Original Research Article

# Role Of Interleukin 6, Ferritin, Troponin I, Procalcitonin and D Dimer in COVID 19: A Tertiary Care Centre Study In Central India

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## Abstract

**Background:** COVID 19, a febrile respiratory illness caused by a novel coronavirus, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), emerged in Wuhan China in December 2019. Cytokine storm and hyper inflammation consisting of elevated serum C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and hyperferritinemia have been reported in COVID 19. Troponin I elevation is found in many studies. This is an attempt to study the role Of Interleukin 6, Ferritin, Troponin I, Procalcitonin and D Dimer in COVID 19 disease in Indian population. **Material and methods:** This is a retrospective observational study on 933 patients admitted for COVID 19. Data on demographic characteristics and laboratory tests were collected from electronic and paper medical records. Patients were categorized into mild and severe groups (MDG and SDG). **Results:** Serum levels of IL 6, ferritin, procalcitonin, troponin I and d dimer were compared in SDG and MDG, with statistically significant rise in SDG found in IL 6, Troponin I and D dimer, p = 0.00001, 0.012 and 0.001 respectively. Mortality rate was found to be 11.36 %. Inflammatory markers and D dimer showed significant rise in deceased patients as compared to survivors. **Conclusion:** Data on inflammatory markers is limited in patients with COVID-19 in India. We observed significantly raised IL 6, troponin I and PCT in severe COVID 19 and results showed their effectiveness of IL 6, PCT, Ferritin and D dimer in assessing disease severity and predicting mortality in patients with COVID-19.

**Keywords:** COVID 19, IL 6, Troponin I, D Dimer



## Introduction

In December 2019, a novel coronavirus, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), emerged from Wuhan, China [1, 2] It led to febrile respiratory illness known as coronavirus disease 2019 (Covid-19). It is supposed to be the third zoonotic coronavirus to infect humans in the past two decades [3]. COVID 19 is associated with severe respiratory compromise and it leads to the mortality rate of 21% in hospitalized patients. Outcome is found to be poorer in patients requiring advanced respiratory support [4, 5, 6]. Comorbidities like cardiovascular disease, hypertension, diabetes, chronic lung disease, malignancy, male gender, and advancing age contributes to the increasing mortality [7]

Novel COVID-19 (nCOVID-19) belongs to a family of viruses known as Coronaviridae. It is classified in four genera: alpha, beta, gamma, and delta. Human CoV belongs to either alpha or beta category. Gamma and delta category cause infection in birds. SARS CoV, MERS CoV, and SARS CoV-2 are highly pathogenic corona virus types. They result in severe pneumonia in humans by infecting the lower respiratory tract causing diffuse alveolar damage and resulting in poor survival, hence increased morbidity and mortality. [8, 9, 10]. Differences between SARS-CoV and nCOVID-19 have been reported in some studies. These studies mention the fluctuation in the amino acid sequences in nCOVID-19 [11] there is a single mutation in nucleocapsid 501 in nCOVID-19's spike protein. This has led to an increase in its pathogenicity and increased its binding affinity with the ACE-2 receptor [12].Cytokine storm syndrome (CSS) is induced by a cascade of cytokine activation which is a critical condition characterized by inordinate systemic inflammation, hyperferritinemia, hemodynamic instability and multiple organ failure (MOF). [13] CSS is characterized by an unchecked activation and amplification of host immune response. This causes a massive release of a wide range of cytokines, such as interferon (IFN)-c, tumor necrosis factor (TNF), interleukin (IL)-1, IL- 6 and IL-18 and others. Unchecked activation and formation of mediators contributes to the cytokine storm [14]. IL-6 (Interleukin 6) is a multi-functional cytokine (a protein) which is produced by a wide range of cells. It is involved in the host defense mechanisms and has a role in the induction of B (lymphocyte) cell differentiation. Increased Ferritin level signifies active infection. Ferritin attempts to inhibit viral growth and defends immune cells. Hence, it plays a vital role in host defense mechanism [15]. Troponin I elevation in the setting of COVID-19 is found in many studies. Elevation in cardiac troponin can be explained by non-ischemic myocardial injury (more commonly). This can be related to different mechanisms like severe hypoxia,sepsis,systemic inflammation,pulmonary thromboembolism, cytokine storm, stress cardiomyopathy. Ischemic myocardial injury due to plaque rupture, coronary spasm, micro thrombi, or direct endothelial or vascular injury also elevate troponin I[16]. Procalcitonin (PCT) is a glycoprotein without any hormonal activity. It is a precursor of calcitonin. Serum PCT levels are usually low or undetectable normally. PCT levels are increased by bacterial infections and are low with viral infections. Hence, it can be used to distinguish between the two. The higher PCT levels in severe COVID-19 patients have been reported in previous studies especially

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those having concomitant bacterial infections [17]. D-dimer is a degradation product of fibrin. It is produced by the conversion of fibrinogen to fibrin using thrombin as a catalyst. D-dimer in the circulation signifies the breakdown of fibrin polymers by plasmin. One D-dimer consists of two D-fragments of fibrin joined by a cross-link (factor XIII). D-dimer also causes platelet activation. [18] A persistent elevated D-dimer level in patients with COVID-19 confers to poor prognosis. Development of DIC is another problem. It is characterized by prolongation of prothrombin time and activated partial thromboplastin time, high fibrin degradation products, and severe thrombocytopenia. [19]

Comorbidities and laboratory markers have been proposed by previous studies for the risk stratification of the patients. [20] There is mounting evidence from the previous studies that in critically ill patients, there is hyper inflammation, which consist of elevated serum C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and hyperferritinemia. Thus, these findings suggest a crucial role of a cytokine storm in COVID-19 pathophysiology. [21]Previous studies also suggested that the serum levels of IL-6 are significantly elevated in complicated Covid-19 disease. Increased levels of IL-6 levels in COVID 19 patients have found to be significantly associated with adverse clinical outcomes [22]. Studies also suggested a positive role of troponin I in COVID 19. Increased troponin I was found in ICU patients who died due to COVID-19 [23-25]This study is an attempt to study the role Of Interleukin 6, Ferritin, Troponin I, Procalcitonin and D Dimer in COVID 19 disease in Indian population.

**Material and Methods**

A retrospective observational study based on data was conducted in Jayarogya Hospital, Gwalior on 933 patients who were admitted in the hospital with covid-19 from August 2020 to December2020. The Super specialty wing of Jayarogya group of hospitals, Gwalior, India was designated to treat COVID-19 patients. All patients were confirmed positive for SARS-CoV-2 by nucleic acid RT-PCR (Ct value≤30.0, BGI, Shenzhen, China) using specimens derived from oropharyngeal swabs or sputum, prior to or during the hospitalization. Patients were categorized into mild and severe groups (MDG and SDG) depending upon the following criteria. Severe disease was defined based on any of the following criteria: 1) shortness of breath, respiratory rate ≥30 beats per min; 2) oxygen saturation ≤93 % at rest; 3) arterial oxygen partial pressure ($PaO_2$)/oxygen concentration ($FiO_2$) ≤300 mmHg (1 mmHg = 0.133 K Pa); and 4) lung images showing obvious progress of lesion size >50 % within 24−48 h. The patients with mild disease had the following criteria: 1) mild clinical symptoms or 2) mild or no lesions on imaging findings. On admission inflammatory markers and D dimer were done.

Data on demographic characteristics and laboratory tests were collected from electronic and paper medical records. Statistical Package for the Social Sciences software version 25.0 (IBM, Chicago, IL) was used for statistical analysis. Continuous and categorical variables were presented as median (IQR) and n (%), respectively. Mann-Whitney U test, $\chi^2$ test, or Fisher's exact test was used to compare continuous and categorical variables.

**Results**

A total of 933 patients admitted with positive RT PCR for novel coronavirus in a designated covid care center in central India from August 2020 to October 2020, were included in this study. Out of these, 655 (70.20%) were males and 278 (29.79 %) were females. Median age was 59.5 years with a range of 22-83 years.

Patients in the SDG were 240 (25.72%) and 693 (74.27%) were categorized in MDG. At the time of admission, Interleukin 6 was found to be raised (>7 pg/ml) in 785 (84.13%) patients with an average rise of 347.34 pg/ml. Considering different physiological normal serum ranges of Ferritin in males and females, ferritin was found to be raised in 127 (45.68%) females with an average rise of 776.55 ng/ml. Males showed raised ferritin in 443 (67.63%) patients with an average rise of 1299.05 ng/ml. Procalcitonin and troponin were found to be raised in 770 (82.52%) and 449 (48.12%) patients respectively. Average rise in procalcitonin and Troponin I was 1.93 ng/ml and 2.62 ng/ml respectively. D dimer as a marker of coagulopathy was assessed in 576 patients and was found to be raised in 434 (75.34%) patients with an average rise of 11.21 µg / ml (FEU).

Emerging evidence of IL 6 as a marker of cytokine storm, when its rise was compared to other markers of inflammation and coagulopathy, it was found to be statistically significant with raised D Dimer, p value = 0.033. Ferritin, procalcitonin and Troponin I didn't show significant correlation with IL 6, P values being 2.86, 1.491 and 1.522 respectively.

Serum levels of IL 6, ferritin, procalcitonin, troponin I and d dimer were compared in SDG and MDG, with statistically significant rise in SDG found in IL 6, Troponin I and D dimer, p = 0.00001, 0.012 and 0.001 respectively (Figure 1 and Figure 2).

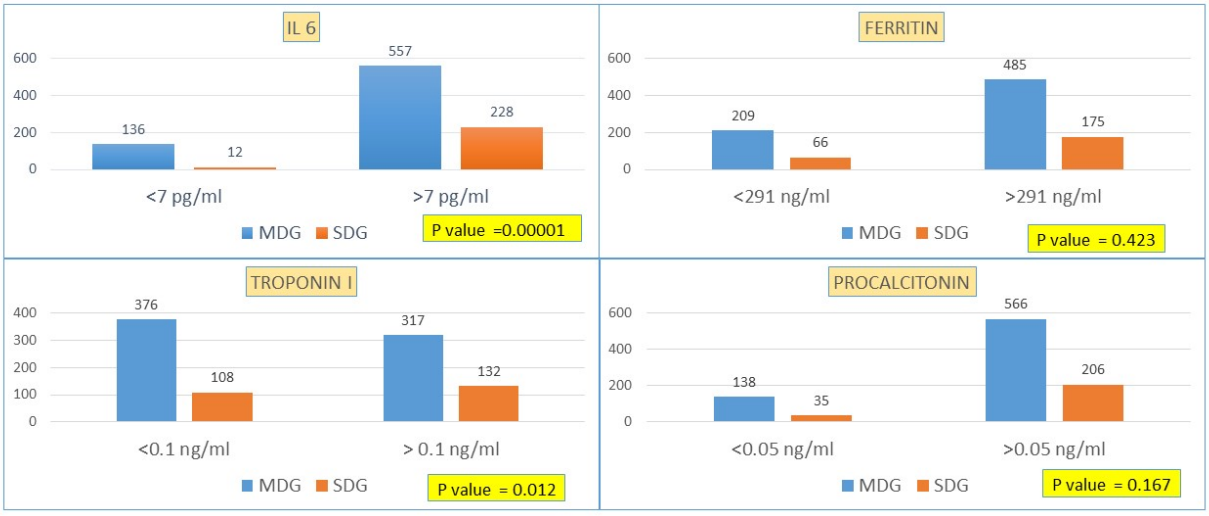


**Fig 1: Comparison between MDG and SDG in levels of IL 6, Ferritin, Troponin I and Procalcitonin**

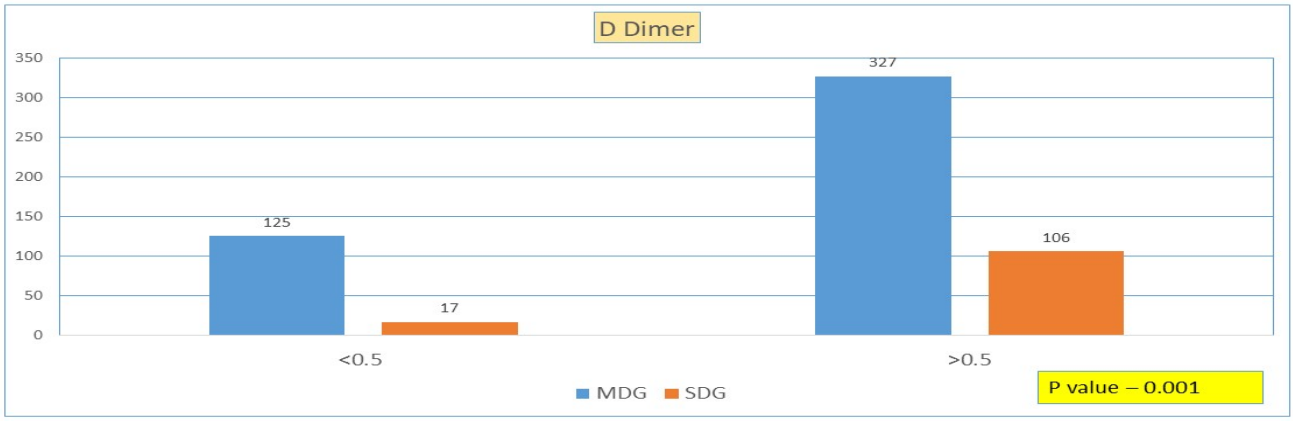


**Figure 2:** Comparison between MDG and SDG in levels of D Dimer

Mortality rate was found to be 11.36 % (106/933), with male to female ratio of 2.65:1. Mean age was 60.2 years. Inflammatory markers and D dimer showed significant rise in deceased patients as compared to survivors (Table -1-5). Average rise of IL- 6 was 839.03 pg/ml, Ferritin was 1321.8 ng / ml, Procalcitonin – 3.92 ng/ml, Troponin I – 0.67 ng/ml and D Dimer – 5 µg / ml (FEU).

**Table 1:** Comparison of IL 6 levels in Deceased patients and survivors of Covid 19

| | **IL 6 < 7 pg/ml** | **IL 6 >7 pg/ ml** | ***P value*** |
|---|---|---|---|
| Deceased | 6 (5.66%) | 100 (94.33%) | 0.003192 |
| Survivors | 140 (16.93%) | 687 (83.07%) | |

**Table 2:** Comparison of Ferritin levels in Deceased patients and survivors of Covid 19

| | **Ferritin < 291 ng/ml** | **Ferritin > 291 ng/ml** | *P value* |
|---|---|---|---|
| Deceased | 16 (15.53%) | 90 (84.90 %) | .00105 |
| Survivor | 257 (31.08 %) | 570 (68.92%) | |

**Table 3:** Comparison of Procalcitonin levels in Deceased patients and survivors of Covid 19

| | **Procalcitonin <0.05 ng/ml** | **Procalcitonin >0.05ng/ml** | ***P value*** |
|---|---|---|---|
| Deceased | 12 (11.32%) | 94 (88.68%) | 0.0136 |
| Survivor | 152 (18.38%) | 675 (81.62%) | |

**Table 4:** Comparison of Troponin I levels in Deceased patients and survivors of Covid 19

| | **Troponin I <0.1 ng/ml** | **Troponin I >0.1ng/ml** | ***P value*** |
|---|---|---|---|
| **Deceased** | 51 (48.11%) | 55 (51.89%) | 0.266313 |
| **Survivor** | 434 (52.48%) | 393 (47.52%) | |

**Table 5:** Comparison of D dimer levels in Deceased patients and survivors of Covid 19

| | **D dimer <0.5 µg / ml (FEU)** | **D dimer >0.5 µg / ml (FEU)** | ***P value*** |
|---|---|---|---|
| Deceased | 6 (8.57%) | 64 (91.43%) | 0 .001228 |
| Survivors | 132 (26.19%) | 372 (73.81%) | |

**Discussion**

Role of inflammatory markers in disease progression and mortality have been extensively studied in Covid 19. However, most of the studies are conducted in China and do not include a large sample size to substantiate their results. [20] Fulfilling the need to analyze markers of inflammation and coagulopathy in COVID 19 in Indian population, this study successfully establishes data pertaining to IL6, Ferritin, Procalcitonin, Troponin I and D Dimer in a large cohort of patients in Central India.

In order to anticipate cytokine storm and treat COVID 19 patients accordingly, IL 6 was measured at the time of admissions and we found a significantly raised levels of IL 6 in SDG as compared to MDG, corresponding to the results of Liu et al [ 17] in a study of 140 Covid 19 patients and a metaanalysis by Coomes et al [22] In some studies, IL-6 level is highly correlated with the disease mortality when COVID-19 survivors and non-survivors are compared.[6, 26] Results from our study confirm significantly higher levels of IL 6 in deceased patients of Covid 19 (p value = 0.003192).

Hyperferritinemia is closely related to poor recovery of COVID-19 patients, and thus has been extensively studied to predict disease severity. Significantly higher levels of ferritin have been reported in more severe patients than that in less severe patients in various studies. [27] However, in the study by Broman Et al no statistical difference was found in Ferritin levels with severity of disease. [28] Although hyperferritinemia was noted in 70.74 % of patients on admission in our study, no significant difference was found between SDG and MDG (p value - 0.423) as opposed to results of Hou et al (SDG vs MDG, p value - 0.001). [29] In a meta-analysis by Huang et al [20], subgroup analysis results demonstrated that ferritin level was higher in non-survivors (mortality) ($p < 0.00001$) and patients with severe COVID-19 ($p$ *value* $= 0.001$). We also report a significantly higher level of Ferritin in non survivors as compared to survivors (p value= 0. 00105) in our study.

Huang et al also reported association of elevated PCT with an increased composite poor outcome in a metaanalysis 16 studies. Subgroup analysis showed that an elevated PCT was associated with increased mortality ($p = 0.005$) and severe COVID-19 ($p = 0.006$). [20] We report a similar trend of significant rise in PCT in deceased patients, however SDG vs MDG was not statistically significant. Zhou et al also found a significant rise in PCT in deceased patients as compared to survivors. [6]

In a metaanalysis by Lippi et al, the values of troponin I were found to be significantly increased in COVID-19 patients with severe disease than in those without, similar to our results (SDG vs. MDG, p value- 0.012). Our results support their hypothesis that initial measurement of cardiac damage biomarkers at the time of admission for Covid 19 and longitudinal monitoring during hospital stay, may help in detecting possible cardiac injury in COVID-19. [30] Zhou et al reported elevated levels of troponin I in non-survivors compared with survivors throughout the clinical course, and increased with illness deterioration. [6], however, we did not find a significant association with mortality.

A hypothesis that Covid 19 infection could induce the dysfunction of the hemostatic system, leading to a hypercoagulable state [31] and causes micro thrombosis in pulmonary blood vessels in critically ill patients [32], leading to elevated D Dimer levels, is supported by our results. We found significantly higher levels of D Dimer in severely ill patients and deceased patients as compared to those with mild disease and survivors. Similar results were reported in a meta-analysis of 11 studies in which an elevated D-dimer was associated with increased mortality ($p = 0.01$), severe COVID-19 ($p = 0.05$). [20]

**Conclusion**

Data on inflammatory markers is limited in patients with COVID-19 in India. We observed significantly raised IL 6, troponin I and PCT in severe COVID 19 and results showed their effectiveness of IL 6, PCT, Ferritin and D dimer in assessing disease severity and predicting mortality in patients with COVID-19.

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