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Biochemical Parameters In Covid-19 Patients For Triage And Management– An Institutional Experience

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Abstract

Introduction

During the COVID- 19 pandemic several studies demonstrated the association of different biomarkers like – D-dimer, Ferritin, C-reactive protein, Procalcitonin to COVID-19 and many drugs were under trial for specific treatment of COVID-19. The lack of specific treatment for COVID-19 propelled the patient's admissions to intensive care unit (ICU) expecting a better outcome. This study aims to brief on association of D-dimer and Ferritin elevation with the severity of COVID-19 that could serve as an additional tool to clinical symptoms in quick triage of the patients at admission for early intervention.

Material And Methods

A retrospective cohort study was conducted by recruiting 200 COVID- 19 adult patients hospitalized in the month of July to October 2020 at Government General Hospital, Ananthapuramu, Andhra Pradesh. Standard sample collection protocols were followed and quantitative estimation for D-dimer and Ferritin was done using kits of Beckman Coulter run on AU480 analyzer. Elevations of D-dimer and Ferritin in severe COVID-19 patients were compared with that of subjects in Non-severe group using t-test for two independent means in Graph pad prism software.

Results

In our study, 112 COVID-19 Patients (66%) were found to suffer from severe disease where as 88 COVID-19 patients (44%) had Non severe presentation at admission.

In severe COVID- 19 patients significant elevation in D-dimer level was demonstrated (n= 112, M = 3.87, SE = 0.43; $p < 0.01$) when compared to the Non-serious COVID-19 patient's group (n= 88, M = 1.14, SE= 0.25) and significant elevation in Ferritin level was also demonstrated (n= 112, M = 461.8, SE = 28.63; p = 0.0001) when compared to the Non-serious COVID-19 group (n= 88, M = 290.48, SE= 34.71). Study also suggests a ratio of D-dimer to Ferritin which was found to be between 0.0021 to 0.0039 in Non-severe COVID-19 patients and 0.004 and above in severe COVID-19 patients.

Conclusions

Severely infected COVID-19 patients showed significant elevation of D-dimer and Ferritin than those with Non-severe disease with a clear demarcating ratio. Physicians should consider D-dimer and Ferritin levels in addition to clinical symptoms as an aid in quick triage and early intervention of COVID19 patients and can detect the disease severity in case of non availability of specific diagnostic test. However further studies are required to establish the ideal range of D-dimer and Ferritin for early identification of severe COVID-19 cases

Keywords: COVID-19, D-Dimer, Ferritin, Triage

Introduction

Corona virus disease-2019 (COVID19) and its causative agent Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2) both were reported initially in Wuhan, Hubei province, China in December 2019. The World Health Organization (WHO) declared Corona virus disease-2019 a pandemic on 11th March. COVID19 emerged as a pandemic making many countries struggle with a lack of resources and resolve. [1] COVID-19 was spreading rapidly with human-to-human transmission and caused varying degrees of illness. [2] Most common presentations of COVID-19 patients on admission were fever, cough, and rarely diarrhoea with most common radiologic finding on chest computed tomography (CT) as ground-glass opacity. [3] COVID-19 patients who required ICU admission were increasing and usually suffered faster respiratory rate, falling peripheral capillary oxygen saturation (SpO2), higher temperature, had a medical history of hypertension and diabetes, higher computer tomography (CT) image quadrant scores and pulmonary opacity percentage; increased C-reactive protein, fibrinogen, and D-dimer on admission and had lower white blood cells, lymphocyte, platelet counts and albumin; suffered severe pneumonia followed by acute respiratory distress syndrome (ARDS) and shock.[4-7] Many drugs used in the treatment of COVID-19 infection including antivirals, antiretrovirals, anti-inflammatory, immunomodulatory, and antibiotics had partial success which has led to increase in ICU admissions expecting better outcome. [8-9] Different biomarkers were used to predict COVID-19 infection and were found to be associated with COVID-19. COVID-19 markers like interleukin-6 (IL-6), D-dimer and fibrin degradation products (FDP) were predictive of COVID-19 severity while higher level of C-reactive protein (CRP), procalcitonin (PCT), D-dimer, serum ferritin and procalcitonin were reported in severe cases than in non-severe disease. [10-13]. D-dimer is a fibrin degradation product used for diagnosis of thromboembolism and is now being studied for triage and prognostic value in COVID-19 pneumonia. [14 -19] Ferritin is one of principal regulator of immune dysregulation and contributes in the cytokine storm. Cytokine storm causes fatal outcome in COVID-19 patients and related to severity of the disease. [20] Rapid spread, lack of specific treatment, increase in severity of COVID -19 set a challenge for detection and stratification of the severe COVID19. Our study aims to brief on association of D-Dimer and Ferritin elevation with the severity of COVID-19 that could serve as an additional tool to clinical symptoms in quick triage of the patients at admission to initiate early suitable therapy.

Material And Methods

A retrospective cohort study approved by Institutional Ethics Committee was conducted by selecting 200 COVID -19 adult hospitalized patients in the month of July to October 2020 at Government General Hospital, Ananthapuramu, Andhra Pradesh. SARS-CoV-2 infection was confirmed by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs. Pregnant women, pediatric COVID-19 patients and patients negative for or awaiting RT-PCR results were excluded. Data regarding clinical presentation, laboratory markers D-dimer, ferritin and oxygen dependence on admission was obtained from patient's medical records. Blood samples were collected as per standard protocol and quantitatively estimated for D-Dimer and Ferritin, using a kit of Beckman Coulter that runs on AU480 analyzer. COVID-19 patients were divided into two groups Severe and Non-severe. At admission, all patients with shortness of breath and who depended on oxygen/ ventilator support were included in severe COVID-19 group and the patients who did not depend on oxygen support were included in Non-severe COVID-19 group. Data was collected, tabulated and analysed for association of biochemical markers: D-dimer and ferritin elevation in COVID-19 groups using T-Test Calculator for 2 Independent Means, Graph Pad Prism 8.0.2, and confidence interval of 99 and $p < .01$ results were considered significant.

Results:

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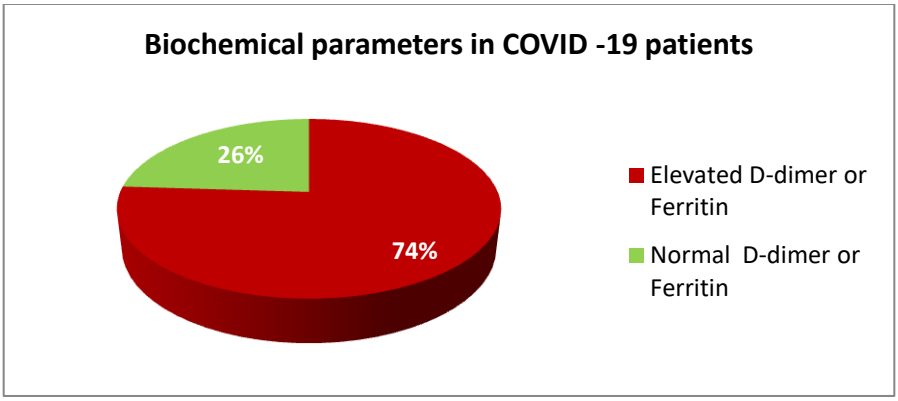
Our study results has demonstrated that 148 COVID-19 subjects (74%) found to have elevated either D-dimer (≥0.5 mcg/ml FEU) or Ferritin plasma concentrations (≥ 250µg/dl) and only 26 % (52) patients had normal value as depicted in Figure 1.

Figure1: Biochemical parameters status in COVID19 patients under study



112 COVID-19 Patients (66%) were found to suffer from severe disease where as 88 COVID-19 patients (44%) had Non severe presentation at admission within the study population. D-dimer and Ferritin both were found elevated in 57% (114) COVID-19 patients irrespective of severity of the disease. (Table 1)

Table 1 Laboratory parameters in COVID19 and disease Severity

	RT-PCR for COVID-19 Positive Patients		
Parameters	**SEVERE (n=112)**	**NON-SEVERE (n=88)**	Total patients n=200
D-dimer Elevated	102	46	148 (74%)
Ferritin Elevated	98	42	140 (70%)
D-dimer or Ferritin Elevated	102	46	148 (74%)
Both D-dimer & Ferritin Elevated	96	18	114 (57%)
D-dimer and Ferritin Normal	8	18	26 (13%)
D-dimer alone Elevated	6	28	34 (17%)
Ferritin alone Elevated	2	24	26 (13%)
D-dimer or Ferritin Normal	10	42	52(26%)

Considering severity, severe COVID-19 group (n= 112) D-dimer was found elevated in 102 (91%) patients and Ferritin was found elevated in 98 (88%) patients.

And in Non-severe COVID-19 group (n= 88) D-dimer was found elevated in 46 (52 %) patients and Ferritin was found elevated in 42 (48 %) patients.

Whereas D-dimer or Ferritin both were found to be normal in 10 and 42 subjects of severe and Non-severe COVID-19 groups respectively. D-dimer or Ferritin status in percentage (%) of COVID-19 patient with disease Severity is depicted in Figure 2 and tabulated in Table1.

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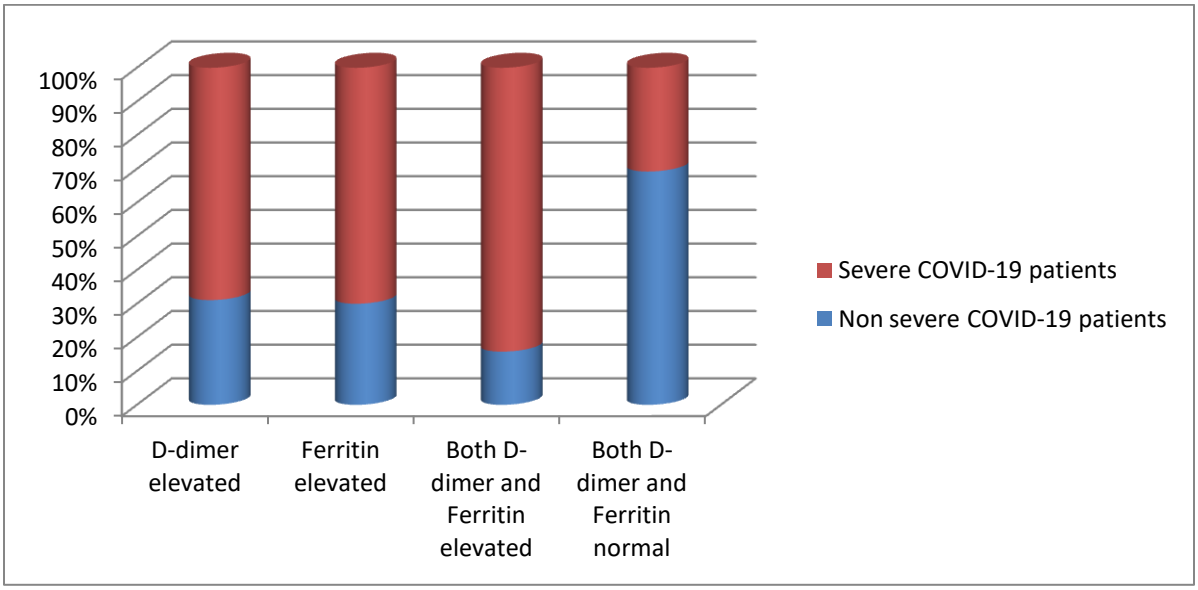
Figure2: Laboratory parameters status in COVID19 patient with disease severity



From the results it was evident that D-dimer and Ferritin plasma concentrations were significantly raised in severe COVID-19 cases than in non-severe cases.

In severe COVID- 19 patients significant elevation in D-dimer plasma concentrations was demonstrated (n= 112, M = 3.87, SE = 0.43; $p < 0.01$) when compared to that of Non-serious COVID-19 patients group (n= 88, M = 1.14, SE= 0.25) and Ferritin level was significantly elevated (n= 112, M = 461.8, SE = 28.63; $p = 0.0001$) when compared to that of Non-serious COVID-19 patients group (n= 88, M = 290.48, SE= 34.71).

The result of significant elevation of biochemical parameters are tabulated in Table 2 and depicted in figure 3 and 4.

Table 2.Biochemical parameters elevation and significance in COVID-19 patients

	RT-PCR for COVID-19 Positive Patient		
Parameters	**SEVERE (n=112)** **MEAN±SE** (**CI**-95%)	**NON SEVERE (n=88)** **MEAN± SE** (**CI**-95%)	**p value***
D-Dimer (mcg FEU /ml)	3.87 ± 0.43	1.14 ± 0.25	< 0.0001*
Ferritin (ng /ml)	461.84 ± 28.63	290.48 ± 34.71	0.0001*

CI= Confidence interval, **SEM**: Standard Error; **FEU** =Fibrinogen Equivalent

***Result is significant at p < .01 with T-Test Calculator for 2 Independent Mean

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Figure 3: Elevated D-dimer and the severity of COVID-19 patients

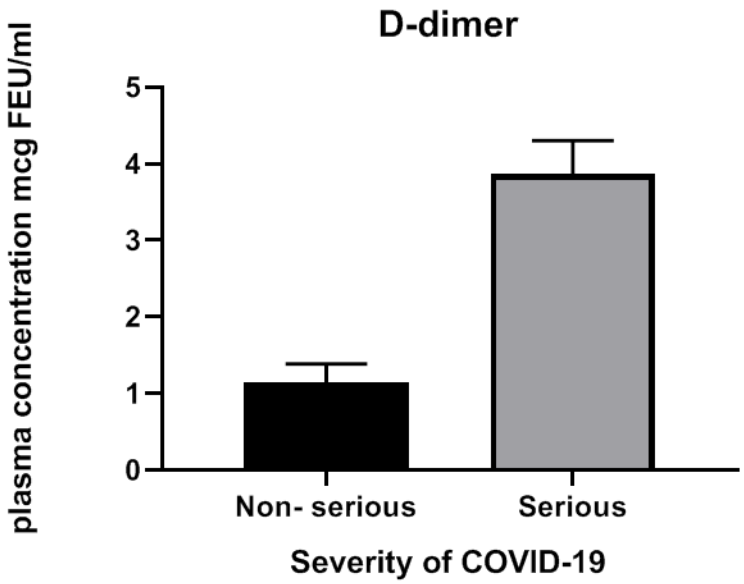
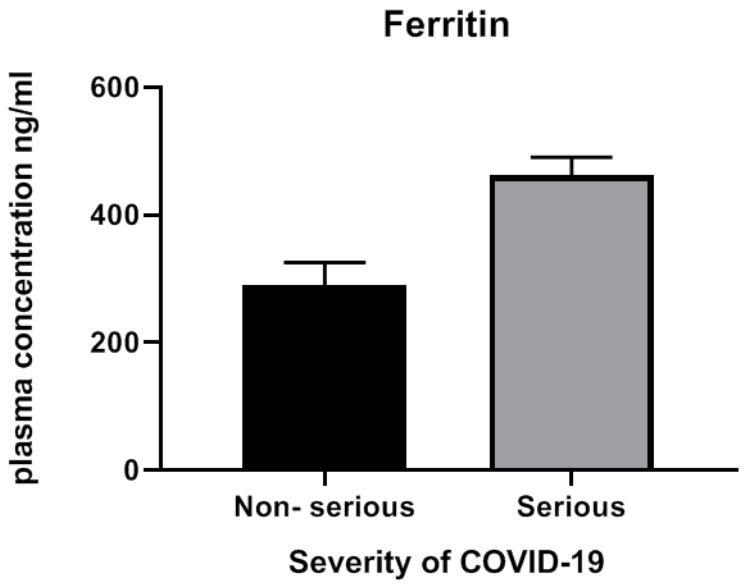


Figure 4: Elevated Ferritin and the severity of COVID-19 patients



Further in this the study a ratio of D-Dimer to Ferritin was evaluated to be > 0.002 up to 0.0039 in Non-severe COVID19 patients and ≥ 0.004 in Severe COVID19 patients.(Table 3)

Table 3.Ratio of the laboratory parameters and the Severity of COVID-19 hospitalised patients

	RT-PCR for COVID-19 Positive Patient	
Parameters Ratio	**SEVERE (n=112)**	**NON SEVERE (n=88)**
Ferritin : D-Dimer (ratio of means)	**1 : 120 = 0.0083**	**1 :255= 0.0039**

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Discussion:

Coronavirus disease-2019 (COVID-19) was spreading rapidly and caused varying degrees of illness along with deranged laboratory markers.[1,4,8] In our study, analyzing the clinical characteristics and biochemical parameters like D-dimer and ferritin of the COVID-19 confirmed patients on admission revealed that all the severe patients presented with shortness of breathing and needed oxygen support at admission. Severe COVID-19 patients were found to have significantly elevated D- dimer or ferritin levels when compared to Non-severe groups. Similar studies were concluded monitoring D-dimer and FDP values may be helpful for the early identification of severe cases.[15,16.] Higher level of D-dimer in severe COVID-19 than those with non-severe disease, and D-dimer greater than 0.5 µg /ml is associated with severe infection in patients with COVID-19. Abnormal coagulation function, including elevated D-dimer to be more common in deceased patients with COVID-19, and increasing odds of in-hospital death was associated with D-dimer greater than 1 µg/ml. Blood coagulation parameters like D-dimer and Ferritin are associated with COVID-19 crucial to discriminate accurately among subjects with COVID-19 who have a high risk of severe infection and resource allocation much needed in a pandemic situation.[15,16, 17] Also a clear demarcation was found in the ratio of D-dimer to Ferritin levels of COVID-19 patients.

Dimer and Ferritin could serve as tool in additional to clinical symptoms of severe COVID-19 for quick triage and guide their admittance to ward or ICU for early suitable treatment. Early intervention in turn could help in reducing mortality and morbidity of a disease. D-dimer and Ferritin can also help to predict the severity when SARS-Cov-2 RT-PCR test results are delayed or unavailable in situations like that of a pandemic.

Conclusion:

Severe COVID-19 patients at admission presents with increased respiratory rate, falling SPO2 requiring immediate oxygen support and or ventilator are vulnerable to high levels of D-dimer or serum ferritin. Significantly elevated levels of D-dimer and Ferritin are associated with severe infection in patients with COVID-19 than in Non- severe cases. Physicians should consider the elevated Dimer and Ferritin in additional to clinical symptoms to predict the severity of COVID-19 for immediate initiation of suitable treatment. They can further use these parameters for triage of COVID-19 when there is tremendous increase in admissions.

However further studies are required on a large population of COVID-19 patients with serial monitoring of parameters to establish the ideal range of D-dimer and Ferritin for early identification of severe cases.

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