

In one study with 20 covid-19 patients, it was found that individuals with severe and very severe covid-19 exhibited increased serum ferritin level, in the very severe covid-19 group significantly higher serum ferritin was seen than in the severe covid-19 group (1006.16 ng/ml [iqr: 408.265-1988.25] vs 291.13 ng/ml [iqr: 102.1-648.42], respectively) [24].

Chen et al. Analyzed the clinical characteristics of 99 patients, in which 63 of them had serum ferritin way above of the normal range [25]. Elevated ferritin levels were found also in autopsies of 12 patients whose cause of death was sars-cov-2 infection [26]. An analysis of the peripheral blood of 69 patients with severe covid-19

revealed elevated levels of ferritin compared with patients with non-severe disease. Therefore, serum ferritin levels were closely related to the severity of covid-19 [27].

Studies have shown that the ferritin levels were significantly higher in more severe patients than that in less severe patients and potential risk factor of poor prognosis in covid-19 patients. So, in this study, covid-19 positive patients were divided based on their ferritin levels into group 1 (<500ng/ml) and group 2(>500ng/ml) and their crp, lymphocyte count, pct were compared among both groups.

Hyperferritinemia caused by the excessive inflammation due to the infection is associated with the admission to the intensive care unit and high mortality, and represents an indication to recognize high-risk patients to guide the therapeutic intervention to control inflammation [28,29,30].

Ferritin is an iron-storing protein, its serum level reflects the normal iron level and helps the diagnosis of iron deficiency anemia.circulation ferritin level increases during viral infections and can be a marker of viral replication[31,32].

Increased levels of ferritin due to cytokine storm and shlh have also been reported in severe covid-19 patients[33,34].

During the cytokine storm in covid-19, many inflammatory cytokines are rapidly produced, including il-6, tnf-α, il-1β, il-12, and ifn-γ, which stimulate hepatocytes, kupffer cells, and macrophages to secrete ferritin[35].

The uncontrolled and dysfunctional immune response associated with macrophage activation, hyper-ferritinemia syndrome, and thrombotic storm finally leads to multiple organ damage. Notably, ferritin is not only the result of excessive inflammation, but also plays a pathogenic role in the inflammation process through its bind with the t-cell immunoglobulin and mucin domain 2 (tim-2) by promoting the expression of multiple pro-inflammatory mediators [28]. Besides, some studies showed that h chain of the ferritin activates macrophages to secrete inflammatory cytokines.

Zhou et al revealed that the increase in ferritin level is associated with the worsening of the covid-19 [36].

The cytokine storm and the exaggerated host immune response (ie, ferritin) participate in the development of ards, which is the leading cause of mortality if progresses to respiratory failure [37].wu et al demonstrated that several factors related to ards are not associated with the death from ards, including ferritin [37].

Linlinchenget al demonstrated that the concentration of serum ferritin increases in patients with high mortality risk, which was observed in a meta-analysis, and its decrease indicates the control of inflammation, thus promoting survival [38].

In our study males were affected more with severe covid-19 infection. The females were of higher mean age(yrs) as compared to males.

In our study as the ferritin shows positive correlation with crp, pct and negative correlation with lymphocytes. This means that as ferritin level increases crp increases, pct increases but lymphocyte count decreases.

There is significant lymphopenia and increase in crp, pct levels in patients with hyperferritinemia (>500ng/ml) which can predict the severity of covid-19 infections suggesting deranged immune response and increased susceptibility to secondary bacterial infections.

Conclusion

This is an observational study concluded that males were affected more with severe covid-19 infection. There is significant lymphopenia and increase in crp, pct levels in patients with hyperferritinemiawhich can predict the severity of covid-19 infections suggesting deranged immune response and increased susceptibility to secondary bacterial infections.this study suggests that inflammatory markers like crp, pct and lymphocyte count have definite association with ferritin levels. Hence ferritin levels can predict severity of covid -19 infections.

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