

# Serum Ferritin Concentration in Corona Virus Disease 19

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## ABSTRACT

**Introduction:** Coronavirus disease 19 (COVID-19) is a complex disease responsible for the development of exacerbated inflammatory response (cytokine storm) that ultimately leads to multiorgan failure and death. Serum ferritin has been recently identified as one of the inflammatory markers responsible for the pro-inflammatory effects. Small amount of ferritin is present in plasma (15-150 ng/mL) which might increase with the severity of COVID-19. Therefore, measurement of ferritin is essential in identifying disease severity and predict disease prognosis.

**Objective:** This study aims to assess the ferritin level in COVID-19 patients.

**Methods:** A cross-sectional study was carried out on 259 COVID-19 patients visiting KIST Medical College and Teaching Hospital (KISTMCTH), Lalitpur, Nepal from November 2020 to April 2021. Serum ferritin was estimated in the automated Siemens ADVIA Centaur CP Chemiluminescence Immunoassay system. All the patients visiting KISTMCTH referred by clinician for ferritin assessment were included in this study. Data collected using the proforma tool was tabulated in SPSS 21 and statistical analysis was done by inferential statistical test.

**Results:** Out of total 259 COVID-19 patients, 58.7% were male and the majority of patients (82.6%) were below 70 years of age. The mean age for all participants was 52.11±16.59 years. Hyperferritinemia was seen in 218 (84.16%) COVID-19 patients. The mean value of serum ferritin was 767.1±789.86 (IQR: 12.8-4590) ng/mL and was significantly higher in males (p<0.001). Comparing the mean values of ferritin between the patients below and above 70 years, no statistical difference was observed (p=0.872).

**Conclusions:** In our study, serum ferritin levels were greatly increased in patients with COVID-19 infection.

**Keywords:** Coronavirus disease 19; cytokine storm; inflammatory marker; serum ferritin.

## INTRODUCTION

Coronavirus disease 19 (COVID-19) is a viral infection caused by newly discovered corona virus; variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first found in Wuhan, China in 2019.<sup>1-3</sup> Most people infected with the COVID-19 virus may experience mild to moderate respiratory illness and recover

spontaneously without aid of treatment. Older people and patients with comorbidities like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more prone to develop serious illness.<sup>4</sup>

Ferritin is an intracellular protein that binds with iron and helps store iron in the body and has been long studied as a marker of iron metabolism.<sup>5</sup> The normal range of ferritin in serum is between 15 ng/mL and 150 ng/mL.<sup>6</sup> Ferritin is also recognized as a biomarker of inflammation and is responsible for immune suppression and uncontrolled pro-inflammatory effects, contributing to the cytokine storm.<sup>7,8</sup> In order to limit severe complications and eventual death, the early identification of COVID-19 patients

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with negative prognostic factors might be useful in the management strategy.<sup>9</sup> Many individuals with diabetes and possibly other disorder like thrombotic disease and cancer exhibit elevated serum ferritin levels, and they are liable to experience serious complications from COVID-19.<sup>10-12</sup> Macrophages release inflammatory cytokine like Interleukins 6 (IL-6), IL-10, and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) which is increased in patients with severe COVID-19 disease, resulting in cell damage to the lungs and other organs. Serum ferritin has been recently cited as one of the indicators of mortality in COVID-19 patients.<sup>13-15</sup> Therefore, measurement of ferritin is crucial in identifying disease severity and foresees disease prognosis.<sup>16</sup> The objective of this study is to assess the level of ferritin in COVID-19 patients admitted to tertiary care hospital.

## METHODS

This is a cross-sectional study carried out on 259 patients with SARS-CoV-2 infection, based on a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test on throat and nasopharyngeal swab, visiting KIST Medical College and Teaching Hospital (KISTMCTH), Lalitpur, Nepal. This study was approved by the Institutional Review Committee (IRC) of KISTMCTH (Ref. No.: 077/78/46). Informed consent was obtained from all the patients.

Patients who did not give the consent were excluded out from the study.

All the patients visiting KISTMCTH referred by clinician for ferritin assessment were included in this study. Prospective data from COVID-19 patients were collected for the duration of 6 months from 1<sup>st</sup> November 2020 to 30<sup>th</sup> April 2021 as referred by the treating physician. For the estimation of serum ferritin levels, 3 ml of venous blood sample was drawn in a gel tube and serum was separated by centrifuge at 3000 rpm for 5 minutes. Serum ferritin was estimated in the automated Siemens ADVIA Centaur CP Chemiluminescence Immunoassay (CLIA) system.

Convenience sampling method was used for sample collection from the COVID-19 patients. Data collected using proforma tool was tabulated in SPSS 21 and statistical analysis was done by independent t-test which is an inferential statistical test. The p-value was set at 0.05.

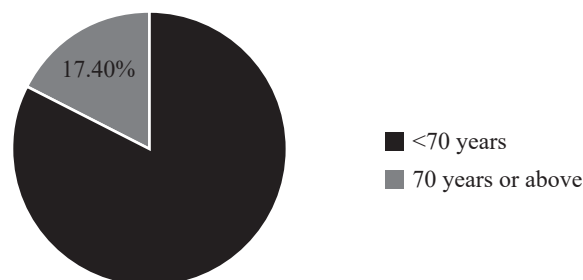
## RESULTS

A total of 259 COVID-19 patients were included in the study. The mean age for all patients was  $52.11 \pm 16.59$  years ranging from 11 to 88 years. Majority of the patient were male (58.7%) as shown in Table 1.

**Table 1: Distribution of COVID-19 patients according to sex.**

Sex	Number (N)	Percentage (%)
Male	152	58.7%
Female	107	41.3%
Total	259	100%

Regarding the distribution of patients with COVID-19, 82.6% of patients were below 70 years and 17.4% were 70 years and above. (Figure 1)



**Figure 1: Distribution of COVID-19 patients according to age group**

**Table 2: Comparison of demographic characteristics and serum ferritin concentration in COVID-19 patients.**

	Number (n)	Mean (ng/mL)	Standard deviation	p value
Age, years				
<70 years	214	770.74	804.91	0.872
70 years and above	45	749.79	722.16	
Sex				
Male	152	927.02	865.44	<0.001
Female	107	539.94	602.32	

Hyperferritinemia was seen in 218 (84.16%) COVID-19 patients. The mean value of serum ferritin was  $767.1 \pm 789.86$  (IQR: 12.8-4590) ng/mL. This high variability in the data of ferritin value was due to the vast differences in the high (4590 ng/mL) and low (12.8 ng/mL) values of ferritin level obtained in COVID-19 patients. The mean value of serum ferritin in males ( $927.02 \pm 865.44$  ng/mL) was significantly higher as compared to the mean value ( $539.94 \pm 602.32$  ng/mL) of females ( $p < 0.001$ ). Comparing the mean values of ferritin between the patients below and above 70 years, no statistical difference was observed ( $p = 0.872$ ) which was shown in Table 2.

## DISCUSSION

SARS-Cov-2 induces an abnormal immune and inflammatory reaction due to the infiltration of many immune cells resulting in the manifestation of a cytokine storm, including the expression of pro-inflammatory cytokines. This leads to increased inflammation that causes cell damage and the release of ferritin.<sup>17, 18</sup>

In the present study, the demographic characteristics of the COVID-19 patients were studied. The average age of the patients was  $52.11 \pm 16.59$  years. Similar results were obtained in various studies done by the different group of researchers.<sup>19, 20</sup> But the study was done in Karnataka, India by Rajanna et al. revealed the average age of their study patients to be  $43.89 \pm 15.58$  years which was lesser than our study.<sup>21</sup> Our study has demonstrated high percentage of males (58.7%) as compared to females. In concurrence with our findings, several studies conducted in different part of the world have observed the male preponderance

in COVID-19 patients.<sup>8, 14, 19, 22</sup> Females are less prone to viral infections. This reduced susceptibility of females could be attributed to the protection from X chromosome and sex hormones, which play an important role in innate and adaptive immunity.<sup>23</sup>

This study found that 218 (84.16%) of the COVID-19 patients had increased serum ferritin levels ( $>150$  ng/mL) i.e. hyperferritinemia. Ferritin is a key mediator of immune dysfunction, more specifically when there is hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, terminating to the cytokine storm.<sup>7</sup> The mean values of serum ferritin in patients below and above 70 years were  $770.74 \pm 804.91$  and  $749.79 \pm 722.16$  respectively. From these findings, we had observed that the mean values of serum ferritin in both groups were similar and there was no statistical difference ( $p = 0.872$ ) according to age group. In our study, the mean value of serum ferritin in males ( $927.02 \pm 865.44$  ng/mL) was higher as compared to females ( $539.94 \pm 602.32$  ng/mL) therefore, we found significant differences in ferritin concentrations between males and females COVID-19 patients ( $p < 0.001$ ). The exact mechanism of the gender difference in ferritin level is unknown. It may be due to the high prevalence of iron deficiency in female. In male, serum ferritin levels tended to increase sharply with progression to puberty whereas in female the serum ferritin levels remained constant until age 14 years and decreased thereafter.<sup>24</sup>

## CONCLUSIONS

In conclusion, the current study showed that serum ferritin concentrations were greatly increased in most of the COVID-19 patients. Our findings suggest the

use of serum ferritin as a marker for COVID-19 infection.

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**Conflict of Interest:** None

**NJHS**

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