DOI: https://doi.org/10.53350/pjmhs2216936

ORIGINAL ARTICLE

Study the Pattern of D-Dimers, HS CRP and Ferritin in Covid-19 Patients

REHMA DAR[1], RABIA BUTT[2], FAUZIA SADIQ[3], MAZHAR FAREED[4], LUBNA SHAHEEN[5], MAHAM SHAKOOR[6]
[1]*Associate Professor Pathology, Services Institute of Medical Sciences Lahore*
[2]*Medical Laboratory Technologist KEMU, Lahore*
[3]*Professor of Pathology, King Edward Medical College, Lahore*
[4]*Senior Demonstrator Pathology, Services Institute of Medical Sciences Lahore*
[5]*Senior demonstrator Pathology, Sargodha Medical College*
M Phil Chemical pathology resident in KEMU
Correspondence to Dr. Rehma Dar, Email: Rehma79@hotmail.com, Tel. 03234681588

ABSTRACT

Background: Corona virus disease is caused by SARS-CoV-2. This pandemic has affected over 200 countries. Most of the patients are asymptomatic. The disease is usually mild but in approximately 14% of patients it worsens to severe respiratory impairment and admission to ICU. Different tests in laboratories have been used to assess severity and prognosis of severely sick Covid-19 patients in addition to clinical and radiological findings.
Aim: To study pattern of Hs- CRP, Ferritin and D-Dimers in Covid-19 patients admitted in Mayo Hospital/ KEMU
Duration: June 2020 to October, 2020.
Methods: It was a descriptive study conducted in Central Diagnostic Laboratory (CDL) of Mayo Hospital/ KEMU, Lahore on 1474 Covid-19 patients. All samples of the Covid-19 patients sent to CDL of Mayo hospital/ KEMU Lahore for D-Dimers, Hs CRP and Ferritin levels were included in the study. The results and other relevant information were recorded on proforma. The collected data was analyzed by SPSS 23.Quantitative variables like age was presented as mean ± SD. Qualitative variables like gender, single, double or triple parameter abnormalities were presented as frequency and percentage.
Results: Out of total 1474, 958(65%) samples were of male and 516(35%) were of female patients. Mean age± SD was50.6±4.2 years. The percentage of abnormal Hs CRP, D Dimers and ferritin was 1386(94%), 1312(89%) and 1135(77%) respectively. The mean±SD value for HsCRP, D-Dimers and ferritin was 56.8±16.9mg/L, 4.4±1.5µg/ml FEU and 770±180 ng/ml respectively. The patients having 3, 2 and 1 abnormal parameter were 988(67%), 456(31%) and 29(2%).
Conclusion: Males were more affected with Covid-19 as compared to females. HsCRP is the most frequently raised biomarker in Covid-19 patients and both inflammatory (HsCRP and Ferritin) and coagulopathy marker (D Dimers) were raised in severely sick Covid-19 patients.
Keywords: D Dimers, Ferritin, Hs CRP, Covid-19 patients.

INTRODUCTION

Corona virus is enveloped RNA virus and the name corona has been given to it because it resembles a crown due to the spiky projections on its surface under the electron microscope[1]. The main structural proteins that make up the basic structure of virus are; nucleocapsid (N), membrane (M), envelope (E) and spike (S) responsible for the virion replication, pathogenesis and spread[2-5].

The disease is called as Covid 19 because the first patient of corona virus was recognized in Wuhan, China in December 2019. The virus causing Covid 19 disease is designated as SARS-CoV-2 because its encoded proteins were homologous to SARS-CoV proteins (95%–100%)[6-8]. Covid 19 was declared as pandemic by WHO as confirmed cases approached $2x10^6$ patients with eight thousand deaths in more than 160 countries[9].

The transmission of virus is mainly via droplets generated by coughing and sneezing by infected patients. The incubation period varies 2-14 days[10]. The virus enters the host cell by binding of its S protein with host cell ACE 2 mainly expressed on type 2 alveolar cells, myocardial cells, proximal tubule cells of the kidney, urothelial cells of bladder and enterocytes of ileum and other parts of small intestine. After entry the viral antigen evoke severe immune response in host resulting in cytokine storm[11-13].

Although acute respiratory distress syndrome (ARDS) is the main pathology, it results in multiple organ failure and even death in severe cases[14]. The disease spectrum for Covid 19 is broad ranging from asymptomatic to critically sick patients. The indicators for severe disease are hypoxemia, tachypnea and lung infiltrates involving more than 50% of the lung area[15,16].

In addition to clinical and radiological features, different laboratory tests are also used to assess severity of disease like increased leukocyte and neutrophil count, lymphopenia, increased N:L, elevated transaminases, LDH, increased acute phase reactants (CRP, ferritin), elevated troponins and CK MB(due to myocarditis), elevated blood urea nitrogen and creatinine (kidney injury), elevated D-dimers (due to coagulopathy), elevated IL-2, IL-6, IL-8, IL-10 (due to cytokine storm)[17].

CRP is a positive acute phase reactant produced by liver. CRP is markedly increased in severe Covid-19 disease under the influence of cytokine storm[18]. D-dimers are produced by the breakdown of cross linked fibrin in the presence of plasmin indicating the coagulation and fibrinolysis. The increased levels have been seen in severe Covid-19 disease as a result of procoagulant cytokines and hypoxia and can be used as prognostic biomarker[19-26].

Ferritin is an iron storage protein, also used as a biomarker of acute and chronic inflammation. In addition to the leakage from cells, active ferritin production occurs during inflammation due to cytokines[27,28]. The levels are found to be raised in critically sick Covid patients. The increased levels of the ferritin in circulation can produce further cell damage because of the oxidative stress[10].

The Objective was To study the pattern of D-Dimers, HsCRP and Ferritin in Covid-19 patients Covid-19 patients of Mayo Hospital/ King Edward Medical University Lahore from June, 2020 to 30TH October, 2020.

MATERIAL AND METHODS

It was a descriptive study conducted at Central Diagnostic Laboratory (CDL) of Mayo Hospital/ King Edward Medical University, Lahore with the approval of the Institutional Review Board. All samples of the Covid-19 patients sent to CDL for D-Dimers, Hs CRP and Ferritin levels were included in the study. Haemolyzed, insufficient sample, clotted sample for D- Dimers were rejected. The relevant information like age, gender and results of D-Dimers, HsCRP and Ferritin was noted on proforma. The blood samples in yellow vial for ferritin and Hs CRP and in blue top citrated vial for D dimers were centrifuged at 3000 rpm for 3-5 minutes to separate serum and plasma. The serum was divided into two aliquots, one for Hs CRP to run on Beckman coulter AU680 Chemistry Autoanalyzer and other for ferritin to run

Received on 24-04-2022
Accepted on 19-08-2022

on Access 2 immunoasay analyzer. The plasma was run on Beckman coulter AU680 Chemistry Autoanalyzer for D dimers. To ensure validity of results, quality control was performed before patients' samples. The result of each sample was analyzed and marked as normal or abnormal. All collected data was entered and analyzed by using SPSS version 23. Quantitative variables like age was presented as mean±SD. Qualitative variables like gender, normal or abnormal D -Dimers, HsCRP and Ferritin results were presented as frequency and percentage.

RESULTS

The study was conducted on 1474 Covid-19 patients. The summary of the results is as following:

Study variables	Results	P value
Age(years)	50.6±4.2	-
Males Females	51.3± 6.5 49.4±8.1	0.23
HsCRP (mg/L)	56.8±16.9	-
Males Females	60.1±18.5 50.6±16.0	0.15
Serum Ferritin (ng/ml)	770 ±180	-
Males Females	741.3±186.6 522.3±83.5	***0.03**
D Dimers (µg/ml FEU)	4.4 ±1.5	-
Males Females	4.70±1.7 4.59±1.4	0.28

**p value < 0.05 significant.*

Independent sample t test was used to compare age, HsCRP, Ferritin & D dimers between male and female Covid patients.

Fig. 1: Frequency of male and female patients

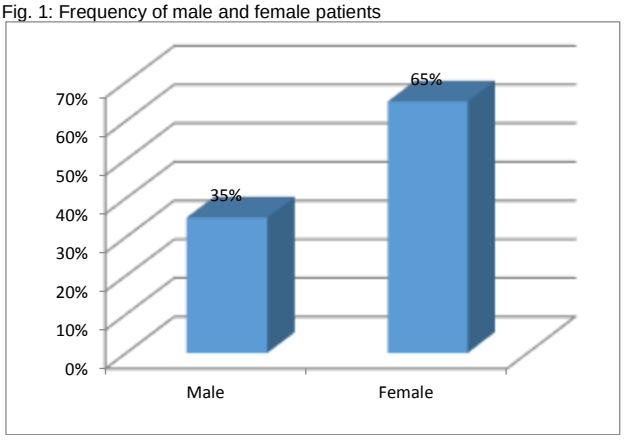


Fig. 2: Normal and abnormal percentage of D- Dimers, HsCRP and Ferritin

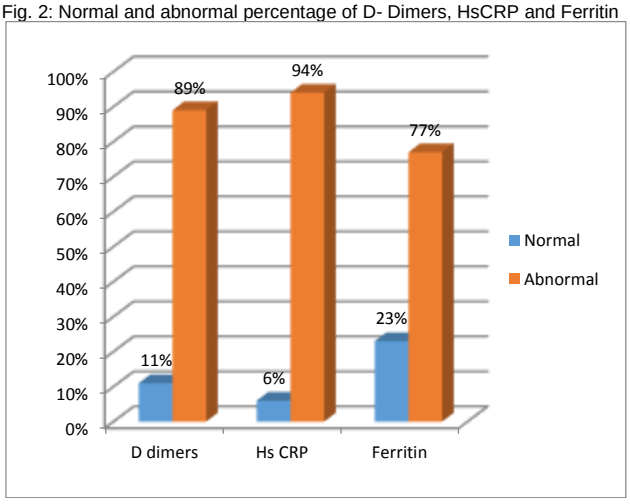


Fig. 3: Frequency of Single, Double, Triple Abnormal parameters in Covid 19 patients.

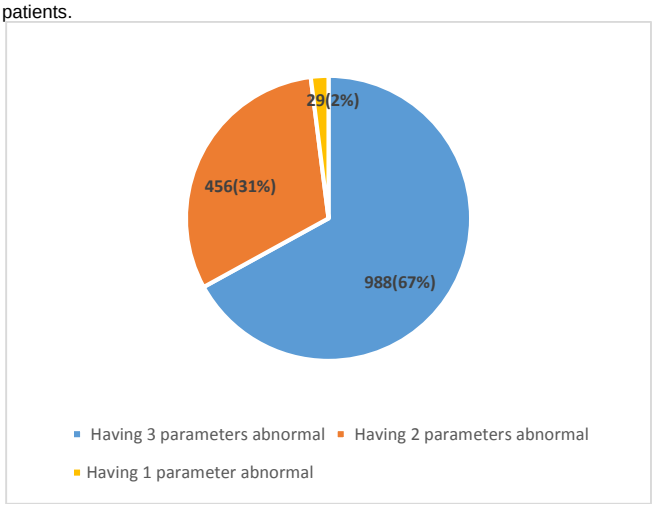
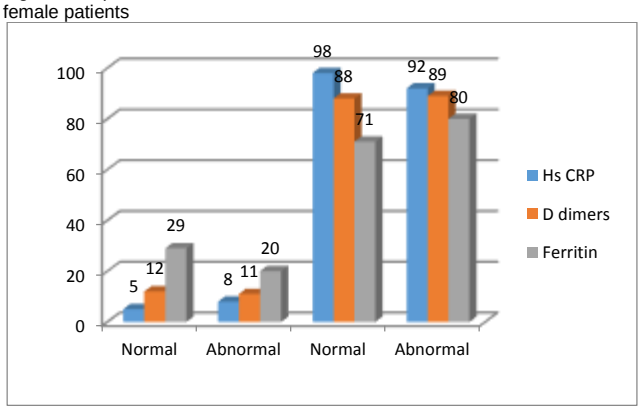


Fig. 4: Comparison of Hs CRP, Ferritin D Dimers levels between male and female patients



Chi square was applied to compare frequency and percentage of CRP, Ferritin D Dimers levels between male and female Covid patients that showed no significant difference (p vaue= 0.211).

DISCUSSION

COVID19 is a pandemic that has affected over 200 countries. The disease spectrum ranges from asymptomatic to critically sick. The major risk factors for development of severe disease are old age, male sex, and co morbidities like diabetes or cardiovascular disease. Different laboratory tests results have been used to assess severity and prognosis of severely sick Covid-19 patients like CRP, ferritin, and procalcitonin, LDH, lymphocyte, neutrophil count, D-dimers, troponins, albumin, aminotransferases and creatinine[29,30].This study was conducted on 1474 Covid 19 patients admitted in hospital.

The mean±SD age of patients in our study was 50.6+4.2; 51.3±6.54 for males and 9.4±8.1 for females and it is comparable to study conducted by Tang et al in which the age was 48.8±18.4 years[20] The age of our studied population is slightly different from study conducted by Yao et al and Li et al in which mean age was 63.0±13.4 and 69.2±7.3 years respectively. The reason might be attributed to poor health status, co morbidities or ethnicity of our population(31,32).

Out of total 1474 patients, 6% had normal and 94% had abnormal Hs CRP levels. The mean±SD value was 56.8±16.90mg/L; 60.05±18.54 in males and 50.6±16.0 in females. The results are comparable to study in Wuhan in which 86·3% of Covid patients had elevated Hs-CRP level. The study by Aurora et al showed that Hs-CRP levels were raised even in asymptomatic

patients so CRP levels can be used for early diagnosis. The raised Hs-CRP levels are due to cytokine storm induced by Covid-19 patients and the levels, are correlated with the severity of inflammation[33,34].

In our study 338(23%) had normal and 1131(77%) had abnormal ferritin levels. The mean±SD Serum ferritin value was 770±180ng/ml, 741.3±186.6 in males and 522.3±83.5 in females. The results are in agreement with the study of Kim et al in which the mean ferritin levels were >800µg/L(ng/ml) in severely sick Covid-19 patients. The raised levels of serum ferritin are as a result of cytokine storm[35].

The dysfunction of the hemostasis resulting in coagulopathy and increased D dimers is also seen in Covid patients. The elevated D dimers is related to poor outcome. The D dimers was found to be abnormal in 1308(89%) patients in our study. The mean±SD value of D dimers was 4.4±.5 µg/ml FEU, 4.70±1.7 in males and 4.70±1.7 in females. The results are comparable to study by Bergeret al in which 76% Covid-19 patients presented with an elevated D-dimer[34] The results of our study are also supported by Zhang et al who stated that d-dimers were relatively higher in covid patients admitted in ICU than those who didn't require it[24]. The raised D- dimers increases the risk of thrombotic event , acute kidney injury and death[34]

On the basis of Hs CRP, ferritin and D-dimers levels, 988(67%) Covid-19 patients had severe disease as all 3 markers were raised. 31 %(456) had moderate disease as 2 markers were abnormal while 2 %(29) had mild sickness as only one marker i.e. Hs CRP was abnormal.. The results of our study are not in agreement with the study by Juradoet al in which 27.4% had mild disease, 42.1% had moderate and 30.5% had severe disease[33]. The difference might be due to our study setting and population that mainly comprises of admitted patients rather patients with mild disease or asymptomatic patients.

CONCLUSION

On the basis of our study findings, males are more affected with Covid-19 as compared to females, HsCRP is the most frequently raised biomarker in Covid-19 patients and most of the patients with severe disease have raised both inflammatory (HsCRP and Ferritin) and coagulopathy markers (D dimers).

Limitations: The patients' radiological and clinical data (demand for oxygen and mechanical ventilation) was not included in the study to determine correlation with the level of biomarkers. Moreover, the follow-up of the patients in terms of morbidity and mortality was not done.

Conflict of interest: There is no conflict of interest

REFERENCES

1. Singhal T. A review of coronavirus disease-2019 (COVID-19). The indian journal of pediatrics. 2020;87(4):281-6.
2. Hussain S, Chen Y, Yang Y, Xu J, Peng Y, Wu Y, et al. Identification of novel subgenomic RNAs and noncanonical transcription initiation signals of severe acute respiratory syndrome coronavirus. Journal of virology. 2005;79(9):5288-95.
3. DeDiego ML, Álvarez E, Almazán F, Rejas MT, Lamirande E, Roberts A, et al. A severe acute respiratory syndrome coronavirus that lacks the E gene is attenuated in vitro and in vivo. Journal of virology. 2007;81(4):1701-13.
4. Neuman BW, Kiss G, Kunding AH, Bhella D, Baksh MF, Connelly S, et al. A structural analysis of M protein in coronavirus assembly and morphology. Journal of structural biology. 2011;174(1):11-22.
5. Beniac DR, Andonov A, Grudeski E, Booth TF. Architecture of the SARS coronavirus prefusion spike. Nature structural & molecular biology. 2006;13(8):751- 752
6. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of autoimmunity. 2020;109:102433.
7. El Zowalaty ME, Järhult JD. From SARS to COVID-19: A previously unknown SARS-related coronavirus (SARS-CoV-2) of pandemic potential infecting humans–Call for a One Health approach. One Health. 2020;9:100124.
8. Xu J, Zhao S, Teng T, Abdalla AE, Zhu W, Xie L, et al. Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-CoV. Viruses. 2020;12(2):244.
9. Spinelli A, Pellino G. COVID-19 pandemic: perspectives on an unfolding crisis. Journal of British Surgery. 2020;107(7):785-7.
10. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. The lancet. 2020;395(10226):809-15.
11. Hamming I, Timens W, Bulthuis M, Lely A, Navis Gv, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. 2004;203(2):631-7.
12. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Frontiers of medicine. 2020:1-8.
13. Zhang H, Li H-B, Lyu J-R, Lei X-M, Li W, Wu G, et al. Specific ACE2 expression in small intestinal enterocytes may cause gastrointestinal symptoms and injury after 2019-nCoV infection. International Journal of Infectious Diseases. 2020;96:19-24.
14. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. Journal of pharmaceutical analysis. 2020;10(2):102-8.
15. Udugama B, Kadhiresan P, Kozlowski HN, Malekjahani A, Osborne M, Li VY, et al. Diagnosing COVID-19: the disease and tools for detection. ACS nano. 2020;14(4):3822-35.
16. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. New England Journal of Medicine. 2020;383(18):1757-66.
17. Assandri R, Buscarini E, Canetta C, Scartabellati A, Viganò G, Montanelli A. Laboratory Biomarkers predicting COVID-19 severity in the Emergency room. Archives of medical research. 2020;51(6):598-9.
18. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Frontiers in immunology. 2018;9:754.
19. Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. Blood, The Journal of the American Society of Hematology. 2009;113(13):2878-87.
20. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of thrombosis and haemostasis. 2020;18(5):1094-9.
21. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. Journal of thrombosis and thrombolysis. 2020:1-4.
22. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of thrombosis and haemostasis. 2020;18(4):844-7.
23. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. Journal of Thrombosis and Haemostasis. 2020;18(7):1738-42.
24. Zhang J-j, Dong X, Cao Y-y, Yuan Y-d, Yang Y-b, Yan Y-q, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-41.
25. Kariyanna PT, Aurora L, Jayarangaiah A, Yadav V, Hossain NA, Akter N, et al. Utility of D-dimer as a Prognostic Factor in SARS CoV2 Infection: A Review. American journal of medical case reports. 2020;8(10):337.
26. Ullah W, Thalambedu N, Haq S, Saeed R, Khanal S, Tariq S, et al. Predictability of CRP and D-Dimer levels for in-hospital outcomes and mortality of COVID-19. Journal of community hospital internal medicine perspectives. 2020;10(5):402-8.
27. Kappert K, Jahić A, Tauber R. Assessment of serum ferritin as a biomarker in COVID-19: bystander or participant? Insights by comparison with other infectious and non-infectious diseases. Biomarkers. 2020:1-10.
28. Gómez-Pastora J, Weigand M, Kim J, Wu X, Strayer J, Palmer AF, et al. Hyperferritinemia in critically ill COVID-19 patients–Is ferritin the product of inflammation or a pathogenic mediator? Clinica Chimica Acta; International Journal of Clinical Chemistry. 2020.
29. Li Q, Ding X, Xia G, Chen H-G, Chen F, Geng Z, et al. Eosinopenia and elevated C-reactive protein facilitate triage of COVID-19 patients in fever clinic: a retrospective case-control study. EClinicalMedicine. 2020;23:100375.
30. Aloisio E, Chibireva M, Serafini L, Pasqualetti S, Falvella FS, Dolci A, et al. A comprehensive appraisal of laboratory biochemistry tests as major predictors of COVID-19 severity. Archives of pathology & laboratory medicine. 2020;144(12):1457-64.
31. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. Journal of intensive care. 2020;8(1):1-11.
32. Li T, Lu L, Zhang W, Tao Y, Wang L, Bao J, et al. Clinical characteristics of 312 hospitalized older patients with COVID-19 in Wuhan, China. Archives of gerontology and geriatrics. 2020;91:104185.
33. Jurado A, Martín MC, Abad-Molina C, Orduña A, Martínez A, Ocaña E, et al. COVID-19: age, Interleukin-6, C-reactive protein, and lymphocytes as key clues from a multicentre retrospective study. Immunity & Ageing. 2020;17(1):1-15.
34. Berger JS, Kunichoff D, Adhikari S, Ahuja T, Amoroso N, Aphinyanaphongs Y, et al. Prevalence and outcomes of d-dimer elevation in hospitalized patients with COVID-19. Arteriosclerosis, thrombosis, and vascular biology. 2020;40(10):2539-47.
35. Gao Yd, Ding M, Dong X, Zhang Jj, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy. 2020.