Study of D-dimer, CRP & Ferritin Status as Independent Risk Factors for Severity of the Clinical Aspects in Patients with COVID-19 in Erbil, Iraq

Nabaz Fisal Shakir Agha[1*], Siyamak Asri Rezaei[2], Zakarea Abdullah Yaseen Al-khayat[3], Barzan Kamal Abdulrahman[4], Kawthar Ibrahim Fatah Alharmni[5] and Derin Nabaz Fisal Agha[6]

[1]Department of Anesthesia, Erbil Polytechnic University, Erbil Medical Technical Institute, Erbil, Iraq; [2]Department of Internal diseases and clinical pathology, Faculty of Veterinary Medicine, Urmia University, Iran; [3]Department of Microbiology, College of Medicine, Hawler Medical University, Erbil, Iraq; [4]Department of Pharmacology, Chemistry, Erbil Polytechnic University, Erbil Medical Technical Institute, Iraq; [5]Department of Anatomy & Histology, College of Medicine, Hawler Medical University, Erbil, Iraq, and [6]Department of Pharmacology, Erbil Polytechnic University, Erbil Medical Technical Institute, Iraq.

***Corresponding author**: Nabaz Fisal Shakir Agha. Email address: nabaz.shakir@epu.edu.iq
ORCID: https://orcid.org /0000-0001-7212-959X
https://dx.doi.org/10.4314/ajhs.v35i6.6

Abstract

BACKGROUND

Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory disease which can evolve into multi-organ failure (MOF), leading to death. Several biochemical alterations have been described in COVID-19 patients. This study aimed to look at the ratio of D-dimer, CRP (C- reactive protein), and ferritin as independent risk variables in COVID-19 illness patients in Erbil Governorate, Iraq.

MATERIALS AND METHODS

In this retrospective data collection study, we aimed to determine the number of patients diagnosed with COVID-19 who were admitted to Rizgary and Komary hospitals. Moreover, we collected data, including demographic features and laboratory analysis results regarding: D-dimer, Ferritin and CRP(C- reactive protein) extracted from the patient's medical records. Patients were Erbil residents admitted to Rizgary & Komary educational hospital from 1st April to 1st November 2020, with a confirmed diagnosis of COVID-19 infection using SARS-CoV-2 viral nucleic acid using RT-PCR. CRP, D-dimer, and ferritin levels had been routinely measured on admission.

RESULTS

CRP, D-dimer, and ferritin levels were measured in 234 individuals (115 men and 119 women). The group aged 15-25 was the least afflicted, while the age group 45-55 had the most COVID-19 patients. The frequency of this disorder did not differ statistically significantly between men and women. According to a massive increase in CRP, men showed a far higher risk than women. In the research groups, there were no statistically significant differences in ferritin changes between males and females. In terms of D-dimer, there was no statistically significant difference between males and females in either of the studied groups.

CONCLUSIONS

Higher CRP levels, indicating a higher risk of disease and predicting and measuring the onset of the disease in the first few days, are mandatory in tracking COVID-19 disease.

***Keywords**: D-dimer, CRP(C - reactive protein), Ferritin, COVID -19, Erbil, Iraq*

***[Afr. J.** Health Sci.* 2022 35(6): 709-720]

Introduction

COVID-19, a novel, highly infectious illness, was first reported in Wuhan, Hubei Province, China, in December 2019 (1). In March 2020, the coronavirus disease-2019 (COVID-19) caused by the severe acute respiratory*[* syndrome-coronavirus 2 (SARS-CoV-2) began a worldwide pandemic (2). The first cases of COVID-19 were reported in Southern Iraq in February 2020. Following the surfacing of these incidents, the Kurdistan Region instituted tight control procedures. These actions included the closure of schools and universities, the closure of borders and airports, the cancellation of public and religious gatherings, and the imposition of compulsory quarantine for anyone returning from outside travel and contacts of confirmed cases (3). COVID-19 patients' clinical features ranged from asymptomatic in moderate instances to acute respiratory distress syndrome and death in severe cases (2). Headache, loss of smell, nasal congestion, cough, asthenia, myalgia, rhinorrhea, sore throat, fever, shortness of breath, nausea or vomiting, and diarrhoea are the most prevalent symptoms of COVID-19.

While most patients had mild symptoms, a minority developed acute respiratory disease and hypoxia, necessitating hospitalization, and a fraction developed acute respiratory distress syndrome, multi-organ failure, or catastrophic results (6a). Male gender, advanced age, and comorbidities such as diabetes and hypertension are clinical risk factors for developing life-threatening illnesses (7). Autoantibodies against type I interferon and host genetic variations of interferon immunity have also been identified as risk factors (8). Haematology, serum liver enzymes, and blood biomarkers appear to be able to differentiate between moderate and severe illness and may be employed as prognostic indicators (9). Various biomolecules such as D-dimer, CRP(C - reactive protein), ferritin, and LDH were higher in COVID-19 critical patients compared to non-severe infected cases (10). Increased factors affecting angiogenesis and inflammation, such as angiopoietin2, IL6, and IL8, have long been recognized as predictors of acute respiratory distress syndrome (ARDS) in the pre-COVID-19 period(11). Interactions between innate immunity, vascular permeability modulation, and alveolar epithelial damage may be significant causes of ARDS in COVID-19. However, it is still crucial to discover surrogate indicators for critically sick COVID-19 patients (12). The purpose of this study was first to determine the number of appropriately diagnosed COVID-19 cases admitted to Rizgary & Komary public hospitals; and secondly, to investigate the ratio of D-dimer, CRP(C-reactive protein), and ferritin as independent risk factors for indicating and assessing the severity of clinical symptoms in patients with COVID-19 illness in Erbil Governorate, Iraq. The importance of the present study is to fill a shortage in knowledge about the risk factors associated with the clinical severity of COVID-19 patients.

Materials and Methods

Study design and procedure

This retrospective data collection study included Erbil residents who had COVID-19 and were admitted to Rizgary & Komary Educational Hospitals from 1st April to 1st November 2020. Diagnostic confirmation of infection was obtained in the hospital laboratory. Respiratory samples such as nasopharyngeal swabs, sputum tracheal aspirates, and bronchoalveolar lavage were collected from patients at admission and then 24 hours later.

The samples were tested for SARS-CoV-2 RNA using a commercial reverse transcriptase real-time PCR assay (RT-PCR assay, Allplex 2019-nCoV Assay, Seegene, Seoul) and the Xpert Xpress SARS- (Cepheid). Blood biomarkers were measured according to the manufacturer's recommendations for D-dimer (Genrui, China), CRP (Genrui, China), and ferritin (ELIITech Group, Framingham, MA).

We collected data from the patient medical records regarding demography and results of D-dimer, ferritin and CRP. We excluded medical records with incomplete data, patients younger than 18 years of age or immigrants from the study.

Ethical considerations

The ethical committee at Hawler Medical University in Erbil, the Committee of the Erbil Medical-Technical Institute of Erbil Polytechnic University in Iraq, and the Erbil Health Directorate gave their approval for the conduct of this study. Informed consent was obtained from every patient.

Statistical analyses

The data were analyzed using descriptive statistics such as frequency and frequency percentage. GraphPad Prism (version 6.0.1.298) was used to analyze blood biomarker data. T-test was used to find significant differences in the study population's abnormal and normal values, and the Chi-square test was used to compare using standard equations. The results were presented with the threshold for significance set at $p \leq 0.05$.

Results

This study abstracted data from the medical records of 234 individuals (115 men and 119 women) diagnosed with COVID-19 (positive PCR test) in the Erbil region of Iraq. Table 1 shows the age distribution of COVID-19 patients. The age group of 46 to 55 years had the most patients, while 15 to 25 years had the fewest cases (10, 4.3 %).

The disparities in gender distribution among age groups were not statistically significant. Patients with COVID- 19 were separated into four groups based on CRP levels.

Table 1:
Gender distribution of patients with COVID- 19 in different age groups

Age range	Men		Women		Total	
	Number	Per cent	Number	Per cent	Number	**Per cent**
25 - 15	6	5.2	4	3.4	10	**4.3**
35 – 26	11	9.6	12	10.1	23	**9.8**
45 – 36	15	13.0	25	21.0	40	**17.1**
55 – 46	29	25.2	25	21.0	54	**23.1**
65 – 56	18	15.7	26	21.8	44	**18.8**
75 – 66	22	19.1	16	13.4	38	**16.2**
Above 75	14	12.2	11	9.2	25	**10.7**
Total	**115**	**100**	**119**	**100**	**234**	**100 Df=6 NS**

Normal range (0 to 6 mg/dL), mild range (7 to 26 mg/dL), moderate range (26-100 mg/dL), and severe range (greater than 100 mg/dL) (Fazal, 2021).

The investigation of CRP levels in COVID- 19 patients revealed that (11, 4.7 %) had normal values, (17, 7.3%) had mild increases, (36, 15.4 %) had moderate increases, and (170, 72.6%) had severe increases in this acute phase protein. (Fig1).

Table 2 depicts the distribution of CRP in COVID- 19 patients according to gender. Obviously, in situations of severe CRP increase, the differences in CRP mean between males and females were highly significant ($p \leq 0.01$). There was no statistically significant difference in CRP levels by patient gender in the other groups under study.

The ferritin measurement results obtained in this study were classified into three categories: deficiency (less than 13 mg/dl), normal (14-150 mg/dl), and rise (greater than 151 mg/dl) (Izcovich *et al*., 2020).

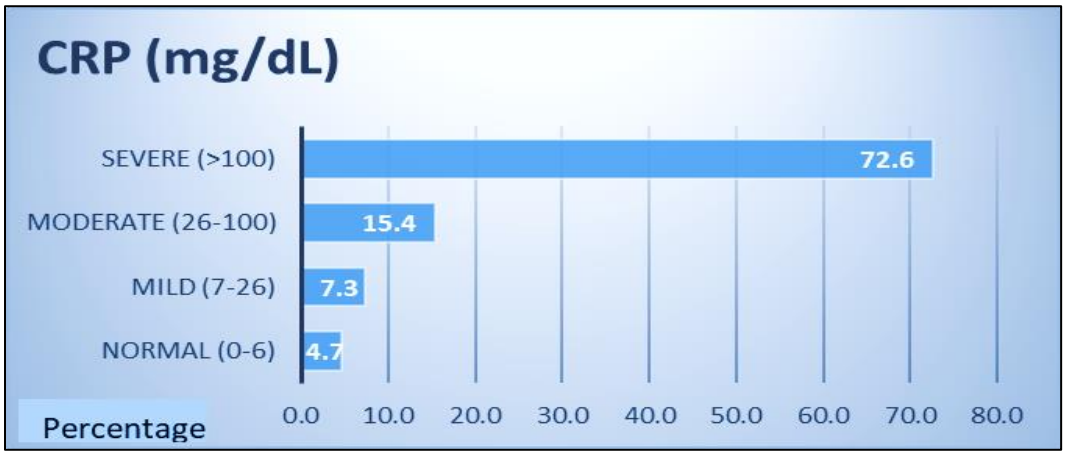

Figure 1:
Frequency Distribution of Patients with COVID- 19 in Terms of CRP Values

Table 2:
Distribution of CRP Values According to the Gender

Patient group in terms of ferritin levels	Gender	Number	Mean ± SD	P Value
	Male	25	9.1 ± 3.7	**t = 0.4736**
Deficiency (<13 mg/dL)	female	31	8.6 ± 4.1	**df = 54 NS**
	Male	71	63.4 ± 34.6	**t = 0.9393**
Normal (14-150 mg/dL)	female	70	59.4 ± 8.56	**df = 139 NS**
	Male	19	189.34 ± 11.651	**t = 1.4235**
High (>151 mg/dL)	female	18	194.29 ± 09.294	**df = 35 NS**

These findings revealed that (56, 23.9 %) of the patients in the research were ferritin deficient, (141, 603 %) were in the normal range, and only (37, 15.8 %) of patients had elevated ferritin levels in their blood (Figure 2). There were no statistically significant variations in ferritin changes between males and females in the research groups (Table 3).

The study population was grouped based on di-dimer values: normal (less than 500 ng/ml), mild increase (500 to 1000 ng/ml), moderate increase (1000 to 2000 ng / ml), and severe increase (more than 2000 ng/ml).

The findings of di-dimer testing in COVID- 19 patients revealed that (120, 51.3 %) of patients had normal d-dimer readings. These findings also revealed that (79, 33.8 %) had a mild rise, (15, 6.4 %) had a moderate increase, and (20, 8.5 %) had a severe increase in D-dimer in the blood (Figure 3). There was no statistically significant differences in Di-dimer alterations across research groups (Table 4).

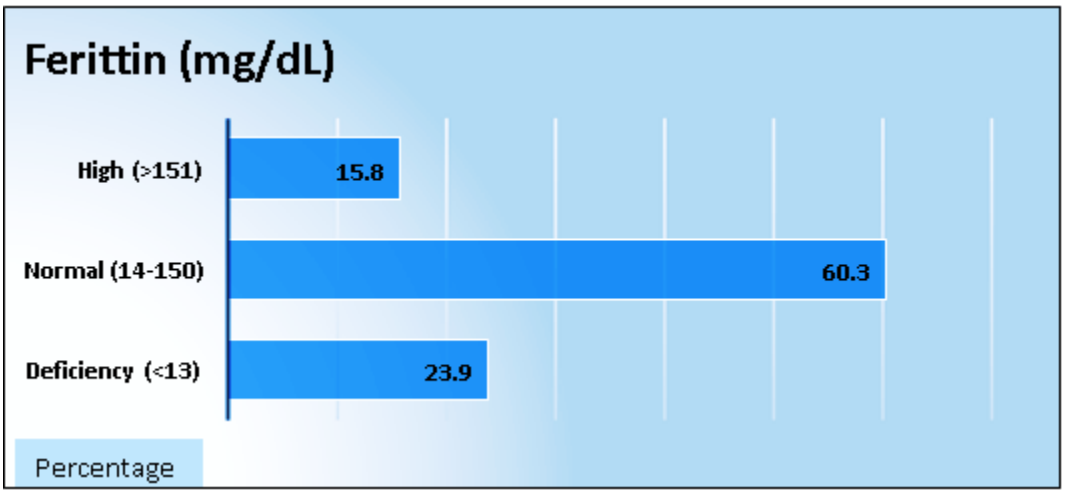

Figure 2:
Frequency Distribution of Patients with COVID- 19 Based on Ferritin Levels

Table 3:
Distribution of Ferritin levels according to the gender

Patient group in terms of ferritin levels	Gender	Number	Mean ± SD	P Value
	Male	25	9.1 ± 3.7	**t = 0.4736**
Deficiency (<13 mg/dL)	female	31	8.6 ± 4.1	**df = 54 NS**
	Male	71	63.4 ± 34.6	**t = 0.9393**
Normal (14-150 mg/dL)	Female	70	59.4 ± 8.56	**df = 139 NS**
	Male	19	189.34 ± 11.651	**t = 1.4235**
High (>151 mg/dL)	Female	18	194.29 ± 09.294	**df = 35 NS**

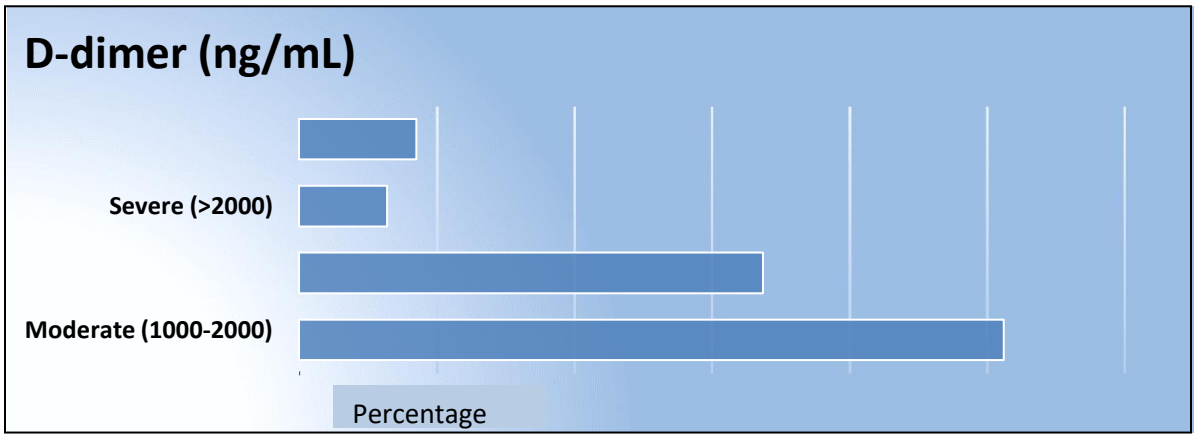

Figure 3:
Frequency Distribution of Patients with COVID- 19 Based on d-dimer Levels

Table 4:
Distribution of Di-dimer levels according to the gender

Patient group in terms of D-dimer values	Gender	Number	Mean ± SD	P Value
	Male	60	353.16 ± 102.324	**t = 0.5981**
Normal (<500 mg/dL)	female	60	364.17 ± 99.323	**df = 118 NS**
	Male	27	836.29 ± 34.739	**t = 1.0035**
Mild (500-1000 mg/dL)	female	52	851.18 ± 72.751	**df = 77 NS**
	Male	12	1553.106 ± 263.148	**t = 0.7570**
Moderate (1000-2000 mg/dL)	female	3	1677.269 ± 197.159	**df = 13 NS**
	Male	16	2846.873 ± 206.532	**t = 1.5292**
Severe (>2000 mg/dL)	female	4	2667.551 ± 225.274	**df = 18 NS**

Table 5:
Comparison of sensitivity and specificity of CRP, Ferritin and D-dimer tests for the diagnosis of COVID-19 disease

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig. b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CRP (mg/dl)	.000	.000	.000	.000	.000
Ferritin (ng/ml)	.700	.085	.025	.532	.867
D-Dimer (ng/ml	.190	.058	.001	.077	.304

The test result variable(s): Ferritin (ng/ml), D-Dimer (ng/ml has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Discussion

The total number of patients enrolled in this study was (234), with (115) being males and (119) being women of various ages. According to our findings, there is no statistically significant difference in the prevalence of this illness between men and women. While certain countries have a higher proportion of male cases and others have a higher proportion of female cases, cultural roles and gender norms in each country may be one reason for the lack of regular patterns in illness incidence across the sexes.

According to a report by (13), gender inequality may have a role in sex differences in epidemiology. However, it is unclear if this represents actual differences in COVID-19 infection risks between men and women or just differences in who seeks or receives testing (14). It is possible that in countries with high gender inequality, men are more likely to be employed, thus, more likely to be exposed to COVID-19 infection.

On the other hand, possibly, men feel more entitled to seek or receive rationed tests due to entrenched cultural norms and institutionalized bias against women in healthcare settings (15). However, the relative numbers of COVID-19 patients in different age groups have revealed substantial variations. The effect of age on COVID-19 infection showed that the age group from (5-25 was the least affected group.

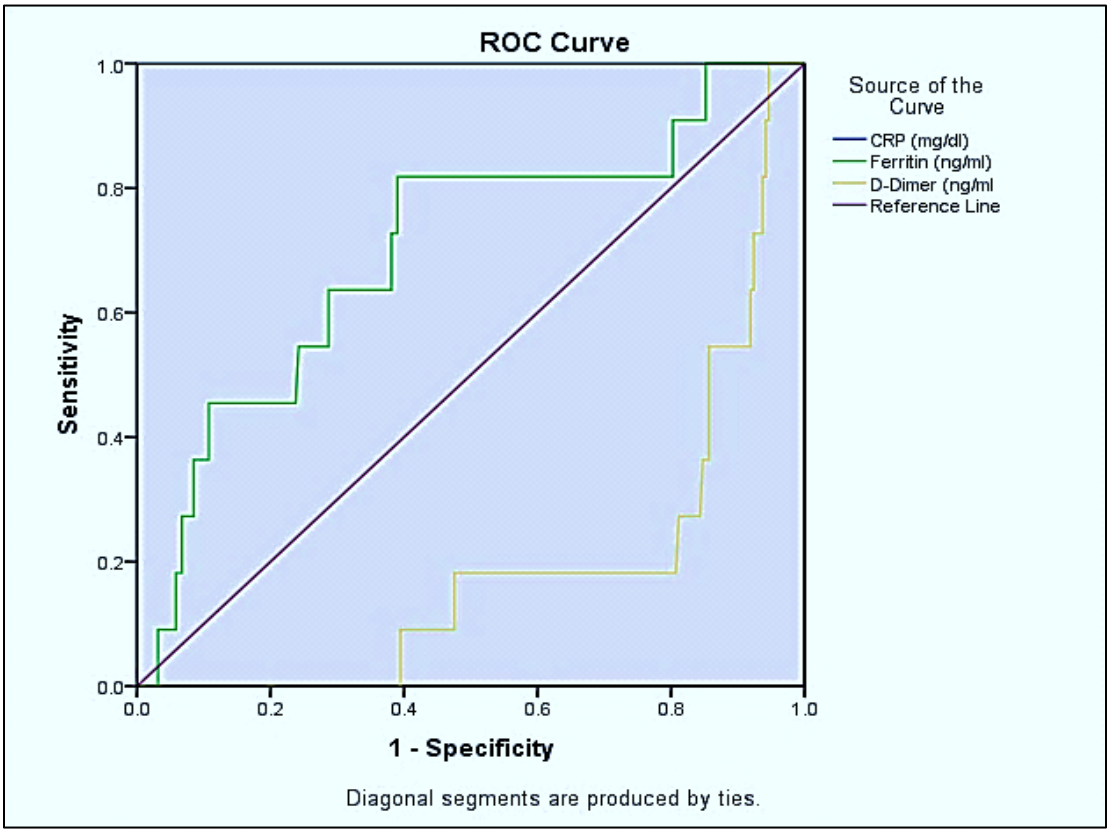

Figure 4:
ROC curve to evaluate the sensitivity and measurement properties of CRP, Ferritin and dimer

Perhaps this is due to reduced interaction between the members of this group since most of them are school and university students, which were closed down during this period to contain the spread of COVID-19. The highest number of patients is in the age range of 46 – 55 years. More mixing is expected in this age group due to the nature of their lifestyle. They are the age group working mainly in the city of Erbil, which leads to this group being more vulnerable to the Coronavirus and contracting COVID-19 disease.

In contrast, a study by (16) stated that the risk of COVID-19 infection increases with age because ageing is accompanied by gradual biological changes in the immune system. Some of these changes contribute to its deteriorating function, such as increased susceptibility to respiratory infections such as the flu and new one's Coronaviruses, like any other system in the body. Age-related immune-mediated inflammation and comorbidities make the elderly more susceptible to latent or new infections, leading to increased COVID-19 morbidity and deaths (17).

This study considered CRP, Ferritin and D-Dimer as risk factors in assessing the severity of clinical manifestations in patients infected with COVID-19.

The findings showed a sharp increase in CRP levels which is significantly higher in men than women. On the other hand, a study by (18) mentioned that males are more likely than women to get severe illnesses due to higher CRP levels than men are more likely to develop. Research by (15) explained that biological sex differences in innate and adaptive immune responses had been proposed to explain the male bias observed in COVID-19 infections. Immune cell subset gene expression shows sex-specific patterns and control. Furthermore, sex chromosomes are involved in immunological control, with partial X chromosome inactivation linked to female-biased autoimmune disorders and vaccination effectiveness (19). In addition, sex hormones such as estrogen and testosterone directly impact immune cell activity (20).

These biological sex differences in immunity suggest that Men may be more prone to COVID-19 infection due to lesser immunological responses, whilst women may be "protected" by a robust immune response(19).

A study by (20) showed a statistically significant relationship between variations in CRP levels and the amount of lung injury. High CRP levels owing to increased IL-6 release indicate the requirement for mechanical ventilation in COVID -19 patients, indicating the probability of utilizing CRP to guide COVID therapy in those individuals who may require mechanical breathing in the future owing to hyperinflammatory syndrome (18). C-reactive protein is a simple, inexpensive, and easy-to-obtain predictive biomarker that correlates with illness severity and death (21).

Regarding ferritin, the present study showed that 23.9% of the patients were within the low limits, 60.3% were within normal limits and only (15.8%) of the patients had a high level of ferritin in the blood.

Ferritin levels rise significantly in patients with severe COVID-19 (22). Ferritin is a significant mediator in immunological dysregulation, particularly in severe hyper-ferritinemia, due to its immunosuppressive and pro-inflammatory activities that result in cytokine storms (23). Elevated ferritin levels may be caused by a balanced breakdown between the adaptive and innate immune systems, resulting in hyper-inflammation and a cytokine response storm (11). When considering age and comorbidities, male patients had a more

significant inflammatory response, with higher levels of LDH, ferritin, and CRP but a lower lymphocyte count than females (1). It is a fact that females have higher innate and adaptive immune responses to viral infections and that sex hormones play an essential role in immune response regulation (24). Another study by (25) revealed that ferritin levels altered with the age of the patients in addition to ESR, D-Dimer, Ferritin, and CRP protein which exhibited different levels in comparison to the control group that was within the normal range. In their study (26) proclaimed that high serum ferritin levels were correlated with an increase in infection severity, with 75 per cent of ICU patients having high ferritin levels compared to 43 per cent of those with mild symptoms, 56 per cent of infected male patients having elevated ferritin levels compared to 36, 6 per cent of infected female patients.

For mortality, 74% of patients who died had high serum ferritin levels compared with 47% of patients who recovered. Research conducted by (27) found that patients with more than 300 ng/mL serum ferritin levels had a higher inpatient mortality rate than patients with serum ferritin levels less than 300 ng/mL.

Regarding di-dimer levels, this study found that only (8.5%) of patients had a severe increase in di-dimer levels. D-dimer readings were impacted by advanced age, male gender, and underlying conditions such as hypertension, coronary heart disease, diabetes, and cerebrovascular disease, all of which impacted patient prognosis. Patients with COVID-19 with the above-mentioned contributing characteristics have a higher risk of death (12). It is crucial to regularly monitor D-dimer levels, diagnose thrombotic issues as soon as feasible, and implement suitable preventive measures to reduce thromboembolism and the risk of bleeding in DIC secondary fibrinolysis, hence minimizing COVID-19 mortality (28). Increased D-dimer concentration is the most prevalent feature of coagulopathy identified in COVID-19 (29). Severe COVID-19 is a prothrombotic condition (11). D-dimer levels are a reliable predictor of in-hospital mortality and correlate with disease severity (25). D-Dimer concentration may indicate the presence of concurrent PE in persons with COVID-19 infection (30). Even when other risk factors were included, D-dimer levels were connected to an increased risk of critical illness, thrombosis, acute renal injury, and all-cause mortality in COVID-19 patients (30).

The ROC curve, or system performance characteristic curve, is a tool to demonstrate the accuracy and efficiency of a classification technique. Examination of the results obtained from the rock curve regarding the comparison of sensitivity and specificity of CRP, Ferritin and D-dimer tests. The result of this study is in harmony with Figure 5, and Table 5 shows that CRP has a very high specificity and sensitivity for the diagnosis of COVID-19 disease. Ferritin also has acceptable sensitivity and properties for the diagnosis of COVID-19 disease. Also, an examination of D-dimer changes showed that this test does not have the sensitivity and specificity required to diagnose this disease.

Study Limitations

The limitations of the present study include small sample size, short duration, bias and shortages in collecting data regarding demography and risk factors like obesity, smoking and co-morbid diseases, which are important determinants of the severity of COVID-19.

Conclusions

CRP levels beyond a certain threshold indicate a higher risk of sickness, as well as forecasting the onset of disease in the early days, and its measurement is required in the disease's follow-up. Ferritin levels were significantly

higher in severe COVID-19 individuals, and ferritin levels rose with age in both sexes. CRP has a high specificity and sensitivity for the diagnosis of Covid 19 illness. Ferritin is also required for the diagnosis of Covid 19 disease. Furthermore, COVID-19 patients' increased baseline D-dimer levels imply that anticoagulant medication may be required.

Recommendations

In addition to traditional biochemical biomarkers, it would be interesting to assess the role of new promising biomarkers, such as presepsin, for the early identification of patients at increased risk of complications. Future studies should focus on the timeline of the changes in levels of biomarkers and the severity of the COVID-19 disease and its associated complications.

Acknowledgements

The authors appreciate the Erbil Health Directorate's administration for enabling them to perform the research. We also want to thank the senior staff and colleagues at both public and private hospitals (Rizgary educational hospital and Komary hospital) for their collaboration and assistance.

Source of funding: None.

Conflicts of interest: There are no conflicts of interest.

Author contact emails

Nabaz Fisal Shakir Agha - nabaz.shakir@epu.edu.iq

Siyamak Asri Rezaei - s.asri@urmia.ac.ir

Zakarea Abdullah Yaseen Al-khayat - dr_zakarea@yahoo.co.uk

Barzan kamal Abdulrahman - barzan1971kamal@gmail.com

Kawthar Ibrahim Fatah Alharmni - kawthar.ibrahim@med.hmu.edu.iq

Derin Nabaz Fisal Agha - deren.faesal@epu.edu.iq

References

1. **Taylor, D.R. *et al.*** (2021). 'Biochemical abnormalities in COVID-19: a comparison of white versus ethnic minority populations in the UK', Journal of Clinical Pathology, p. *jclinpath*-2021-207446. doi:10.1136/jclinpath-2021-207446.
2. **Alfadda, A.A. *et al.*** (2021). 'Clinical and biochemical characteristics and outcomes of suspected COVID-19 hospitalized patients: RT-PCR swab positive and negative comparison', *Journal of Infection and Public Health*, 14(11), pp. 1623–1629. doi:10.1016/j.jiph.2021.09.014.
3. **Hussein, N.R., Naqid, I.A. and Saleem, Z.S.M.** (2020) 'A retrospective descriptive study characterizing coronavirus disease epidemiology among people in the Kurdistan Region, Iraq: Characterization of COVID-19 in Kurdistan Region, Iraq', *Mediterranean Journal of Hematology and Infectious Diseases*, 12(1), p. e2020061. doi:10.4084/mjhid.2020.061.
4. **Mannan, A. *et al.*** (2021). 'A multi-centre, cross-sectional study on coronavirus disease 2019 in Bangladesh: clinical epidemiology and short-term outcomes in recovered individuals', *New Microbes and New Infections*, 40, p. 100838. doi:10.1016/j.nmni.2021.100838.
5. **Mahavar, S. *et al.*** (2021). 'Clinical and epidemiological profile of Indian COVID-19 patients from Jaipur: a descriptive study, *Monaldi Archives for Chest Disease*, 91(2). doi:10.4081/monaldi.2021.1377.
6. **Izcovich, A. *et al.*** (2020). 'Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review', *PLOS ONE*. Edited by C. Lazzeri, 15(11), p. e0241955. doi:10.1371/journal.pone.0241955.
7. **Docherty, A.B. *et al.*** (2020). 'Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective

observational cohort study, *BMJ*, p. m1985. doi:10.1136/BMJ.m1985.

8. **de Prost, N. *et al*.** (2021). 'Plasma Exchange to Rescue Patients with Autoantibodies Against Type I Interferons and Life-Threatening COVID-19 Pneumonia', *Journal of Clinical Immunology*, 41(3), pp. 536–544. DOI: 10.1007/s10875-021-00994-9.
9. **Velavan, T.P. and Meyer, C.G.** (2020) 'Mild versus severe COVID-19: Laboratory markers', International Journal of Infectious Diseases, 95, pp. 304–307. doi:10.1016/j.ijid.2020.04.061.
10. **Ahmed, T.H. and Al-Mousawi, N.H.** (2021) 'Post-Hospitalization, Levels of D-dimer, C-Reactive Protein, Ferritin, And Lactate Dehydrogenase in Recovered COVID- 19 Iraqi Patients', *Systematic Reviews in Pharmacy*, 12(1), p. 8. ID: covidwho-971258
11. **Zhou, B. *et al***. (2021). 'COVID-19 pathogenesis, prognostic factors, and treatment strategy: Urgent recommendations', Journal of Medical Virology, 93(5), pp. 2694–2704. doi:10.1002/jmv.26754.
12. **Zhao, R. *et al***. (2021). 'Associations of D-Dimer on Admission and Clinical Features of COVID-19 Patients: A Systematic Review, Meta-Analysis, and Meta-Regression', *Frontiers in Immunology*, 12, p. 691249. doi:10.3389/fimmu.2021.691249.
13. **Tadiri, C.P. *et al*.** (2020). 'The influence of sex and gender domains on COVID-19 cases and mortality', *Canadian Medical Association Journal*, 192(36), pp. E1041–E1045. doi:10.1503/cmaj.200971.
14. **Qian, J. *et al*.** (2020). 'Age-dependent Gender Differences in COVID-19 in Mainland China: Comparative Study', *Clinical Infectious Diseases*, p. ciaa683. doi:10.1093/cid/ciaa683.
15. **Lau, E.S. *et al*.** (2021). 'Sex differences in inflammatory markers in patients hospitalized with COVID-19 infection: Insights from the MGH COVID-19 patient registry', *PLOS ONE*. Edited by A.R. Zivkovic, 16(4), p. e0250774. doi:10.1371/journal.pone.0250774.
16. **Bajaj, V. *et al*.** (2021) 'Aging, Immunity, and COVID-19: How Age Influences the Host Immune Response to Coronavirus Infections?', *Frontiers in Physiology*, 11, p. 571416. doi:10.3389/fphys.2020.571416.
17. **Ahrenfeldt, L.J. *et al*.** (2021) 'Sex and age differences in COVID-19 mortality in Europe', Wiener klinische Wochenschrift, 133(7–8), pp. 393–398. doi:10.1007/s00508-020-01793-9.
18. **Fazal, M.** (2021). 'C-Reactive Protein a Promising Biomarker of COVID-19 Severity', *The Korean Journal of Clinical Laboratory Science*, 53(3), pp. 201–207. doi:10.15324/kjcls.2021.53.3.201.
19. **Marik, P.E. *et al*.** (2021). 'Gender-based disparities in COVID-19 patient outcomes', *Journal of Investigative Medicine*, 69(4), pp. 814–818. doi:10.1136/jim-2020-001641.
20. **Wang, G. *et al***. (2020) 'C-Reactive Protein Level May Predict the Risk of COVID-19 Aggravation', *Open Forum Infectious Diseases*, 7(5), p. ofaa153. doi:10.1093/ofid/ofaa153.
21. **Sadeghi-Haddad-Zavareh, M. *et al*.** (2021) 'C-Reactive Protein as a Prognostic Indicator in COVID-19 Patients', *Interdisciplinary Perspectives on Infectious Diseases*. Edited by M. Lanzafame, 2021, pp. 1–5. doi:10.1155/2021/5557582.
22. **Lin, Z. *et al*.** (2020). 'Serum ferritin as an independent risk factor for severity in COVID-19 patients', *Journal of Infection*, 81(4), pp. 647–679. doi:10.1016/j.jinf.2020.06.053.
23. **Vargas-Vargas, M. and Cortés-Rojo, C.** (2020) 'Ferritin levels and COVID-19', *Revista Panamericana de Salud Pública*, 44, p. 1. doi:10.26633/RPSP.2020.72.

24. **Gandini, O. *et al*.** (2021). 'Sex-disaggregated data confirm serum ferritin as an independent predictor of disease severity both in male and female COVID-19 patients', *Journal of Infection*, 82(3), pp. 414–451. doi:10.1016/j.jinf.2020.10.012.
25. **Hussein, A.M. *et al***. (2021) 'D-Dimer and Serum Ferritin as an Independent Risk Factor for Severity in COVID-19 Patients', Materials Today: Proceedings, p. S2214785321028583. doi:10.1016/j.matpr.2021.04.009.
26. **Naemi, F.M.A. *et al*.** (2021). 'Association between HLA genotype and ferritin levels in COVID-19 infection: a study of a Saudi cohort', Infectious Diseases, 53(12), pp. 891–899. doi:10.1080/23744235.2021.1955149.
27. **Zhou, F. *et al*.** (2020). 'Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, *The Lancet*, 395(10229), pp. 1054–1062. doi:10.1016/S0140-6736(20)30566-3.
28. **He, X. *et al*.** (2021) 'The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients', *Scientific Reports*, 11(1), p. 1830. doi:10.1038/s41598-021-81300-w.
29. **Ayanian, S. *et al*.** (2020). The Association Between Biomarkers and Clinical Outcomes in Novel Coronavirus (COVID-19) Pneumonia in a US Cohort. Preprint. *Infectious Diseases* (except HIV/AIDS). doi:10.1101/2020.05.27.20115105.
30. **Nadeem, I. *et al***. (2021). 'Relationship of D-dimer and prediction of pulmonary embolism in hospitalized COVID-19 patients: a multicenter study, *Future Microbiology*, 16(12), pp. 863–870. doi:10.2217/fmb-2021-0082.