ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

To study of D-dimer and ferritin in the blood of 330 people with severe corona virus sickness in 2019: A comparative study

Dr. J. Sudha Rani, Dr. P. Mahesh Kumar, Rangaswamy M
Assistant Professor, Department of Biochemistry, MRMCW, Suraram X Road, Hyderabad, Telangana, India

***Corresponding Author**
Dr. J. Sudha Rani
Assistant Professor, Department of Biochemistry, MRMCW, Suraram X Road, Hyderabad, Telangana, India

ABSTRACT
Objectives and Background: Individuals who are severely affected by the coronavirus disease-2019 (COVID-19) exhibit a state of excessive inflammation, known as hyperinflammation. The identification and analysis of biomarkers linked with this hyperinflammatory response should prove advantageous in assessing the level of risk in these patients. The objective of this study was to assess the correlation between blood levels of D-dimer and Ferritin in individuals diagnosed with severe coronavirus illness 2019.
Materials and Methods: The current investigation involved the analysis of a subset of patients (n=330) out of a larger population (n=1200) who presented with severe breathlessness and chest discomfort. These individuals, aged between 40 and 60 years, were proven to have contracted Covid-19 through the use of Reverse Transcription Polymerase Chain Reaction (RTPCR) testing. The data collection period for this study spanned from June 2020 to August 2020, and the patients were admitted to a Gayatri Vidya Parishad, Institute of Health Care and Medical Technology.
Results: There were a total of 660 participants, 330 each in the control and case groups. These findings are compared to those of 330 healthy individuals used as controls in the study. Any outliers from the norm were confirmed through statistical analysis. Values for serum Ferritin and D-dimer were compared between cases and controls, as were values for serum Ferritin and D-dimer in both sets of data. There is strong statistical evidence for this rise.
Conclusion: This study demonstrates that the serum activities of D-Dimer and Ferritin levels were significantly elevated in male and female COVID-19 patients experiencing severe breathlessness and chest discomfort.

Keywords: Corona, chest ache and breathlessness, Ferritin and D-dimer

INTRODUCTION

The World Health Organization (WHO) has designated Coronavirus disease-2019 (COVID-19) as an emerging infectious illness of global significance, warranting the classification of a global public health emergency. Since its emergence in Wuhan, China, the global tally of confirmed COVID-19 cases has surpassed 3,500,000, with a corresponding mortality toll of 243,403. The sickness in question is a transmissible condition resulting from the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1-3]. The initial documented instance was recognized in Wuhan, China, during the month of December in the year 2019. The disease has since disseminated on a global scale, resulting in an ongoing epidemic [4, 5]. The symptoms associated with COVID-19 exhibit a wide range of severity, encompassing both minor manifestations and more severe forms of sickness. Typical manifestations encompass cephalalgia, olfactory and gustatory impairment, nasal congestion, rhinorrhea, coughing, myalgia, pharyngalgia, pyrexia, gastrointestinal distress, and respiratory distress. Individuals afflicted with the identical virus may exhibit varying symptoms, which have the potential to evolve over the course of time. As the ongoing pandemic persisted, concurrent investigations yielded a plethora of empirical evidence that contributed to a more comprehensive understanding of the disease's etiology, thereby enhancing therapeutic approaches. It has been shown that a prominent characteristic of severe COVID-19 disease is the presence of a hypercoagulable condition, which is characterized by an extended prothrombin time and elevated levels of fibrinogen and fibrin breakdown products, including D-dimer. The activation of coagulation cascades in individuals diagnosed with COVID-19, particularly those who are critically ill, has been found to have a substantial impact on the morbidity and mortality rates within this specific patient population [6-8].

Severe COVID-19 infection often need immediate administration of supplemental oxygen therapy, which can be effectively administered via standard techniques or may require invasive mechanical ventilation. The timely anticipation of the requirement for invasive mechanical ventilation has the potential to greatly enhance the clinical results of those afflicted with COVID-19. The study aimed to assess the predictive value of various biomarkers, including plasma levels of D-dimer and inflammatory markers, as well as complete blood counts, measured within the initial two days of hospital admission for COVID-19 patients. Specifically, the study investigated the significance of these biomarkers in predicting the subsequent requirement for invasive mechanical ventilation support, as well as their potential as predictors of morbidity and mortality following ventilation [9, 10].

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

There are three prevalent groupings of symptoms that have been observed: the first cluster consists of respiratory symptoms such as cough, sputum production, shortness of breath, and fever; the second cluster involves musculoskeletal symptoms such as muscle and joint pain, headache, and fatigue; and the third cluster encompasses digestive symptoms including abdominal discomfort, vomiting, and diarrhea. The etiology behind the development of severe illness in certain individuals, as opposed to others who remain unaffected, continues to be an unresolved enigma. Risk categorization has been suggested based on the presence of co-morbidities and laboratory indicators [11, 12].

There is a growing body of research indicating the presence of hyper-inflammation features, such as high serum D-dimer levels and hyper-ferritinemia, in critically ill individuals. The aforementioned data indicate a potentially significant role of in individuals affected by COVID-19. While the majority of individuals afflicted with COVID-19 experience a mild influenza-like illness or may remain asymptomatic, a minority of patient's progress to severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and mortality. The user's text is too short to be rewritten academically. The etiology of critical illness, and the factors that contribute to its development in certain individuals while others remain unaffected, continues to elude researchers [11-13].

In the midst of a pandemic, it is crucial to have laboratory biomarkers that can accurately predict the severity of COVID-19. This is particularly important in order to effectively allocate resources, especially when it comes to preparing for respiratory support [12-14]. The current investigation involved a systematic review and meta-analysis to examine the correlation between various biomarkers, including as serum CRP, PCT, D-dimer, and serum ferritin, and the severity of COVID-19. The primary objective of this study was to assess the correlation between blood levels of D-dimer and ferritin in individuals diagnosed with severe coronavirus illness 2019.

MATERIALS AND METHODS

A prospective observational study was undertaken at the Gayatri Vidya Parishad, Institute of Health Care and Medical Technology. The study focused on patients who tested positive for COVID-19 at this single-center facility. The period of analysis encompassed the months of from June 2020 to August 2020. The patients were diagnosed using the interim guidance for COVID-19 provided by the World Health Organization (WHO). The confirmation of all COVID-19 diagnoses was conducted by the utilization of RT-PCR, and the commencement of the study occurred subsequent to obtaining approval from the institutional ethics council.

Inclusion criteria:

- The study comprised 330 of 1200 Covid 19 patients. Healthy people, 40-60 years old, male/female, chest pain, dyspnea, systemic co-morbidities (diabetes, hypertension). Patients also reported cough, shortness of breath, rhinorrhea, sore throat, loss of smell, dysgeusia, fever, and vomiting.

Exclusion criteria:

- COVID-19 patients without PCR confirmation, age <40 >60, thrombo embolism history, vitamin D insufficiency, Ferritin medication, cardiovascular illness.

Statistical analysis

The data were presented as either mean values or percentages. A chi-square test was used to compare the categorical variables between the two groups, namely the cases and controls. The ferritin values are observed in both males and females, as are the D-dimer values. Statistical significance was observed in both D-dimer and Ferritin values for both male and female individuals.

RESULTS

The ferritin levels were determined using the Fully Automated Bio directionally Interfaced Chemi Luminescent Immune Assay Method. Table 1 presents the mean serum Ferritin levels in a sample of 30 individuals, including both males and females. The data indicates that the mean serum Ferritin levels in the cases are greater compared to the mean levels observed in the control group. The observed rise exhibits statistical significance.

Table 1: The fully automated bio directionally interfaced chemi luminescence immune assay method was used to measure ferritin (ng/ml) in male and female patients and controls

Gender	Group	N	Mean	SD
Male	Case	25	591.08	208.76
	Control	25	177.57	76.34
Female	Case	5	575.02	333.21

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

	Control	5	59.68	37.97
Total	Case	30	666.44	367.64
	Control	30	168.02	89.55

Table 2: The solid phase two site chemiluminescent enzyme technique estimates serum D-dimer levels in male and female patients and controls

Sex	Group	N	Mean	SD
Male	Case	130	5.3055	2.4104
	Control	130	0.1234	0.2133
Female	Case	70	4.9571	2.3642
	Control	70	0.1144	0.0887
Total	Case	200	5.2516	2.1271
	Control	200	0.3200	0.2082

Table 2 illustrates that the average serum D-dimer levels in a combined sample of 200 patients (both male and female) are significantly higher compared to the mean value observed in the control group. The observed rise exhibits a high level of statistical significance.

Table 3: Ferritin and D-dimer levels in men and women 50 cases, 50 controls

Sex	Group	Fer			D-dimer		
Male		N	Mean	SD	N	Mean	SD
	Case	45	5.305	2.4102	45	5.12	4.92
	Control	45	0.223	0.2131	45	91.11	47.14
Female	Case	05	4.857	2.3642	05	4.35	4.9
	Control	05	0.118	0.0971	05	93.89	11.12
Total	Case	50	6.181	2.1270	50	5.09	4.726
	Control	50	0.230	0.2081	50	92.87	20.18

Table 3 presents the mean ± standard deviation (SD) values of serum ferritin in cases and controls, as well as the D-dimer levels in both male and female subjects within the cases and controls groups. The total number of cases and controls in this study is 100, including both males and females. The cases exhibit greater levels in comparison to the mean value of the controls. The observed rise exhibits statistical significance.

DISCUSSION

The utilization of D-dimer and Ferritin readings in the serum of patients has been extensively employed in clinical practice for numerous decades. D-dimer, also known as D dimer, is a byproduct of fibrin degradation, specifically a small fragment of protein that may be detected in the bloodstream following the breakdown of a blood clot through the process of fibrinolysis. This process involves a series of enzymatic reactions that ultimately result in the conversion of fibrinogen into fibrin. The process of fibrinolysis, also known as the reversal of clot formation, involves the enzymatic breakdown of fibrin into soluble fragments, resulting in the destruction of fibrin clots.

The nomenclature of this entity is derived from its composition, which consists of two D segments of the fibrin protein that are interconnected through a cross-link. D-dimers are typically absent in the plasma of human blood, but individuals with conditions such as deep vein thrombosis, pulmonary thromboembolism, atherosclerosis, disseminated intravascular coagulation, sepsis, cancer, and other thrombotic disorders have been observed to exhibit heightened levels of D-dimer. These levels can be determined through a blood test, aiding in the diagnostic process for thrombosis [15, 16]. According to Siddiqi and Mehra, during the systemic hyperinflammation phase of COVID-19, there is a notable increase in various inflammatory cytokines and biomarkers. These include interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), ferritin, procalcitonin (PCT), and D-dimer. This phase encompasses the most pronounced expression of the cytokine storm, characterized by an overwhelming hyperinflammatory response that can result in the collapse of the cardiopulmonary system and failure of several organs [17-19].

A study shown a positive correlation between an increased serum C-reactive protein (CRP) level and a higher 30-day death rate. However, it is important to note that conflicting findings have been reported in other studies. The observed inconsistencies could perhaps be attributed to variations in the employed cutoff levels. The study conducted by Koozi *et al*. utilized a threshold value of ⩾1000mg/L to determine an increased serum CRP level, whereas the study conducted by Ryoo *et al*. employed a cutoff point of ⩾140mg/L. In their study, Liu *et al*. put out a threshold of 41.8mg/L or higher as a predictive indicator for severe cases of COVID-19 [20-23]. The investigation revealed a considerable range of serum CRP cutoff levels, spanning from greater than 3mg/L to greater than 100mg/L. The results

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

of this study underscore the critical need of determining the most effective serum CRP cutoff value for predicting the prognosis of COVID-19. The timing of serum CRP measurement was crucial due to the rapid increase in serum CRP levels, which reaches its peak 72 hours after the initial assaults. Although serum C-reactive protein (CRP) levels have proven to be valuable in predicting an unfavorable prognosis in COVID-19, it is important to acknowledge that several factors have the potential to influence these levels. These factors encompass age, gender, smoking habits, body weight, lipid profiles, blood pressure, and liver impairment. When assessing the serum CRP level, it is important to consider these parameters. Moreover, recent empirical findings have indicated that the measurement of serum C-reactive protein (CRP) levels may serve as a valuable tool for monitoring the advancement and amelioration of individuals afflicted with COVID-19 [24-26].

The tests are commonly employed as a component of a diagnostic strategy in order to rule out the presence of thrombosis. Nevertheless, both pathological and non-pathological processes that enhance fibrin synthesis or degradation also result in elevated levels of plasma D-dimer. In the population of adults presenting to the emergency department, it has been observed that infections are more frequently associated with elevated D-dimer levels compared to venous thromboembolism/pulmonary embolism. The current investigation revealed that none of the patients exhibited verified pulmonary embolism (PE) or deep vein thrombosis (DVT), so providing further evidence for the utilization of D-dimer testing in the context of COVID-19. The utilization of this diagnostic technique extends beyond its application solely for thromboembolism [25-28].

The presence of an excessive amount of iron within the intracellular environment leads to the interaction between iron and molecular oxygen, resulting in the production of reactive oxygen species (ROS). This phenomenon may significantly contribute to the occurrence of oxidative damage in the cellular components of several organs, including the lungs, liver, kidneys, and heart. There is a growing body of research that establishes a connection between elevated levels of ferritin and a range of inflammatory conditions, including cardiovascular events. Furthermore, the intricate relationship between iron metabolism and reactive nitrogen species (RNS) and reactive sulfur species (RSS), alongside reactive oxygen species (ROS), implies a distinct correlation between iron metabolism and the recently established interactome of reactive species [29-32]. The present study is subject to many limitations. Initially, it is important to note that the present investigation was conducted within a singular research facility. Furthermore, the research conducted in this study is retrospective in character. The individuals included in the study were not subjected to a systematic assessment for the existence of chest discomfort or breathlessness. Instead, these symptoms were only evaluated when there was a clinical suspicion. Furthermore, our investigation did not encompass an examination of the significance of serial ferritin and D-dimer monitoring as a means of evaluating individuals with COVID-19 [33-37].

CONCLUSION

This study demonstrates that there is a significant increase in serum activity of D-Dimer and Ferritin levels among male and female COVID-19 patients experiencing severe breathlessness and chest discomfort. Moreover, our study did not include an analysis of the importance of serial ferritin and D-dimer monitoring in the assessment of persons with COVID-19.

Funding None
Conflict of Interest None

REFERENCES

1. Islam MA. Prevalence and characteristics of fever in adult and paediatric patients with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis of 17515patients. PLOSONE. 2020;e0249788.
2. Kesharwani RK, Keservani RK, Sharma AK, editors. Nutraceuticals and Functional Foods in Immunomodulators. Springer Nature; 2023.
3. Pranata R, Huang I, Lukito AA. Elevated N- terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID- 19: systematic review and meta-analysis. Postgrad Med J. 2020;137884.
4. Ahire ED, Sonawane VN, Surana KR. Role of drug repurposing in current treatment strategies against COVID-19; systemic review. Pharm Reson. 2020:24-9.
5. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – a systematic review, meta-analysis, and meta-regression: diabetes and COVID-19. Diabetes Metab Syndr Clin Res Rev. 2020;14:395-403.
6. Talele SG, Ahire ED, Surana KR, Sonawane VN, Talele GS. Corona Virus Disease (COVID-19): A past and Present Prospective. Asian Journal of Pharmaceutical Research. 2022;12(1):45-53.
7. Pranata R, Huang I, Lim MA. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19 – systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis. 2020;29:104949.
8. Ahire ED, Sonawane VN, Surana KR, Jadhav KR, Sonawane DD, Shah AA. Convalescent plasma therapy: A promising approach in the treatment of Covid-19. Int J Pharm Sci Res. 2020;11:4078-86.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

9. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. J Intensive Care. 2020;8:36.
10. Ahire ED, Kshirsagar SJ. Immune responses induced by different vaccine platforms against coronavirus disease-19. Explor. Immunol. 2021;1:243-57.
11. Mehta P, McAuley DF, Brown M. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033-4.
12. Adam SS, Key NS, Greenberg CS. "D-dimer antigen: current concepts and future prospects". Blood. 2009;113(13):2878-87.
13. Gunjal SS, Ahire SG. KRS, Vijayraj N. Sonawane, Khushali R. Pagar. Influence of Allopathy, Homeopathy, Ayurveda and Unani Systems of Medicine in the Management of COVID-19. COVID-19 Pandemic: Questions, Answers and Hypotheses.;1.
14. Ahire ED, Surana KR, Sonawane VN, Talele SG, Kshirsagar SJ, Laddha UD, Talele GS. Role of Synthetic Medicines as Immunomodulators for the Cure of COVID-19. COVID-19 and Immunomodulation with Special Emphasis on Nutraceutical and Herbal Formulation. 2023 Oct 20.
15. Rowbotham BJ, Carroll P, Whitaker AN, Bunce IH, Cobcroft RG, Elms MJ *et al*. Measurement of cross- linked fibrin derivatives - use in the diagnosis of venous thrombosis. Thromb Haemost. 1987;57:59- 61.
16. Assmann G. Association of variables of coagulation, fibrinolysis and acute-phase with atherosclerosis in coronary and peripheral arteries and those arteries supplying the brain. Thromb Haemost. 1995;73:374-9.
17. Salomaa V, Stinson V, Kark JD, Folsom AR, Davis CE, Wu KK. Association of fibrinolytic parameters with early atherosclerosis. The ARIC Study.Atherosclerosis Risk in Communities Study. Circulation. 1995;91:284-90.
18. Carey MJ, Rodgers GM. Disseminated intravascular coagulation: clinical and laboratory aspects. Am J Hematol. 1998;59:65-73.
19. Angstwurm MW, Dempfle CE, Spannagl M. New disseminated intravascular coagulation score: A useful tool to predict mortality in comparison with Acute Physiology and Chronic Health Evaluation II and Logistic Organ Dysfunction scores. Crit Care Med. 2006;34:314-20.
20. Hesselvik JF, Blomba¨ck M, Brodin B, Maller R. Coagulation, fibrinolysis, and kallikrein systems in sepsis: relation to outcome. Crit Care Med. 1989;17:724-33.
21. Gando S, Nanzaki S, Sasaki S, Aoi K, Kemmotsu O. Activation of the extrinsic coagulation pathway in patients with severe sepsis and septic shock. Crit Care Med. 1998;26:2005-9.
22. Rocha E, Pa´ramo JA, Ferna´ndez FJ, Cuesta B, Herna´ndez M, Paloma MJ, *et al*. Clotting activation and impairment of fibrinolysis in malignancy. Thromb Res. 1989;54:699-707.
23. Bongard O, Wicky J, Peter R, Simonovska S, Vogel JJ, de Moerloose P, *et al*. D-dimer plasma measurement in patients undergoing major hip surgery:use in the prediction and diagnosis of postoperative proximal vein thrombosis. Thromb Res. 1994;74:487-93.
24. Wang F, Hou H, Luo Y. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI insight. 2020;5:e137799.
25. Zhou F, Yu T, Du R. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
26. Renfei Lu, Jianru Qin, Yan Wu. Epidemiological and clinical characteristics of COVID-19 patients in Nantong, China. J Infect Dev Ctries. 2020;14:440-6.
27. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics. 2014;6(4):748-73.
28. Kno-vich MA, Storey JA, Coffman LG, Torti SV, Torti FM. Ferritin for the clinician. Blood Rev. 2009;23(3):95-104.
29. Lippi G and Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID19): a meta-analysis. Clin Chim Acta 2020; 505: 190–191.
30. Levi M and van der Poll T. Coagulation and sepsis. Thromb Res 2017; 149: 38–44.
31. Lin L, Lu L, Cao W, *et al*. Hypothesis for potential pathogenesis of SARS-CoV-2 infection– a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect 2020; 1–14.
32. Lue W, Yu H, Gou J, *et al*. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). Preprints 2020; 1–18.
33. Thachil J, Tang N, Gando S, *et al*. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020; 1023–1026.
34. Karakike E and Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: a distinct entity leading to early death in sepsis. Front Immunol 2019; 10: 55.
35. Ramos-Casals M, Brito-Zerón P, LópezGuillermo A, *et al*. Adult haemophagocytic syndrome. Lancet 2014; 383: 1503–1516.
36. Veronese N, Demurtas J, Yang L, *et al*. Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. Front Med 2020; 7: 1–6.
37. Pranata R, Lim MA, Huang I, *et al*. Hypertension is associated with increased mortality and severity of disease in

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. J Renin Angiotensin Aldosterone Syst 2020; 1–11.