International Journal of Research in Medical Sciences
Jangamgudem S. Int J Res Med Sci. 2022 Mar;10(3):655-659
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20220513

Original Research Article

A comprehensive analysis of serum D-dimer and Ferritin levels, in 347 patients with severe (breathlessness and chest discomfort) corona virus disease 2019

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Received: 05 November 2021
Revised: 05 February 2022
Accepted: 07 February 2022

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ABSTRACT

Background: This study aimed to evaluate the association between serum D-dimer and Ferritin levels, in patients with severe (Breathlessness and chest discomfort) corona virus disease 2019.
Methods: The present study included a 347 (out of 1500) patients with severe Breathlessness and Chest discomfort age between 40 to 60 years who were confirmed to have Covid-19 based on RTPCR in a GVPIHC&MT referral hospital between 2020 June and 2020 August, were analysed.
Results: A total No of 694 cases were studied by dividing them into two groups controls 347 and cases 347. The results so obtained compare with 347 healthy controls included in this study. Statistical evaluation was carried out to confirm any deviation from the normal values. The Mean± SD Serum FERRITIN Cases (654.45±317.45), controls (157.03±87.43), D-dimer values of cases (6.1517±3.4270), controls (0.2204±0.1083) and both serum Ferritin and D-dimer values in cases (3.443230±3.625471), controls (0.201372±0.121560). This increase is statistically P value highly significant (<0.001)
Conclusions: It has been shown from this study with, the serum activities of D-Dimer and Ferritin levels were markedly increased in Severe Breathlessness and Chest discomfort in male and female COVID-19 patients.

Keywords: Corona, Breathlessness and chest discomfort, D-dimer and ferritin

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in Wuhan, China, in December 2019. The disease has since spread worldwide, leading to an ongoing pandemic.[1-2]

Symptoms of COVID-19 are variable, ranging from mild symptoms to severe illness Common symptoms include headache, loss of smell and taste, nasal congestion, runny nose, cough, muscle pain, sore throat, fever diarrhea, and breathing difficulties. People with the same infection may have different symptoms, and their symptoms may change over time.

Three common clusters of symptoms: respiratory symptom combination with cough, sputum, shortness of breath, and fever; musculoskeletal symptom combination with muscle and joint pain, headache, and fatigue; combination of digestive symptoms with abdominal pain, vomiting, and diarrhea.[3-9]

The reason why some individuals become critically ill, while others do not, remains an unsolved riddle. Co-morbidities and laboratory markers have been proposed for risk stratification.[10-13]

There is accelerating evidence that in critically ill patients, there are characteristics of hyper-inflammation, which consist of elevated serum D-dimer, and hyper-ferritinemia. These findings suggest a possibly crucial role of in COVID-19 ptients.[14]

The present study aimed to evaluate the association between serum D-dimer and ferritin levels, in patients with severe (Breathlessness and chest discomfort) corona virus disease 2019.

METHODS

A single-center, prospective, observational study was conducted among COVID-19 positive patients in our Gayatri Vidya Parished Institute of Health Care and Medical Technology (GVPIHC and MT covid 19 referral hospital) Marikavalasa, Visakhapatnam. between 2020 June and 2020 August were analysed. Diagnosis of the patients was carried out based on the interim guidance for COVID-19 issued by the WHO. All COVID-19 diagnosis were confirmed by using RT-PCR and the study was started after taking the institutional ethical committee approval.

The present study included patients age between 40-60 years who were confirmed to have COVID-19 based on real-time reverse transcription polymerase chain reaction assessment of oropharyngeal and nasopharyngeal samples. Patients who had chest discomfort, breathlessness, vomiting, diarrhea, weakness, systemic diseases and lower oxygen saturation were hospitalized.

Inclusion criteria

It included 347 (out of 1500) covid 19 patients. Healthy adults, age between 40-60 years, gender (male/female), chest discomfort, breathlessness, systemic co-morbidities (diabetes mellitus, hypertension). Moreover, patients, symptoms, such as cough, shortness of breath, rhinorrhea, sore throat, loss of smell, dysgeusia, fever and vomiting, were documented.

Exclusion criteria

Patients without polymerase chain reaction confirmed COVID-19, age <40 >60, with a history of thrombo embolism, with vitamin D deficiency, receiving vitamin D or Ferritin treatment, With a cardiovascular disease.

Sample collection

Fasting blood samples (between 2020 June and 2020 August) were collected from COVID 19 positive and healthy, controls (non-COVID) in our GVPIHC hospital, Marikavalasa, Visakhpatnam.

5 ml of venous blood was collected from each subject in fasting condtions and dispensed into lithium heparin bottles. Plasma was obtained by centrifugation for 5 min at 3,000 rpm and separated into plain bottles and send to the outside thyrocare lab for analysis of ferritin and D-dimer concentrations, with a fully automated bio directionally interfaced chemi lumine for ferritin and D-dimer done by the Solid Phase Two Site Chemiluminescent Enzyme Method in both cases and controls.

Statistical analysis

The data were expressed as mean or percentage, compared the categorical variables between the two groups (cases and controls) using chi-square test. 1) ferritin values only in both (male and female) $p<0.001$. 2) D-dimer values in both (male and female) $p<0.0001$. 3). Both D-dimer and Ferritin values in (male and female) $p<0.001$ was considered statistically significant.

RESULTS

Estimation of serum

Ferritin levels by the Fully Automated Bio directionally Interfaced Chemi Luminescent Immune Assay Method.

Table 1 shows that mean serum Ferritin in total 33 both (male, female) cases (654.45±317.45), is having higher level as compared to the mean value of controls (157.03±87.43). This increase is statistically P value highly significant (<0.001).

Table 1: Ferritin (ng/ml) levels study done by the fully automated bio directionally interfaced chemi luminescent immune assay method in both (male and female) cases and controls.

Gender	Group	N	Mean	SD	P value
Male	Case	27	694.09	308.77	<0.001
	Control	27	179.56	79.22	
Female	Case	6	476.03	320.20	0.01
	Control	6	55.67	34.84	
Total	Case	33	654.45	317.45	<0.001
	Control	33	157.03	87.43	

Table 2: Estimation of serum D-dimer levels by the solid phase two site chemiluminescent enzyme method in both (male and female) cases and controls.

Sex	Group	N	Mean	SD	P value
Male	Case	132	6.3056	3.4105	<0.0001
	Control	132	0.2235	0.1132	
Female	Case	69	5.8572	3.4643	<0.0001
	Control	69	0.2145	0.0989	
Total	Case	201	6.1517	3.4270	<0.0001
	Control	201	0.2204	0.1083	

Table 3: Ferritin and D-dimer levels in both (male and female) 113 cases and 113 controls.

Sex	Group	Fer			P value	D-dimer			P value
		N	Mean	SD		N	Mean	SD	
Male	Case	102	639.02	377.73	<0.001	102	4.19	5.79	<0.001
	Control	102	161.03	80.67		102	90.21	124.39	
Female	Case	11	492.67	211.24	<0.001	11	3.11	5.2	0.01
	Control	11	116.36	46.52		11	91.96	105.13	
Total	Case	113	624.77	366.81	<0.001	113	4.08	5.72	<0.001
	Control	113	156.68	78.99		113	90.38	122.23	

Table 2 shows that mean serum D-dimer values in total 201 both (male, female) cases (6.1517±3.4270), is having higher level as compared to the mean value of controls (0.2204±0.1083). This increase is statistically P value highly significant (<0.0001).

Table 3 shows that mean±SD serum Ferritin cases (624.77±366.81) and controls (156.68±78.99) D-dimer levels in both (Male and Female) cases and controls. Cases (4.08±5.72), controls (90.38±122.23) values in total 113 both (male, female) cases having higher level as compared to the mean value of controls. This increase is statistically P value highly significant (<0.001).

DISCUSSION

The D-dimer and Ferritin measurements in the serum of patients have been widely used in clinical practice for several decades.

D-dimer (or D dimer) is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis, includes a cascade of enzymatic reactions that lead to the conversion of fibrinogen into fibrin. The reverse process is called fibrinolysis and this destroys fibrin clots through the enzymatic cleavage of fibrin into soluble fragments.

It is so named because it contains two D fragments of the fibrin protein joined by a cross-link. D-dimers are not normally present in human blood plasma, but elevated levels of D-dimer have been found in the blood of patients with deep vein thrombosis, pulmonary thromboembolism, atherosclerosis, disseminated intravascular coagulation, sepsis, cancer, and other diseases, as well as after major surgery. D-dimer concentration determined by a blood test to help diagnose thrombosis.[15-27]

The assays are routinely used as part of a diagnostic algorithm to exclude the diagnosis of thrombosis. However, any pathologic or non-pathologic process that increases fibrin production or breakdown also increases plasma D-dimer levels.[28]

Among adults admitted to the emergency room, infections, instead of VTE/PE, are the most common reason for D-dimer elevation. In the present study, no patient had confirmed PE/DVT, which supports the application of D-dimer in COVID-19 not just as a diagnostic tool for thromboembolism.[29]

Ferritin (storage protein) is involved in iron metabolism, which contains L and H subunits expressed in the lung and heart, respectively. The 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 major role in immune-modulatory and pro-inflammatory activities by activating several inflammatory mediators such as IL-1β. Ferritin was found only in the lymph node B area, indicating its role as an antigen, which stimulates macrophage activation related to hyperferritinemia.[30]

There are multiple studies correlating elevated ferritin levels and other pro-inflammatory markers in COVID-19 with poor outcomes. Elevated levels of ferritin, or hyperferritinemia, indicate the viral or bacterial load in the body.[31-37]

Hyperferritinemia, or hyperferritinemic syndrome, is a condition activating macrophages to secrete cytokines, causing a cytokine storm in severe cases, which can be a sign of severe disease. Increased serum ferritin levels as a result of COVID-19 related hyper-inflammation signify a vicious cycle of events where increased ferritin levels may lead to further tissue damage.[38,39]

Excess intracellular iron interacts with molecular oxygen, generating reactive oxygen species (ROS). This may largely contribute to oxidative damage of cellular components of different organs (lungs, liver, kidney, heart). Mounting evidence links increased ferritin levels to various inflammatory pathologies including cardiovascular events.[39,40]

Moreover, the complex interplay between iron metabolism and reactive nitrogen species (RNS) and reactive sulfur species (RSS) in addition to ROS suggests a clear interaction between iron metabolism and the newly defined reactive species interactome.[41]

This study has some limitations. First, the current study was done in a single center. Second, the study is retrospective in nature. The patients included were not systematically assessed for the presence of chest discomfort, Brethlessness, but only when clinically suspected. Third, we did not look into the value of serial ferritin, D-dimer monitoring in assessing COVID-19 patients.

CONCLUSION

It has been shown from this study with, the serum activities of D-Dimer and Ferritin levels were markedly increased in Severe Breathlessness and Chest discomfort in male and female COVID-19 patients.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Jangamgudem S. A comprehensive analysis of serum D-dimer and Ferritin levels, in 347 patients with severe (breathlessness and chest discomfort) corona virus disease 2019. Int J Res Med Sci 2022;10:655-9.