

# Comparison of Diagnostic Accuracy of CRP Versus Ferritin in COVID Patients as a Marker of Severity of Disease Taking WHO Severity Classification as Gold Standard

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## ABSTRACT

**Objective:** To determine the diagnostic accuracy of elevated C reactive protein (CRP) and ferritin in predicting severe Covid-19 infection using the World Health Organization's (WHO) Covid-19 severity classification as gold standard.

**Study Design:** Descriptive study.

**Place and Duration of Study:** This study was conducted at the Pak Emirates Military Hospital, Rawalpindi, from January 1<sup>st</sup> 2021 till April 30<sup>th</sup> 2021. Ethical review committee's (ERC) approval was taken and good clinical practice guidelines were followed.

**Material and Methods:** Baseline blood samples were sent to the hospital laboratory for the measurement of C reactive protein and ferritin levels. PCR was taken as gold standard for the diagnosis of Corona virus disease. Patients were classified into severe and non-severe categories using WHO classification of severity. Sensitivity, specificity, diagnostic accuracy, negative predictive value and positive predictive value were calculated for elevated CRP and ferritin.

**Results:** There were 65 (57.5%) patients who had severe Covid-19 disease and 48 (42.5%) patients who had non-severe Covid-19 disease. Among the patients with severe Covid-19, 57 (87.7%) had elevated CRP levels, and 50 (76.9%) patients had elevated ferritin levels. Testing ferritin levels, against the severity of Covid-19 patients, there was a sensitivity of 76.9%, specificity of 79.2%, positive predictive value (PPV) of 83.3%, negative predictive value (NPV) of 71.7% and diagnostic accuracy of 77.8%. Testing CRP levels, there was a sensitivity of 87.7%, specificity of 85.4%, PPV of 89.1%, NPV of 83.6% and diagnostic accuracy of 86.7%.

**Conclusion:** The results from our study show that CRP has a slightly improved diagnostic accuracy as compared to ferritin. However, both these markers have value in the prediction of severity of Covid-19 infection.

**Keywords:** Covid-19, elevated C reactive protein and ferritin.

## INTRODUCTION

SARS-CoV-2 had its first case in China and then it became a pandemic. Corona virus is a respiratory tract infection. Covid-19 is transmitted rapidly from one individual to another by respiratory droplets<sup>1</sup>. The World Health Organization (WHO) had declared Covid-19 to be public health emergency of international concern (PHEIC)<sup>2</sup>. The clinical presentation of corona virus is diverse, it also has a multidimensional pathophysiology and a wide range of findings, depending on disease course and its severity<sup>3</sup>. For instance, Covid patients could present with acute respiratory distress syndrome, pneumonia, and multi-organ failure. On the other hand, Covid-19 patients could be asymptomatic or have a mild influenza-like illness<sup>4</sup>. Researchers are exploring as to why Covid-19 has such a varied presentation<sup>4</sup>. It has been suggested that the role of laboratory markers should be explored for Covid-19 infection's risk stratification<sup>4</sup>. Researchers have accumulated evidence that among the severely ill corona virus patients there are characteristics of hyperinflammation, which comprises of raised serum C-reactive protein (CRP), and hyperferritinemia. These discoveries indicate a potential role of a cytokine storm in SARS-CoV-2 pathophysiology<sup>4</sup>. World is striving to control the pandemic particularly the developing world is still struggling to treat and control Covid-19 disease.

Detection of Covid-19 needs a confirmed diagnosis. Reverse transcriptase polymerase chain reaction (RT PCR) is used for the diagnosis<sup>5</sup>. However, scientists are looking for more economical ways to detect SARS-CoV-2<sup>6</sup>. Literature shows that comparison of hematological parameters between mild and severe Covid-19 patients has demonstrated significant disparities in C-reactive protein (CRP) and ferritin levels<sup>7-9</sup>. Raised ferritin levels are noted in Covid-19 patients owing to the cytokine storm in severe Covid-19 patients<sup>3,9</sup>. Cytokine storm is an abnormal immune reaction in the immunopathogenicity of corona virus which is equivalent to the response that occurs in influenza; cytokines containing TNF- $\alpha$ , IL-6, IL-8, and IL-12 are discharged in an enormous amount as Covid-

19 disease progresses. The result of this cytokine storm is an acute respiratory distress syndrome (ARDS)<sup>10</sup>. During this process Covid-19 infection worsens and ferritin levels rise. Such severe patients require admission to the intensive care unit and their lungs are affected and are associated with poor prognosis<sup>3</sup>. Nevertheless, most of these researches<sup>3</sup> had a limited sample size or were single center studies. However, alternate research noted no such relationship between severity of corona virus and ferritin levels<sup>11</sup>. This implies that there is still a gap in literature. The other biomarker, C reactive protein (CRP) levels are also raised in inflammatory diseases. CRP is not noted to be an accurate marker of Covid-19, however, the bulk of patients do appear to have an increase in CRP levels, although several cases without Covid-19 also show an increase in CRP levels. These laboratory markers are tested among patients with corona virus infection and may have a role in the triage of patients with potential corona virus infection and for their treatment<sup>3</sup>, especially in low resource settings. Ferritin's role and diagnostic accuracy still needs to be determined. There is a dearth of literature on the role of ferritin and C reactive protein levels in patients with severe Covid, dwelling in developing countries. In addition, there are conflicting outcomes exhibited by several studies on the possible association with severity of Covid-19 and these lab markers. Our study was aimed at evaluating diagnostic accuracy of CRP versus ferritin in corona virus patients as a marker of severity of disease taking World Health Organization's (WHO) severity classification as gold standard.

## PATIENTS AND METHODS

We had obtained permission from the ethics review committee (ERC) prior to conducting the study. Informed consent was taken from patients willing to be part of the study. Data were collected in a structured questionnaire. We assigned a unique identifier to each case in the data sheet. The data was kept in the principal

investigator's office, under lock and key and confidentiality was maintained throughout the study period.

There were 113 patients in this descriptive study conducted from January 1<sup>st</sup> 2021 till April 30<sup>th</sup> 2021. Patients between age of 20-70 years from either gender, who had presented with a confirmed diagnosis of Covid-19 at Pak Emirates Military Hospital, Rawalpindi, were included in this research. In our research we had looked at the clinical features and patient's history. Data regarding patient's age, sex, CRP levels, ferritin and severity of Covid-19 were noted. Patients who had interstitial lung disease, pulmonary tuberculosis, chronic liver disease, immunosuppression, heart failure, recent history of cardiothoracic surgery, stroke, chronic kidney disease, or asthma and chronic obstructive pulmonary disease (COPD) were excluded from the study.

Both CRP and ferritin levels were noted. A cut off was used to determine high and low levels. The cut off of CRP for our study was taken 25 mg/L. The cut off for ferritin was 500 mg/L. Using the WHO classification of Covid-19 severity, for this study we combined the categories "severe illness and critical illness" as "severe Covid-19". We classified "mild, moderate and asymptomatic" as non-severe Covid-19 disease. The WHO classification of severity and was taken as gold standard as given in Table 3.

Standard deviation and mean were calculated for quantitative data. Percentages and frequency were calculated for qualitative variables. Spearman's correlation coefficient (rho) was calculated to determine correlation between severity of Covid-19 and raised CRP and ferritin levels, respectively. p value cut off of <0.05 was considered statistically significant. Specificity, sensitivity, diagnostic accuracy, negative and positive predictive values of the CRP levels and ferritin levels were calculated taking severity of Covid-19 as gold standard for diagnostic confirmation. Data was analyzed by using SPSS Version 20.

**RESULTS**

There were 113 patients in our study. In our data set there were 70 (61.9%) males and 43 (38.1%) females. There were 35 (31%) patients who were between 20 to 40 years of age, and 78 (69%) who were older, that is, between 41 to 60 years of age. Few patients had comorbidities as well: 22 (19.5%) had diabetes mellitus, and 28 (24.8%) hypertension. In our study, 64 (56.6%) had elevated CRP and 60 (53.1%) had elevated ferritin. (Table 1)

Table 1: Patient Characteristics

Characteristics	Category	n	%
Gender	Male	70	61.9
	Female	43	38.1
Age in years	20 to 40	35	31
	41 to 60	78	69
Diabetes Mellitus	Yes	22	19.5
	No	91	80.5
Hypertension	Yes	28	24.8
	No	85	75.2
Elevated CRP	Yes	64	56.6
	No	49	43.4
Elevated ferritin	Yes	60	53.1
	No	53	46.9
Severe Covid-19	Yes	65	57.5
	No	48	42.5

Table 2: Comparison of Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value and Diagnostic Accuracy of CRP with Ferritin

Variables	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
CRP	87.7%	85.4%	89.1%	83.6%	86.7%
Ferritin	76.9%	79.2%	83.3%	71.7%	77.8%

Assessing the Covid-19 severity distribution, we found that there were 65 (57.5%) patients who had severe Covid-19 disease and 48 (42.5%) patients had who did not have severe Covid-19

disease. Among the severe Covid-19 patients, 57 (87.7%) had elevated CRP levels, and 8 (12.3%) patients did not have elevated CRP levels. Among the non-severe Covid-19 patients 41 (85.4%) patients did not have elevated CRP levels. There was a statistically significant difference between the CRP levels among non-severe and severe Covid patients (p value <0.001). Looking at ferritin levels, we noted that among the 65 severe Covid-19 patients, there were 50 (76.9%) who had elevated ferritin levels, whereas 15 (23.1%) patients did not have elevated ferritin levels. Among the 48 non-severe Covid-19 patients, there were 38 (79.2%) patients who did not have elevated ferritin levels. There was a statistically significant difference between the ferritin levels among non-severe and severe Covid-19 patients (p value <0.001). Among patients with severe Covid-19, 46 (70.8%) were between 41 to 60 years of age, and 43 (66.2%) were males. There was a positive and statistically significant correlation between severity of Covid-19 and raised CRP levels ( rho = 0.729, p val <0.001). Similarly, there was a positive and statistically significant correlation between severity of Covid-19 and raised ferritin levels (rho = 5.56, p val <0.001).

Table 3: Who Classification of Covid-19 Severity

Severe Covid-19 Disease	Non-Severe Covid-19 Disease
<p>"Severe Illness: Individuals who have SpO<sub>2</sub> &lt;94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) &lt;300 mm Hg, respiratory frequency &gt;30 breaths/min, or lung infiltrates &gt;50%.</p> <p>Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction."</p>	<p>"Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test (NAAT) or an antigen test) but who have no symptoms that are consistent with Covid-19.</p> <p>Mild Illness: Individuals who have any of the various signs and symptoms of Covid-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.</p> <p>Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO<sub>2</sub>) ≥94% on room air at sea level."</p>

Table 4: Distribution by Covid Severity

Variables	Severe Covid-19		Non-Severe Covid19		P-value	
	n	%	n	%		
Age in years	20 to 40	19	29.2	16	33.3	0.39
	41 to 60	46	70.8	32	66.7	
Gender	Males	43	66.2	27	56.3	0.19
	Females	22	33.8	21	43.8	
Diabetes Mellitus	Yes	9	13.8	13	27.1	0.06
	No	56	86.2	35	72.9	
Hypertension	Yes	16	24.6	12	25.0	0.56
	No	49	75.4	36	75.0	
Elevated CRP	Yes	57	87.7	7	14.6	0.01
	No	8	12.3	41	85.4	
Elevated Ferritin	Yes	50	76.9	10	20.8	0.01
	No	15	23.1	38	79.2	

Testing ferritin levels, against World Health Organization's (WHO) Covid-19 severity classification as gold standard, there was a sensitivity of 76.9%, specificity of 79.2%, negative predictive value (NPV) of 71.7%, positive predictive value (PPV) of 83.3% and diagnostic accuracy of 77.8%. Testing CRP levels, against World Health Organization's (WHO) Covid-19 severity classification as gold standard, there was sensitivity of 87.7%, specificity of 85.4%, negative predictive value (NPV) of 83.6%,

positive predictive value (PPV) of 89.1% and diagnostic accuracy of 86.7%. (Table 2)

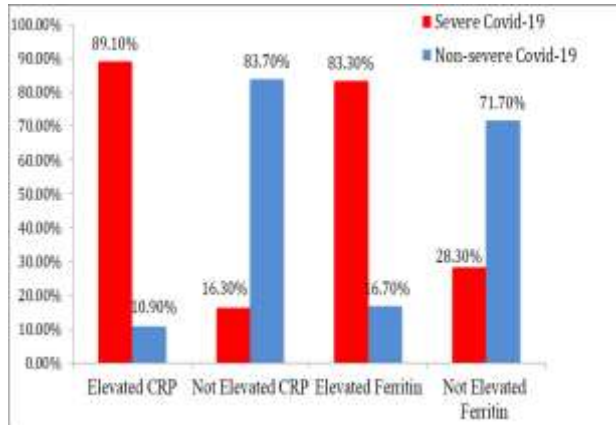


Figure 1: Percentage (%) Distribution of CRP and Ferritin Levels Among Covid-19 Patients

## DISCUSSION

Our data show that the diagnostic accuracy of ferritin was 77.8% and of CRP was 86.7%. These results add to the discourse about the utility of the laboratory markers ferritin and CRP as predictors of severity of Covid-19. Pandemic caused by corona virus have led health care personals to reflect about more efficient ways for allocation of resources. This is particularly the scenario in countries like Pakistan, where there are already pressing circumstances. C-reactive protein and ferritin are potential biomarkers in Covid-19<sup>14</sup>. Ferritin is present in the form of a cytosolic protein. Ferritin is raised in many conditions, such as chronic kidney disease, rheumatoid arthritis, and autoimmune disorders<sup>15</sup>. In a study from China with twenty corona virus patients, it was learnt that patients with severe disease usually present with increased serum ferritin levels<sup>16</sup>. Researchers suggest measuring ferritin levels as a proxy measure for severity of Covid-19<sup>17</sup>. Ferritin is a biomarker, which is inexpensive and hence commonly used for assessing the severity of Covid-19 infection<sup>8</sup>. A study from Pakistan demonstrated serum ferritin levels are a reliable predictor of mortality in Covid-19 cases<sup>9</sup>. The results from our study show that among the severe Covid-19 patients, 57 (87.7%) had elevated CRP levels and there were 50 (76.9%) who had elevated ferritin levels. These results are comparable to a study of 157 corona virus patients<sup>8</sup> which had demonstrated that ferritin was able to differentiate mortality with an AUC of 0.69. Another study by Bennouar S et al. looked at 330 patients and had noted an AUC of 0.63 for Covid-19 severity<sup>18</sup>. In a systematic review regarding the use of ferritin in corona virus patients has shown that ferritin concentrations in non-severe corona virus patients were mostly within the normal range<sup>19</sup>, and the results are corroborated by our research and another study by Pastora J et al.<sup>18</sup> where ferritin levels among patients of Covid-19 who had survived and non-survived were very different

CRP is a protein made by liver which is increased during inflammation<sup>11,18</sup>. More often than not, CRP tends to have a greater rise with bacterial infections when compared with viral infections<sup>19,20</sup>. Covid-19 patients are noted to have raised CRP levels<sup>21,22</sup>. One recent research<sup>8</sup>, showed that CRP level could predict death among severe Covid-19 with a specificity of 51% and a sensitivity of 82%. However, it was noted that severity of Covid-19 was predicted with a specificity of 50% and a sensitivity of 80%<sup>8</sup>. These were comparable to the results from our study where we found a sensitivity of 87.7%, however, our data showed an improved specificity of 85.4%. The reason of improved specificity could be that we had a high proportion of true negatives in our data set. By true negatives we mean patients who did not have a severe Covid-19 infection. This implies that our cut off values or our diagnosis algorithm was suitable for our sample. It is important for

researchers to stratify that sampling methodology by different cutoffs, in order to determine which cutoff works in the most suited manner for the data set. It may vary by geography or race. Chen et al's paper showed the value of using different cut off for sensitivity and specificity<sup>22</sup>.

There was a positive and statistically significant correlation between severity of Covid-19 and raised CRP levels ( $\rho = 0.729$ ,  $p$  val  $< 0.001$ ). Similarly, there was a positive and statistically significant correlation between severity of Covid-19 and raised ferritin levels ( $\rho = 5.56$ ,  $p$  val  $< 0.001$ ). Similar trend was noted in Chen et al study<sup>22</sup> where the authors noted a positive correlation between CRP level and Covid 19 severity. Though in that study the authors had used computed tomography (CT) grading to determine severity. The availability of CT may be limited in the developing world. Not every hospital and not every patient has access to CT scan. That is why the decision algorithms need to be feasible for all in the poor countries. Hence, it is crucial to find biomarkers that are cheaper and accurate so that physicians and health care administrators can find improved ways of treating severe Covid-19 patients presenting to their hospital.

## CONCLUSION

The results from our study show that CRP has a slightly improved diagnostic accuracy as compared to ferritin. However, both these markers have value in the prediction of severity of Covid-19 infection. However, this is a single center study. More such studies, with larger sample sizes are needed to determine the reliability of these biomarkers in predicting Covid-19 severity

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