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Relationship between Radiological Lung Findings and Laboratory Ferritin and D-Dimer Levels in Patients with COVID-19 Infection

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Abstract

Introduction: Pulmonary symptoms of COVID-19 infection range from asymptomatic infection to severe pneumonia. Pathogenesis and severity of symptoms were found to be related to the body's immune response. **Objectives:** Ferritin and D-Dimer in COVID-19 confirmed cases can predict lung injury and possible poor patient prognosis. **Materials and Methods:** Patients who had been admitted to Dr. Sulaiman Alhabib-Arryan Hospital with positive COVID-19 polymerase chain reaction (PCR) tests between March 2020 and December 2021 were studied for blood ferritin and D-Dimer levels in relation to pulmonary radiological findings. **Results:** A total of 494 cases are included in this study. Male patients represent 74.1% of the cases, and the mean age is 51.68 ± 13.37 years. Increased age, ferritin, D-Dimer levels, and respiratory symptoms are factors that showed a statistically significant association with positive computed tomography (CT) findings. Receiver operator characteristic curve (ROC) showed that ferritin has a higher capability than D-Dimer to detect CT findings and that both are equal in predicting possible patient mortality. Suggested cutoff values for Ferritin > 336 ng/mL, with 78.21% sensitivity and 86.42% specificity and for D-Dimer > 0.55 mg/L FEU, with sensitivity of 74.82% and specificity of 75.31%. For mortality, the suggested cutoff point for ferritin is >864.6 ng/mL, which gives a sensitivity of 80.26 and a specificity of 64.83%. The suggested cutoff point for D-Dimer is >1.46 mg/L FEU, which gives a sensitivity of 65.79% and a specificity of 78.23%. **Conclusion:** Laboratory markers such as Ferritin and D-Dimer can be an accurate predictor of lung injury in COVID-19 patients and their increased values can predict the poor patient prognosis and possible mortality if aggressive hospital care is not provided.

Keywords

Ferritin, COVID-19, D-Dimer

1. Background

Outbreaks of COVID-19 infection started to affect the world since last 2019 when it erupted in Wuhan, China and then the whole world. The WHO considered it a worldwide pandemic in March 2020 [1] [2].

Symptoms of COVID-19 infection range from asymptomatic infection to severe pneumonia, sepsis, acute respiratory distress syndrome and mortality due to respiratory failure and multi-organ dysfunction [2] [3].

The pathogenesis and severity of symptoms were found to be related to the body's immune response that will affect many body systems, including the hematological, epithelial, and vascular system [4].

Lung and vascular injuries occur secondary to the release of large amounts of inflammatory cytokines [4]. Virus replicating in respiratory epithelial cells will result in release of large amounts of these cytokines, causing severe lung disease [5].

The condition of the high inflammatory cytokines in the circulation of COVID-19 patients is known as cytokine storm. This storm is strongly associated with symptoms severity. Interleukins 2, 6, 7 and 10, TNF α and interferon γ [1] [3] [4] [5], are examples of some of those mediators. This rise in the inflammatory cytokines and associated apoptosis are the main causes of lymphopenia observed in COVID-19 patients, which was a feature in the severely ill and many hospitalized patients [6] [7] [8].

This massive release of inflammatory cytokines in COVID-19 patients is also associated with activation of the coagulation pathway and elevation of serum ferritin, making COVID-19 one of the causes of hyperferritinemic syndrome [9].

Activation of the coagulation pathway will cause arterial and venous thrombosis that will be aggravated by the presence of co-morbidities such as hypertension, lung disease, and diabetes [10].

Elevation of inflammatory biomarkers such as C-reactive protein (CRP), D-Dimer, procalcitonin, ferritin, lactate dehydrogenase (LDH) and interleukin-6 (IL-6) are found to be associated with severe COVID-19 infection [10].

Imaging studies gained by using computed tomography (CT) scan are considered a sensitive method for early detection of lung injury in pneumonia. Most CT findings are in the form of ground glass opacity (GGO), with or without consolidation, interlobular septal thickening, lymphadenopathy, and pleural effusion [10].

Aim of the Work

The present study was designed to clarify the diagnostic accuracy of using laboratory markers such as ferritin and D-Dimer in COVID-19 confirmed cases to

predict lung injury and to limit the unnecessary use of radiological investigations (CT scans), thus decreasing the burden of its usage in diagnosing lung involvement in COVID-19 cases, especially during pandemic situations. This would decrease the time patients spend in the triage area waiting for CT results.

2. Methodology

2.1. Study Design

Observational retrospective Cohort study was performed after ethical approval was obtained from the Institutional Review Board (IRB) of Dr. Sulaiman Alhabib Medical Group, holding approval number HAP-01-R-082. No consent was needed.

2.2. Study Population

The study was performed on patients who had been admitted to Dr. Sulaiman Alhabib-Arryan with a positive COVID-19 PCR test.

2.3. Study Subject

Data was collected from patients confirmed to have positive COVID-19 Real Time Polymerase Chain Reaction (RT-PCR) test at time of admission to Dr. Sulaiman Alhabib-Arryan Hospital in the duration between March 2020 and December 2021. Test done by utilizing specific and sensitive Nucleic Acid Amplification Techniques (NAAT)/(RT-PCR). The viral genes targeted are E, N, and RdRp/ORF. The sample was collected using a nasopharyngeal swab and viral RNA was extracted and subjected for testing to confirm the presence of the known gene sequence/s of SARS-CoV-2 Virus in the designated samples. Inclusion criteria of adult patients with age ranging from 18 - 75 years old, with available pulmonary CT, and laboratory result for ferritin and D-Dimer. The exclusion criteria were patients aged more than 75 and less than 18, pregnant females, any patient with iron deficiency anemia and any hyperferritinemic states such as sepsis due to bacterial, fungal or viral sources other than COVID-19, iron overload due to hemochromatosis or chronic transfusions, and chronic hemolytic anemia. Radiological and laboratory findings are collected from available data in the hospital information system (VIDA).

2.4. Study Variables

Patients were positive for COVID-19 by RT-PCR.
Pulmonary CT findings.
Ferritin.
D-Dimer.

2.5. Data Collection/Data Source

Data was collected from the hospital information system (VIDA) in Dr. Sulaiman Alhabib-Arryan Hospital. Collected data included age, gender, date of ad-

mission, respiratory symptoms, comorbidities relevant to COVID-19 infection, laboratory results of ferritin, D-Dimer, and pulmonary CT findings. Respiratory symptoms include dyspnea, chest pain, shortness of breath, or cough. Comorbidities that may worsen patient's outcome include diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD), and chronic lung diseases. Radiological images were examined by an experienced radiologist for the presence or absence of any findings significant for COVID-19 pneumonia in the form of either unilateral or bilateral ground glass opacities (GGOs), parenchymal consolidations, septal thickening, pleural effusion, or enlarged mediastinal lymph nodes (11).

2.6. Statistical Analysis

Descriptive statistics are presented in the form of mean with standard deviation or median with Q1 and Q3 for numeric variables, while frequencies and percentages are used for categorical variables. Multiple logistic regression for the factors associated with positive CT findings while controlling for other variables. Receiver operating characteristic (ROC) curve with area under the curve (AUC) were used to study the diagnostic ability and get the suitable cutoff points with corresponding sensitivity and specificity. The IBM SPSS Version 28 software for Windows was used for the statistical analysis, and MedCalc Version 20 was used for developing the ROC curves.

3. Results

A total of 494 cases are included in this study. Male patients represent 74.1% of the cases, and the mean age is 51.68 ± 13.37 years. 47.4% of the patients had comorbidities, and 80.8% had respiratory symptoms. 83.6% had positive CT findings, and mortality was observed in 15.4% of the cases. The median ferritin level for the patients was 691.71 ng/mL (Q1, Q3: 225.29 ng/mL, 1443.09 ng/mL), and the median D-Dimer level was 0.88 mg/L FEU (Q1, Q3: 0.45 mg/L FEU, 1.87 mg/L FEU) (Table 1).

Multiple logistic regression for the factors associated with positive CT findings while controlling for other variables. The factors that showed statistically significant associations with positive CT findings are age, having respiratory symptoms, ferritin, and D-Dimer levels. Higher age is associated with higher odds of having positive CT findings (OR = 1.028, 95% CI: 1.005% - 1.052%), p-value = 0.018. Those with respiratory symptoms have higher odds for positive CT findings as compared to those with no respiratory symptoms (OR = 4.573, 95% CI: 2.436% - 8.585%), p-value < 0.001.

Higher ferritin level is associated with higher odds of having positive CT findings (OR = 1.002, 95% CI: 1.001% - 1.003%), p-value < 0.001. Higher D-Dimer level is associated with higher odds of having positive CT findings (OR = 1.612, 95% CI: 1.053% - 2.465%), p-value = 1.612 (Table 2).

ROC curve (Figure 1), is used to study if ferritin or D-Dimer can be used to

Table 1. Characteristics of the study sample.

		N	%
Gender	Female	128	25.9
	Male	366	74.1
Age in years.	Mean (SD)	51.68 (13.37)	
Comorbidities	No	260	52.6
	Yes	234	47.4
Respiratory symptoms	No	95	19.2
	Yes	399	80.8
CT findings	No	81	16.4
	Yes	413	83.6
Mortality	No	418	84.6
	Yes	76	15.4
Ferritin (ng/mL)	Median (Q1, Q3)	691.71 (225.29, 1443.09)	
D-Dimer (mg/L FEU)	Median (Q1, Q3)	0.88 (0.45, 1.87)	

Table 2. Multiple logistic regression for the factors associated with positive CT findings.

	Odds ratio	P-value	95% CI for odds ratio	
Age	1.028	0.018	1.005	1.052
Respiratory symptoms				
No	1			
Yes	4.573	<0.001	2.436	8.585
Ferritin	1.002	<0.001	1.001	1.003
D-Dimer	1.612	0.028	1.053	2.465

CI: Confidence Interval.

predict positive CT findings and to get the corresponding cutoff points with sensitivity and specificity. Ferritin showed better diagnostic capability as compared to D-Dimer as it has higher AUC (0.891) as compared to that of the D-Dimer (0.783), p-value < 0.001 (**Table 3**).

ROC curve is used to study if ferritin or D-Dimer can be used to predict mortality and to get the corresponding cutoff points with sensitivity and specificity (**Figure 2**). Ferritin showed no difference in diagnostic capability as compared to D-Dimer as its AUC (0.781) was not different from that of the D-Dimer (0.799), p-value = 0.584 (**Table 4**).

For positive CT findings, the suggested cutoff point for ferritin using Youden's index is >336 ng/mL, which gives a sensitivity of 78.21% (95% CI: 73.9% - 82.1%), and a specificity of 86.42% (95% CI: 77.0% - 93.0%). The suggested cutoff point for D-Dimer using Youden's index is >0.55 mg/L FEU, which gives a sensitivity of 74.82% (95% CI: 70.3% - 78.9%) and a specificity of 75.31%

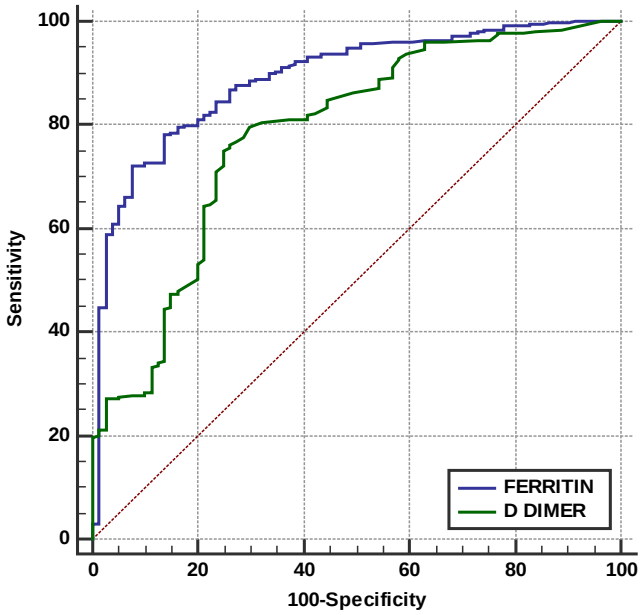

Figure 1. ROC curve for positive CT findings using ferritin and D-Dimer.

Table 3. AUC for ferritin and D-Dimer to predict positive CT findings.

Variable	AUC	95% CI	P-value
Ferritin	0.891	0.860 to 0.917	<0.001
D-Dimer	0.783	0.744 to 0.818	

AUC: Area Under the Curve; CI: Confidence Interval.

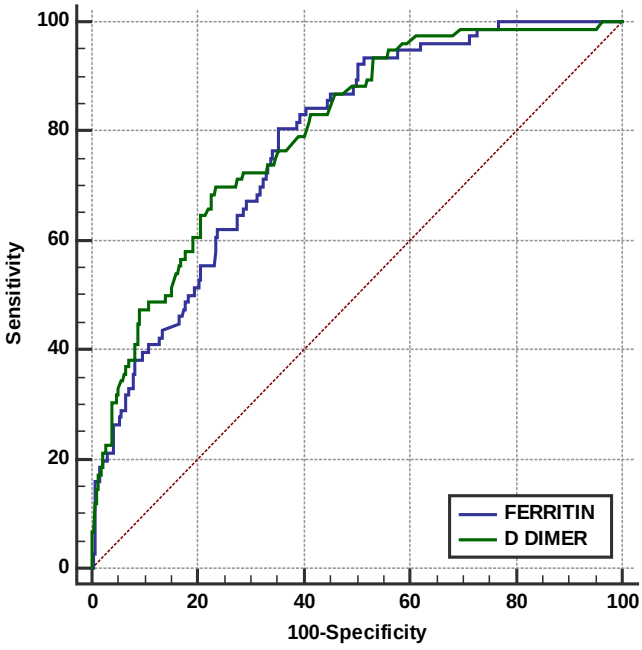

Figure 2. ROC curve for mortality using ferritin and D-Dimer.

Table 4. AUC for ferritin and D-Dimer to predict the occurrence of mortality.

Variable	AUC	95% CI	P-value
Ferritin	0.781	0.742 to 0.817	0.584
D-Dimer	0.799	0.761 to 0.833	

AUC: Area Under the Curve; CI: Confidence Interval.

(95% CI: 64.5% - 84.2%). For mortality, the suggested cutoff point for ferritin using Youden's index is >864.6 ng/mL, which gives a sensitivity of 80.26% (95% CI: 69.5% - 88.5%) and a specificity of 64.83% (95% CI: 60.0% - 69.4%). The suggested cutoff point for D-Dimer using Youden's index is >1.46 mg/L FEU, which gives sensitivity of 65.79% (95% CI: 54.0% - 76.3%), and specificity of 78.23% (95% CI: 74.0% - 82.1%) (Table 5).

4. Discussion

Our study presents information on COVID-19 positive patients admitted to our hospital after being confirmed by a real-time PCR test, with their CT, laboratory findings of ferritin and D-Dimer, together with associated respiratory symptoms and their prognosis of mortality or discharge. We found that higher age, having respiratory symptoms, high ferritin, and high D-Dimer levels at time of patient admission to hospital are significantly associated with positive CT pulmonary findings with high odds ratios (OR) for all. These go in accordance with the, significant findingsof A. Yilmaz *et al*., in their earlier study. However, still the number of studies that describe the association between positive CT findings and blood levels of ferritin and D-Dimer is very limited [11].

By comparing the significance of both laboratory tests in relation to patient prognosis, mortality, and the positive CT findings, while both tests have equal capabilities to detect poor patient outcome with no significant difference and nearly equal AUC in ROC curve analysis, high ferritin levels are more able to predict lung injury and positive CT lung findings with a significant difference between the AUC of both tests and a higher AUC in ferritin than that of D-Dime. The p-value was significant.

Using sensitive and specific cutoff values for both laboratory markers to predict possible lung injury and possible poor patients outcomes may help a lot in triage area, to appropriately identify patients who may need pulmonary CT, and or hospital admission for providing more aggressive treatment and closer monitoring. From ROC curve using Youden's index, we suggested a cutoff value of >336 ng/mL for ferritin as a predictor for positive CT findings, which gives a sensitivity of 78.21% (95% CI: 73.9 - 82.1%), and a specificity of 86.42% (95% CI: 77.0% - 93.0%). The suggested cutoff point for D-Dimer is >0.55 mg/L FEU, which gives a sensitivity of 74.82% (95% CI: 70.3% - 78.9%), and a specificity of 75.31% (95% CI: 64.5% - 84.2%).

For possible poor prognosis and mortality, the suggested cutoff point for

Table 5. Suggested cut off points with corresponding sensitivity and specificity.

	Ferritin			D-Dimer		
	cutoff point ng/mL	Sensitivity (95% CI)	Specificity (95% CI)	Cutoff point (mg/L FEU)	Sensitivity (95% CI)	Specificity (95% CI)
Positive CT findings	>336	78.21% (73.9 - 82.1)	86.42% (77.0 - 93.0)	>0.55	74.82% (70.3 - 78.9)	75.31% (64.5 - 84.2)
Mortality	>864.6	80.26% (69.5 - 88.5)	64.83% (60.0 - 69.4)	>1.46	65.79% (54.0 - 76.3)	78.23% (74.0 - 82.1)

CI: Confidence Interval.

ferritin use is >864.6 ng/mL, which gives a sensitivity of 80.26% (95% CI: 69.5 - 88.5%), and a specificity of 64.83% (95% CI: 60.0 - 69.4%). The suggested cutoff point for D-Dimer is >1.46 mg/L FEU, which gives a sensitivity of 65.79% (95% CI: 54.0 - 76.3%), and a specificity of 78.23% (95% CI: 74.0 - 82.1%).

B.S. Gopala Krishna *et al*. suggest that a significant worsening in C.T. scores is correlated with an increase in D-Dimer levels, which is a signal of lung deterioration and progression. Regarding the poor prognosis, he found that D-Dimer has a higher diagnostic accuracy when compared to ferritin, with an AUC value of 0.598 for ferritin and 0.88 for D-Dimer. The optimal cutoff suggested by them as a poor prognosis predictor was 727 ng/mL for ferritin, with a positive predictive value of 35.5% and a negative predictive value 76.5%. The cutoff for D-Dimer was 2.2 mg/L FEU with a positive predictive value 72.5% and a negative predictive value 88% [12].

However, in another study, Zayed *et al*. showed significant elevation of the ferritin levels in severe COVID-19 patients, with 91% sensitivity and 74 % specificity at a cutoff level of >548.5 ng/mL, AUC value was 0.87 (CI 0.79% - 0.94%), with a significant p-value (<0.001). They suggested using ferritin as an independent predictor of severe COVID-19 [13].

Alvaro *et al*. investigated the significant predictive values of ferritin and D-Dimer to identify patients at risk of developing severe lung injury, Adult Respiratory Distress Syndrome (ARDS). They discovered that there was a significant increase in initial ferritin level at time of hospital admission with an AUC value of 0.86 CI (0.8% - 1%) and a significant p-value (0.001), while D-Dimer level was not initially significant as an indicator of lung injury, but after few days of admission started to be of significant value (p-value < 0.001) [14].

5. Limitations

Being a retrospective study, during the data collection phase, many patients who were eligible for our criteria were excluded due to missing information such as ferritin or D-Dimer results. In addition, time from illness onset to hospital presentation may affect ferritin and D-Dimers values.

6. Conclusion

In this study, we found that laboratory markers such as ferritin and D-Dimer can be an accurate predictor of lung injury in COVID-19 patients and their increased values above our suggested cutoff (>336 ng/mL for ferritin, and >0.55 mg/L FEU for D-Dimer), are correlated with the presence of radiological CT findings not only that but also levels above 864.6 for ferritin and >1.46 mg/L FEU for D-Dimer can predict the poor patient prognosis and possible mortality if patient did not receive enough hospital care and close monitoring in hospital. We thus argue that D-Dimer and ferritin levels measured at the time of admission to the emergency department can be taken into consideration to predict disease severity.

Author's Contribution Statement

All authors contributed to data acquisition. Data analysis, interpretation and manuscript drafting were done by DR. Mona Fathy the corresponding author. Administrative support is done by DR. Ahmed Al Akidi. All authors reviewed and approved the final version of the manuscript.

Data Sharing Statement

Most of the data supporting our findings is contained within the manuscript, and all others, excluding identifying or confidential data, will be shared upon request from the corresponding author.

Ethical Consideration

Participants' anonymity was assured by assigning each participant a code number for the purpose of analysis. There is no need to sign a consent form.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

WHO (World Health Organization).

TNFα (Tumor necrosis factor alpha).

PCR (Polymerase chain reaction).

Q1 and Q3 (The first and third quartiles, respectively).

RNA: Ribonucleic acid.

SARS-CoV-2: The severe acute respiratory syndrome-coronavirus 2.