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Original Research Article

# Estimation of Serum Ferritin, D-Dimer, Lactate Dehydrogenase in COVID-19 Patients

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**Abstract**

**Background:** Severe COVID-19 illness is associated with intense inflammation, leading to high rates of thrombotic complications that increase morbidity and mortality. New laboratory tests capable of differentiating between severe and non-severe cases and appropriate management of COVID-19.

**Aims and Objective:** Aim to investigate the association between several biomarkers like Lactate Dehydrogenase, D-dimer, and serum ferritin, and COVID-19 severity.

**Methodology:** The study was conducted during September 2020-Dec-2021 among Covid patients confirmed by RT-PCR and admitted to Government general hospital. LDH was estimated in semi-auto analyzer by UVkinetic method and serum Ferritin, D-dimer was estimated by Immunoturbidometric method.

**Results:** Amongst 1200 SARS-CoV-2 patients, Elevated D-Dimer is seen in 94 percent of patients, Ferritin in 83 percent of patients, LDH in 93 percent of patients.

**Discussion:** Elevated D-dimer, serum ferritin levels were associated with an increased poor outcome that comprises mortality, severe COVID-19, ARDS, and the need for ICU care in patients with COVID-19.

**Keywords:** SARS-CoV-2, Lactate Dehydrogenase, D-Dimer, and Serum Ferritin.

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## Introduction

Unknown pneumonia broke out in Wuhan City in December 2019, and it was confirmed as an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, formerly known as 2019-nCoV). The disease was subsequently named coronavirus disease 2019 (COVID-19) by the WHO on 11 February 2020.

Coronaviruses belong to the subfamily Coronavirineae in the family of coronaviridae of the order nidovirales (reviewed in Becker) [1]. The genome is a single-stranded positive-sense RNA (30 kb) with a 5′ cap structure and a 3′poly-A tail. Homotrimers of S proteins make up the spikes on the virus surface and enable binding to host receptors. Coronaviruses contain at least six open-read frames (ORFs) that encode primary structural proteins that include spike (S), membrane (M), envelope (E), and nucleocapsid (N). S proteins are responsible for attachment to host receptors. M proteins contain transmembrane domains that contribute to virus shape and binding to the nucleocapsid. The E protein is involved with virus assembly and pathogenesis. The N protein packages and encapsulates the genome into virions and antagonizes silencing RNA (reviewed in Becker) [2] SARS-CoV-2 binds to the host cell via angiotensin-converting enzyme- 2 (ACE2), an intrinsic membrane protein with enzymatic activity that physiologically counters the activation of the renin-angiotensin-aldosterone system. ACE2 is expressed broadly in epithelial, endothelial, and enterocytic cells, nasopharynx, oropharynx, lungs, alveolar pneumocytes, stomach, small intestine, spleen, liver, kidney, and brain and play essential roles in the initiation of Infection and its phenotypic expression, including venous, arterial and microvascular thrombosis. [3]

Most patients with COVID-19 predominantly have a respiratory tract infection. A proportion of patient's progress to more severe and systemic disease. Many patients with severe COVID-19 are present with coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as DIC (Disseminated intravascular coagulation) or thrombotic microangiopathy, but COVID19 has distinct features [3]. One of the most significant poor

prognostic features in these patients is the development of coagulopathy. Organ insufficiency and coagulopathy were closely associated with high mortality [4]

New laboratory tests capable of differentiating between severe and non-severe cases and appropriate Management of COVID-19. Biomarkers play a crucial role in clinical decision-making in various infectious diseases, so it is essential to assess the Biomarkers in Diagnosis, Risk Stratification, and Management of covid 19 disease. Given that abnormal coagulation parameters might be associated with poor prognosis monitoring hemostatic markers in all patients with COVID-19 might be advisable. The aim of this study was, therefore, to evaluate the relationship between coagulation abnormalities and prognosis

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme that is widely expressed in tissues. The enzyme converts pyruvate, the final product of glycolysis, to lactate when oxygen is in short supply. LDH comprises two separately enclosed subunits, resulting in five isozymes. Each isozyme is expressed in a specific organ: LDH 1 in cardiomyocytes, LDH 3 in lung tissue, and LDH 5 in hepatocytes. Increased LDH was observed in different conditions such as tissue injury, necrosis, hypoxia, hemolysis, or malignancies. LDH could be identified as a decisive predictive factor for early recognition of lung injury and severe COVID-19 cases [5]

The D-dimer molecule is a product of the degradation of the fibrin protein. It arises after the cross-linking of two D-fragments of the fibrin protein after lysis by the thrombin, plasmin, and factor XIIIa enzymes. Its clinical elevation is strongly indicative of ongoing coagulation.[6] D-dimer may have potential as a predictive tool in patients with severe clinical manifestations of COVID-19.

Ferritin is the primary site of iron storage in the cell, mainly in its ferric state (Fe3+). Ferritin can carry up to 4500 iron molecules in its core (Kell and Pretorius, 2014). Generally, systemic inflammations are associated with increased serum ferritin levels. During a heightened inflammatory state, cytokines, particularly IL-6, stimulate ferritin and hepcidin synthesis.

Hyper-ferritinemia has been described as a cardinal feature that predicted with high significance the increased mortality risk [7]

**Materials and Methods**

After obtaining IEC clearance, a cross-sectional study was conducted from Oct 2020 – Dec 2021. Study population 1200 patients were patients confirmed by RT-PCR

**Inclusion Criteria:**

1. Individuals with a positive COVID-19 by RT-PCR method aged > 20 years.

2. Subjects were having available data regarding serial follow-up of coagulation and hematological parameters.

**Exclusion Criteria:**

1. Subjects had COVID-19 Infection with short (2-3 days) hospital stay.

2. Patients with missing data regarding laboratory investigations, especially those who were minimally symptomatic. Pregnancy, cancer, Hematologic Malignancy, Chronic Liver Disease.

After obtaining consent from study participants, their blood samples were collected, Lactate Dehydrogenase, D-dimer, and serum ferritin were analyzed. LDH was estimated in semi-auto analyzer by UV kinetic method and serum Ferritin D-dimer was estimated by Immunoturbidometric method.

**Statistical Analysis:** The statistical software, namely the statistical package for the social sciences (SPSS) version 22 is used to analyze data. Analysis of variance (ANOVA) is used to compare the variables. Data are expressed as mean± standard deviation.

The p-value was calculated for each parameter, and $p<0.05$ is considered statistically significant. Bar diagrams were used for the graphical representation of this data.

**Results**

**Table 1: Age distribution.**

| Age | Total[N%] |
|---|---|
| <30yrs | 54 |
| 31 to 40yrs | 140 |
| 41 to 50 yrs | 70 |
| 51to 60 yrs | 30 |
| > 60 yrs | 6 |
| Total | 300 |

**Table 2: Co-morbidities among the study population.**

| comorbidity | Frequency |
|---|---|
| No comorbidities | 220 |
| Hypertension | 45 |
| Diabetes mellitus | 30 |
| Others | 5 |

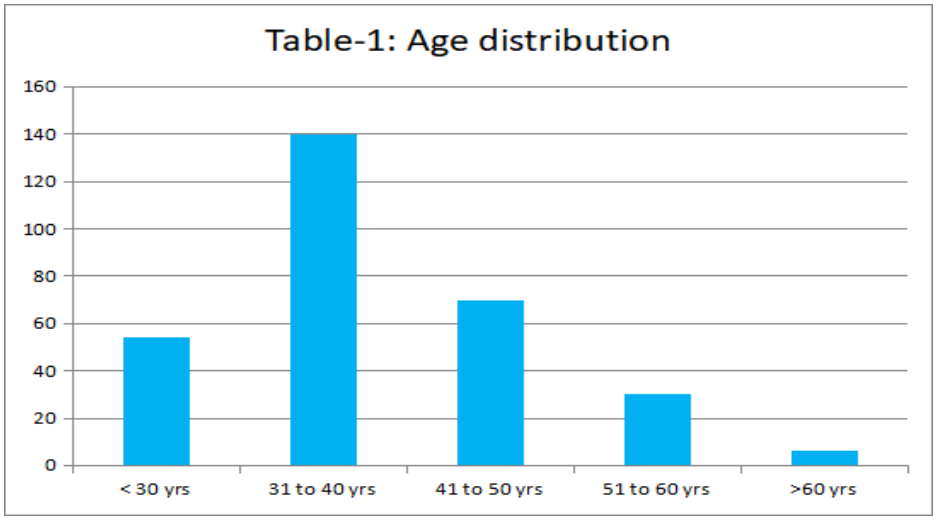


**Figure 1: Age distribution**

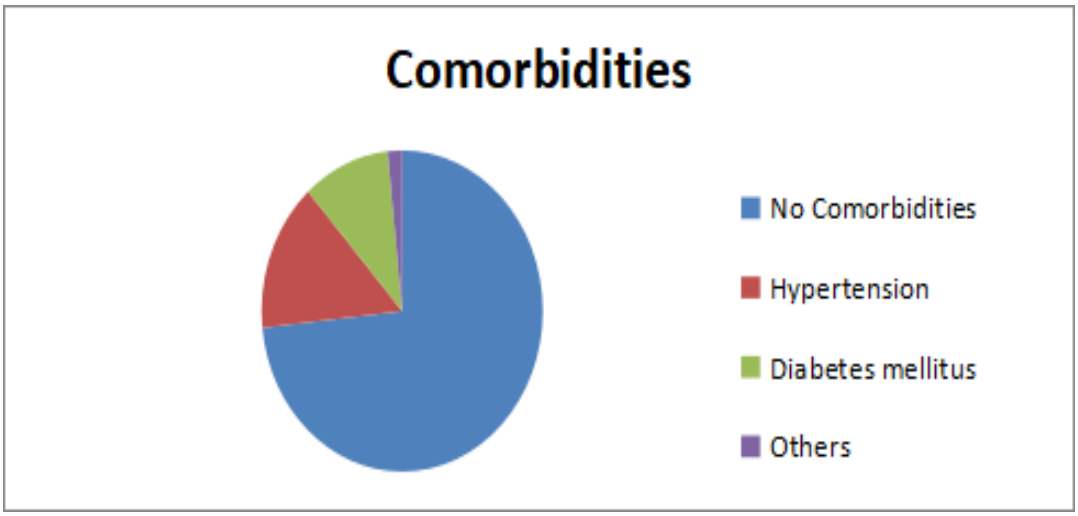


**Figure 2: Comorbidities**

All patients were tested for markers including LDH, Ferritin, D-dimer. Among the study participants, the majority belonged to the age group 31 to 40 yrs, followed by 41 to 50 yrs. Out of 300 study participants, 220members had no comorbidities. Among those with comorbidities, Hypertension was the most common comorbidity, followed by diabetes mellitus.

**Table 3: Statistical variables**

| | Variables | | |
|---|---|---|---|
| | **D-Dimer** | **Ferritin** | **LDH** |
| N | 300 | 300 | 300 |
| Mean | 2293±81.71 | 478.82±42.4 | 316.4±30.4 |
| Source | ss | MS | |
| Between variables | 20177635.05 | 10088817.52 | F=181.52 |
| Within variables | 496892.12 | 55580.65 | |
| Total | 69866727.16 | | |

Fisher's exact test was then applied to compare the rate with abnormal LDH, PCT, Ferritin, and D –Dimer. The f-ratio value is 181.51676. The p-value is <0.00001. The result is significant at p<0 .05. We noted significantly increased LDH, D-Dimer, and Ferritin with increased poor outcomes. Elevated D-Dimer is seen in 94 percent of patients, Ferritin in 83 percent of patients, LDH in 93 percent of patients.

**Table 4: Correlation coefficient and P value between items and disease severity**

| | r value | p-value |
|---|---|---|
| D-Dimer | 0.65 | 0.001 |
| Ferritin | 0.36 | 0.001 |
| LDH | 0.46 | 0.001 |

Significant correlations were found for D-dimer, LDH, and Ferritin.

D-dimer (r = 0.65), Ferritin (r =0.36) LDH (r = 0.46), were positively correlated.

**ROC curve**

For D-Dimer cutoff value 4mg/L FEU had a sensitivity of 76% and specificity of 78% (AUC 0.80, P<0.001).

For LDH, the cutoff value of 450 IU/L had a sensitivity of 86% and specificity of 80% in ARDS cases.(AUC) 0.72, P<0.001.

For ferritin cutoff value 480 ng/ml had a sensitivity of 76% and specificity of 78% (AUC 0.78, P<0.001).

**Discussion**

Our study showed that elevated serum PCT, D-dimer, and serum ferritin levels were associated with an increased composite poor outcome that comprises mortality, severe COVID-19, ARDS, and ICU need care in patients with COVID-19.Disseminated intravascular coagulation in covid 19 was also accompanied by the significant decrease of fibrinogen and marked increase of FDP formation and D dimer. Increased FDP and D dimer are characteristics of DIC with hyper fibrinolysis. In contrast, DIC caused by Infection is accompanied by plasminogen activator inhibitor-I release and suppression of Fibrinolysis.[8]LDH is present in tissues throughout the body and is involved in the interconversion between pyruvate and lactate through NADH-dependent reactions. Abnormal LDH levels can result from decreased oxygenation, leading to an upregulation of the Glycolytic pathway and multiple organ injury.

The mechanism through which lactate leads to injury is via Metalloproteinasesa and enhanced macrophage-mediated angiogenesis.[9]The elevated levels of CRP might be linked to the overproduction of inflammatory cytokines in severe patients in Covid patients. Cytokines fight against microbes, but they can damage lung tissue when the immune system becomes hyperactive. Thus CRP production is induced by inflammatory cytokines and Tissue destruction in covid patients.[9].Ferritin is involved in Iron metabolism, which contains L and H subunits expressed in Lung and Heart. H subunit involves the inflammatory mechanism by participating in Myeloid, and Lymphoid cell proliferation and stimulating TIM-2,a specific ferritin receptor.H ferritin plays a significant role in Immunomodulatory and Proinflammatory activities by activating several inflammatory mediators such as IL-1 β.Ferritin was found only in the lymph node B area, indicating its role as an antigen, which stimulates macrophage activation related to hyperferritinemia.[10] Some studies showed that patients with bacterial Infection had higher ferritin levelsthan viral Infection [11]. Chen et al., Ruanet al. Zhou et al., Jiet al. showed that an elevated serum CRP, Ferritin, D-Dimer, LDH was associated with an increased composite poor outcome [12-14]

**Conclusion**

This study showed that an elevated levels of LDH, D-dimer, and serum ferritin were associated with a poor composite outcome in patients with COVID-19. Estimation of Serum Lactate Dehydrogenase, D-dimer, and serum ferritin acts as markers for potential progression to critical stage and outcome of COVID 19.

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