(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 1, Page No: 584-589
January-February 2022

IJMSCR

Elevated Levels Of D-Dimer, Ferritin And Crp In Covid-19 Patients

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Aim & Objectives: The aim of this study is to estimate the levels of Serum D-dimer, Ferritin and CRP in COVID-19 patients and healthy controls.

Materials And Methods: In this study, 25 COVID-19 patients and 25 healthy controls of both gender matching in age and sex were included. The analysis of biochemical parameters was done by using autoanalyzer using diagnostic reagent kit.

Results: In the present study Mean of Serum D-dimer, Ferritin and CRP was higher in COVID-19 patients than controls.

Conclusion: Significant changes were observed in Serum D-dimer, Ferritin and CRP. They are favourable prognostic biomarkers with high accuracy for predicting the in-hospital mortality in patients with COVID-19.

Keywords: Renin–angiotensin–aldosterone system (RAAS), ACE2 (angiotensin-converting enzyme 2) etc

Introduction

At the winter of 2019, Coronavirus Disease 2019 (COVID-19), an emerging infectious disease with unclear etiology broke out in Wuhan City, Hubei Province, China [1]. Later, this unknown virus was clarified and named as severe acute respiratory syndrome coronaviruse-2 (SARS-CoV-2) [2, 3]. Now, it has been pandemic across the world. Up to January 1st, 2021, there were approximate 90 million accumulated confirmed patients of SARS-CoV-2 infections in 220 countries, of them about one million cases have died [4]. All humanity is sustained huge disaster from SARS-CoV-2 [5, 6].

Previous studies have demonstrated that COVID-19 patients mainly accompanied with fever, diarrhea, dry cough, lymphocyte reduction and radiographic evidence of pneumonia [7].

SARS-CoV-2 seems to employ mechanisms for receptor recognition similar to those used by prior virulent coronaviruses such as SARS-CoV, the pathogen responsible for the SARS epidemic of 2003. [8-11] The coronavirus spike protein facilitates entry of the virus into target cells. The spike subunit of SARS-CoV and that of SARS CoV-2 engage ACE2 (angiotensin-converting enzyme 2) as an entry receptor (Fig. 1). In addition, cell entry requires priming of the spike protein by the cellular serine protease TMPRSS2 or other proteases.[12] Co-

expression on the cell surface of ACE2 and TMPRSS2 is required for the completion of this entry process. In addition, the efficiency with which the virus binds to ACE2 is a key determinant of transmissibility, as shown in studies of SARS-CoV.[13] Recent studies have demonstrated higher affinity of binding of SARS-CoV-2 to ACE2 than of SARS-CoV to ACE2, which may partially explain the increased transmissibility of SARS-CoV-2.[14–16] Key mechanisms that may have a role in the pathophysiology of multi-organ injury secondary to infection with SARS-CoV-2 include direct viral toxicity, endothelial cell damage and thrombo inflammation, deregulation of the immune response, and deregulation of the renin–angiotensin–aldosterone system (RAAS) (Fig. 1). The relative importance of these mechanisms in the pathophysiology of COVID-19 is currently not fully understood. While some of these mechanisms, including ACE2-mediated viral entry and tissue damage, and dysregulation of the RAAS, may be unique to COVID-19, the immune pathogenesis caused by the systemic release of cytokines and the microcirculation dysfunctions may also occur secondary to sepsis.[17]

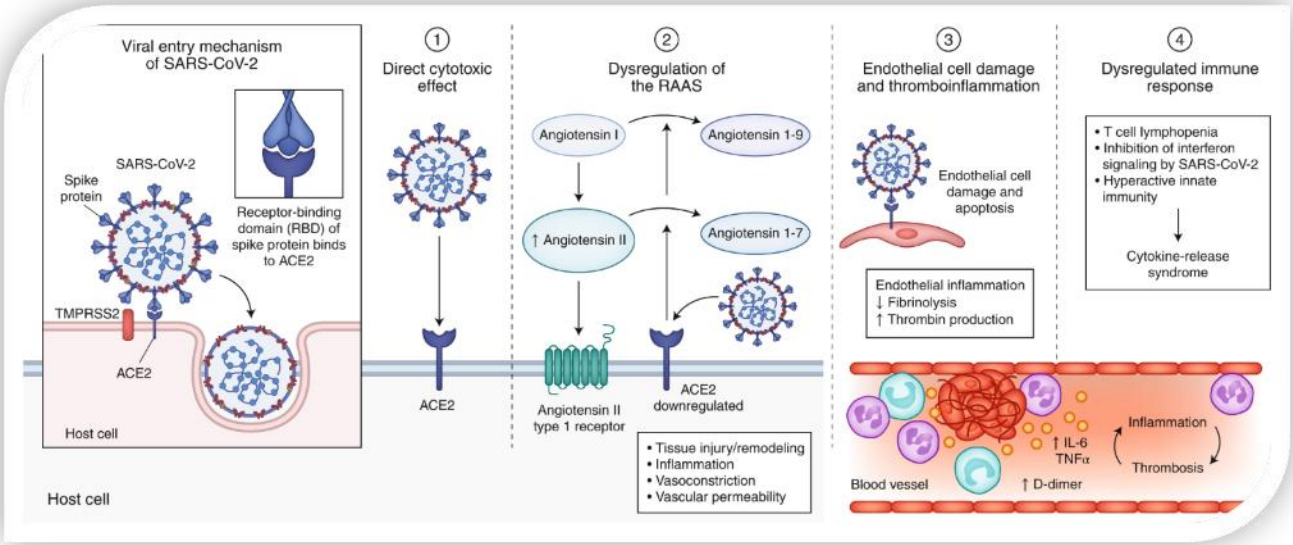

Fig. 1 | SARS-CoV-2 enters host cells through interaction of its spike protein with the entry receptor ACE2 in the presence of TMPRSS2 (far left). Proposed mechanisms for COVID-19 caused by infection with SARS-CoV-2 include (1) direct virus-mediated cell damage; (2) deregulations of the RAAS as a consequence of down regulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II; (3) endothelial cell damage and thrombo inflammation; and (4) deregulations of the immune response and hyper inflammation caused by inhibition of interferon signaling by the virus, T cell lymph depletion, and the production of pro inflammatory cytokines, particularly IL-6 and TNFα.

Recent studies have focused on the role of serum inflammatory markers that predict Covid-19, such as lymphocyte counts and C-reactive protein (CRP), homocysteine and D-dimer levels. The levels of ferritin, a crucial immune response mediator, increase in severe Covid-19 cases.[18]D-dimer is a fibrin degradation product used to exclude the diagnosis of thrombosis. Increased D-dimer levels have been observed in severe Covid-19 cases accompanied by micro -angiopathy and a hyper coagulable state. [19]

The present study aimed to evaluate levels of serum D-dimer, ferritin and C - reactive protein in patients with Covid-19.

Material And Methods

This study was carried out on COVID-19 patients admitted in Prakash Hospital and Research center ,Urun-Islampur. Twenty-five patients with confirmed COVID-19 according to ICMR guidelines and

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Twenty-five healthy age and sex matched non covid-19 controls were included in the study often obtaining their informed consent. The study was conducted on with age group between 20 to 60 years. The analysis of biochemical parameters was done using standard grade reagent chemicals.

The exclusion criteria included subjects of any systemic or metabolic disease, liver disease, vascular diseases, renal artery stenosis, alcoholics, pregnant female and those who were taking any kind of medication last few years. A record was maintained containing current history, diet along with laboratory investigations and previous history of any disease.

CRP was analyzed using immunoturbidimetry method [20] D-dimer and Ferritin was analyzed using latex turbidimetry method.[21,22]

Distribution Of Study Subjects:

Group I	**N = 25 COVID-19 patients.**
Group II	**N= 25 Healthy controls.**

Collection Of Blood Samples:

Blood was collected from each subject under aseptic conditions by using vacutainers. The blood samples were allowed to clot at room temperature for 20–30 minutes & serum was separated from cells by centrifugation for analysis of biochemical parameters. The analysis of biochemical parameters was done by using standard grade reagents and chemicals. Use reagents as per the manual provided by the manufacturer.

Results

Table no. 1: The mean value of D-Dimer, CRP and Ferritin in COVID-19 patients and controls

Name Of the Parameters	Covid-19 Patients (N=25)		Controls (N=25)		Significance
	Mean ±SD	Std. Error of Mean	Mean ±SD	Std. Error of Mean	
D-Dimer	0.71 ±0.15 ***	0.031	0.24 ±0.07	0.14	**P = < 0.001**
CRP	8.38±12.75 ***	2.55	0.8±0.17	0.34	**P = 0.005**
Ferritin	385.4±67.98	13.59	59.29±14.52	2.90	**P =<0.001**

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The statistical method uses to compare data was unpaired' test

*P> 0.05……Not Significant

**P<0.05……...Significant

***P<0.001…...Highly Significant

There is highly statistically significant difference in means of mean value of D-Dimer, CRP and Ferritin as compare to controls.

In the present study mean value of D-Dimer, CRP and Ferritin was higher in COVID-19 patients than controls.

Discussion

Ferritin is an acute phase reactant, and, as such, is typically raised in any inflammatory response. To assess for the most typically seen cytokine storm syndromes laboratory findings include a complete blood count, serum ferritin levels, and liver function tests. Most medical facilities provide these testing.[23] Tang et al studies found that higher fibrin-relevant (d-dimer and fibrin degradation product) levels were significantly associated with non-surviving COVID-19 patients when compared to survivors, as was the use of low molecular heparin in severe SARS-CoV-2 infected patients with elevated d-dimer or sepsis-induced disseminated intravascular coagulation.Increased d-dimer levels may be a good predictor of COVID-19 severe and fatal cases in hospital admission .[24] Several studies have shown that ferritin in hospitalized patients has a considerable elevation, but typically not a particular marker for hemophagocytic lymphohistiocytosis. Ferritin is an acute protein that increases in response to a wide range of inflammatory conditions, including malignancies, overload of iron, and liver or kidney diseases. [25] When ferritin levels begin to rise, a time bomb of inflammation is likely to be present. Patients with COVID-19 have reported that inflammatory process also produce high levels of ferritin. In severe cases serum ferritin levels were substantially higher .[26]

In response to infections, the liver synthesizes significant quantities of acute-phase proteins (APPs), such as CRP [27, 28].Crp-is acute inflammatory protein is a highly sensitive biomarker for inflammation, tissue damage, and infection [29]. It has been shown that CRP levels are correlated with levels of inflammation [30]. CRP levels can promote phagocytosis and activate the complement system [31]. In other words, CRP binds to microorganisms and promotes their removal through phagocytosis [32].

Liu et al. reported that more severe cases infected with COVID-19 expressed significantly higher CRP levels than nonsevere patients [33]. Qin et al. observed higher CRP levels in severe COVID-19 patients than in nonsevere cases, suggesting that this biomarker can be monitored to evaluate disease progression [34]. Sahu et al. performed a meta-analysis to assess CRP levels as a potential biomarker of the COVID-19 prognosis. Their results indicated that CRP concentrations remain high in expired patients and could be a promising biomarker for assessing mortality [35]

D-dimer is the main fibrin disintegration fragment and is used in the synthesis and degradation of fiber as a biomarker. Healthy people have modest levels of d-dimer in circulation while high levels are detected in thrombosis-related diseases. For the diagnosis, surveillance and treatment of venous thromboembolism, for which d-dimer is commonly employed, extensively investigated. Many studies have demonstrated that D-dimer is a good marker for coagulation and fibrinolysis activation. Berger et al investigation found that abnormal d-dimer levels were often detected with COVID-19 admission and were associated with an increased risk of critical disease, thrombotic events, acute renal injury, and death. [36] D-dimer comes from cross-linked fibrin synthesis and lysis and is responsible for coagulation activation and fibrinolysis. COVID-19 has been reported to be connected with hemostatic anomalies, and significantly high amounts of d-dimer in non-survivors have been recorded. [37]In early stage of COVID-19 disease studies have shown an increase in d-dimer and fibrinogen levels. The increase of d-dimer levels by 3 to 4 times is related to poor

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forecasts. Increasing d-dimer levels in COVID-19 individuals could also be triggered by underlying conditions such as diabetes, cancer, stroke, and pregnancy. In the control and management of COVID-19 the measurement of d-dimer and coagulation parameters at an early stage of the disease can also be important. [38]

In Our study we also found that highly significant Serum D-dimer, Ferritin and CRP level in COVID-19 patients compared to controls. According to our and other study, these findings confirmed that the Covid-19 infectious disease plays major role in Serum D-dimer, ferritin and CRP tests.

Conclusion:

Serum D-dimer, Ferritin and CRP can be used as a biomarkers in the Covid-19 patients by measuring levels of Serum D-dimer, Ferritin and CRP and analysis the mortality and severity. Serum D-dimer, Ferritin and CRP tests should be included in the future studies to predict the severity in the patients diagnosed with covid-19 disease.

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