ORIGINAL PAPER

# Predictive Value of C–reactive Protein, Lactate Dehydrogenase, Ferritin and D-dimer Levels in Diagnosing COVID-19 Patients: a Retrospective Study

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**ABSTRACT**

**Background:** Since December 2019. millions of people in the world have been affected with the novel Coronavirus disease-2019 (COVID-19) pandemic, and high economic impact has affect many countries especially low socioeconomic one like Iraq due to the high cost and limited availability of RT-PCR for diagnosis of COVID-19, so there should be predictive low cost easily available laboratory tests that can be used before proceeding to the high cost techniques. **Objective:** In this retrospective study we aimed to evaluate the diagnostic accuracy of CRP, ferritin, LDH and D-dimer in predicting positive cases of COVID-19 in Iraq. **Methods:** It is a retrospective observational cohort study based on STARD guidelines to determine the diagnostic accuracy of (CRP, LDH, ferritin and D dimer) for COVID-19 of electronic medical records of private medical center in Najaf city, at which 566 individuals were recruited. The investigated subjects were either in close contact with previously COVID-19 positive patients or have one or more symptoms of COVID-19. They were categorized into 2 groups, 205 subjects diagnosed with RT-PCR as COVID-19 negative, and 361 COVID-19 positive patients, results of study variables of the cohort were recruited from the medical records. **Results:** Combining of these parameters had the following findings: CRP + ferritin; AUC: 0.77 with 55% sensitivity and 97% specificity, Ferritin + LDH; AUC: 0.83 with 65% sensitivity and 92% specificity, CRP+LDH; AUC: 0.78 with 56% sensitivity and 98% specificity, CRP + LDH + ferritin; AUC: 0.85, with 73% sensitivity and 88% specificity, CRP + LDH + ferritin + D dimer; AUC: 0.85 75% sensitivity and 87% specificity. **Conclusion:** Combination of routine laboratory biomarkers (CRP, LDH and ferritin ±D dimer) can be used to predict the diagnosis of COVID-19 with an accepted sensitivity and specificity before proceeding to definitive diagnosis by RT-PCR.

**Keywords: COVID-19, CRP, LDH, ferritin and D-dimer.**

## 1. BACKGROUND

In December 2019 an acute respiratory disease known as the novel coronavirus infection (COVID-19) has appeared in the city of Wuhan, Hubei Province, China since December 2019. It is manifested as an acute respiratory disease, promptly spreading globally (1). The World Health Organization (WHO) has declared on January 2020 the outbreak of COVID-19 as a global pandemic and a Public Health Emergency of International Concern (PHEIC).

Till January 12, 2021, the confirmed cases of COVID-19 reached above 90.000.000 with more than 1.900.000 deaths (2). Iraq is one of the top ranking countries affected by COVID-19 with more than 600.000 confirmed cases and more than 12.000 death (2).

The clinical presentation of the disease is highly variable, ranging from asymptomatic or only mild symptoms (80%), to severe multi organ failure and even death. Symptoms include fever, loss of sense of smell and or taste, sore throat, shortness of breath, non-productive cough, general fatigue, myalgia, and headache. Some patients (15-20%) may develop acute respiratory distress syndrome (ARDS), and in some cases kidney and heart failure (3-5). COVID-19 had a similar clinical course and patho-

logical findings with the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) due to the genetic homologies between coronaviruses (6). Severe states of COVID-19 cause a hyper inflammatory response, leading to a pathological dysfunction of innate host defense mechanisms, causing complications like multiple organ failure and or cytokine release syndrome (cytokine storm) (7). C-reactive protein (CRP) is an acute-phase protein appears in blood within 6–10 hours of any tissue damaging event and has a plasma half-life of 19 hours, its synthesized by the liver when the body is affected by inflammation, such as bacterial or viral infection or tissue destruction (8).

Ferritin is an iron storage form; it is one of the biomarkers of inflammation. In bacterial or viral infection, an increase in ferritin occurs due to ironreleasein the endoplasmic reticulum and to a decline in its transport capacity due to spleen and liver damage (9). Lactate dehydrogenase (LDH) is an enzyme involved in glycolysis, catalyzes pyruvate to lactate conversion and present in all tissues. It is released from cells upon damage of their cytoplasmic membrane by for example viral infection (10). D-dimmers are multiple peptide fragments synthesized as a result of cross linked fibrin degradation mediated by plasmin. Its level would elevate in any process that involve production and breakdown of fibrin, such as acute infections, surgery and acute or chronic inflammatory states (11).

COVID-19 has been reported to be associated with coagulopathy and 3.75–68.0% of the COVID-19 patients have been found to have raised D-dimer levels (12, 13). Till now no FDA-approved therapeutics for COVID-19 were registered. Thus, the continuous seeking for markers associated with the course of the disease can aid to better diagnostic accuracy, probably may also explore the severity of the disease. Such attempts may help clinical decision-making and reduction of the use of high cost techniques for diagnosis such as RT-PCR and CT scanning. Despite the increasing number of studies on COVID-19 in the last months, there are limited data on laboratory features of COVID-19 cases in Arab populations especially Iraq.

## 2. OBJECTIVE

In this retrospective study we aimed to evaluate the diagnostic accuracy of CRP, ferritin, LDH and D-dimer in predicting positive cases of COVID-19 in Iraq.

## 3. METHODS

**Study design**

It is a retrospective observational cohort study based on STARD guidelines to determine the diagnostic accuracy of (CRP, LDH, ferritin and D dimer) for COVID-19 of electronic medical records at a private medical center in Najaf city. Najaf is a large city lie in the south of Iraq, and as a part of the screening program for COVID-19 adapted by the Ministry of health (MOH), hundreds of tests has been done each day for COVID-19 through a RT-PCR of nasopharyngeal swabs at the Central Laboratory of MOH in Najaf city. The diagnosis of COVID-19 was based on WHO guidelines (14).

Many of these individuals presents to outpatient private medical center at Najaf city for consultation.

**Study subjects**

Sample size was based on minimum sensitivity and specificity of 95%, we randomly selected medical records of 938 subjects suspected to have COVID-between May and December 2020.

**Inclusion criteria**

Men and women aged (30-70 y), They were either in close contact with previously COVID-19 confirmed positive patients or have one or more symptoms of COVID-19 such as: fever, cough, sore throat, dyspnea, muscle aches and loss of smell or taste. 566 subjects were divided into two groups. Group one consisted of 205 individuals who have COVID-19 negative result and group two comprised of 361 patients who have positive COVID-19 result.

**Exclusion criteria**

Individuals of incomplete laboratory records or has medical history of renal failure, liver failure, diabetes mellitus, hypertension, active tumor, active infection, pregnant women and children, 372 subjects were excluded.

**Study variables**

The index test for diagnosis of COVID-19 was RT-PCR for detection of viral RNA in nasopharyngeal swab this test was used according to WHO guidelines for diagnosis of COVID-19 and it's done by governmental center (Central Laboratory of MOH in Najaf). The laboratory records that have been recruited from study individuals included: CRP, ferritin, LDH and D dimer. CRP level was measured by latex enhanced immunoturbidimetric method using Randox Daytona plus (Randox Laboratories Ltd., Crumlin, UK). LDH activity was estimated through the conversion of lactate to pyruvate procedure using Randox Daytona plus (Randox Laboratories Ltd., Crumlin, UK). D dimer was determined by immunofluorescent method using VIDAS (Bio Mérieux, Marcy L'Etoile, France).

Ferritin was assessed by electro-Chemiluminescence immune method using Cobas Roche e411 auto analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The study was approved by the Ethical committee at Kufa University. Informed consent was obtained from participants after elaborating the plan of the study.

**Statistical analysis**

Statistical analyses have carried out by the using IBM-SPSS statistics software (version 25; IBM, New York, USA). Shapiro [-Wilk test has been used to test for normality of data, Numerical variables were displayed as median with inter-quartile range (IQR). Categorical variables have been tested by the Mann-Whitney U test. The association of independent variables among groups has been evaluated with the use of univariate and multivariate logistic regressions. The odds ratio (OR) with 95% confidence interval (95%CI) has been estimated. Spearman's correlation analysis has been applied to determine the variable correlations. Receiver operating characteristic (ROC) analysis was used to assess the sensitivity and specificity of each parameter and of combined parameters through the area under the curve (AUC). Youden index has been applied to determine the cutoff value of each diagnostic

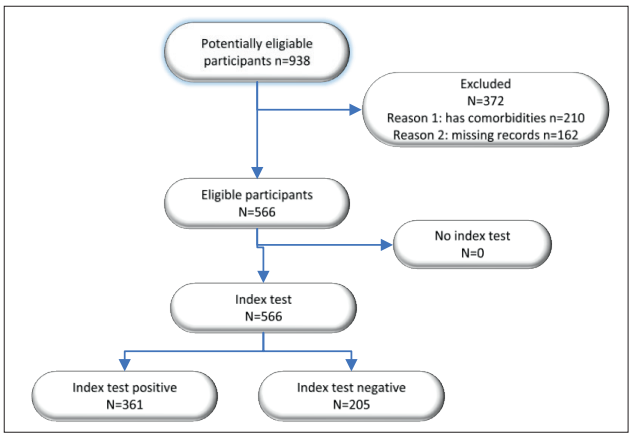


**Figure 1. Study participants flow chart**

| Number of analyzed participants | 566 |
|---|---|
| Median age (range) | 49 (30-70) |
| Gender<br>Number of males (%)<br>Number of females (%) | <br>292 (50.9)<br>274 (47.4) |
| Number ofCOVID-19 negative persons (%) | 205 (36.2%) |
| Number of COVID-19 positive persons (%) | 361(63.8%) |

**Table 1. Demographic characteristics of study subjects**

| | COVID-19negative(N=205) Median (IQR) | COVID-19positive (N=361) Median (IQR) | P value |
|---|---|---|---|
| Age (y) | 49 (20) | 48(22) | 0.77 |
| CRP (mg/L) | 6 (9) | 18 (46) | < 0.001 |
| Ferritin (ng/mL) | 96 (139) | 281 (1996) | < 0.001 |
| LDH (U/L) | 230 (54) | 257 (74) | < 0.001 |
| D-dimer (mg/L) | 0.2 (0.3) | 0.3 (0.6) | 0.03 |

**Table 2. Median comparison of laboratory parameters between study subjects using Mann Whitney test. All data expressed as median (IQR). P value < 0.05 considered statistically significant. QR: inter quartile range**

test. P values of less than 0.05 were considered statistically significant.

## 4. RESULTS

Figure 1 shows the flow chart of study participants and Table 1 shows the demographic characteristics of the study persons. The total analyzed persons were 566; their age's median was 49 y with a range of 30-70 y. There were 292 (51.6%) males and 274 (48.4%) females. Those of COVID-19 negative RT-PCR outcomes (Group 1) were 205 (36.2%) while those of COVID-19 positive results (Group 2) were 361 (63.8%). No significant differences were indicated for gender and ages among the 2 groups. Table 2 shows the comparison of the median values of laboratory parameters in the 2 study groups using Mann Whitney test. Significant (P: <0.01,<0.01,<0.01 & 0.03 respectively) increases of CRP, LDH, ferritin and D-dimer levels were evident in COVID-19 positive subjects when compared with those of the negative outcomes. Table 3 demonstrates theuni- and multivariable logistic regression analysis of the laboratory parameters in the 2 groups. CRP, LDH and ferritin levels were seemed to be significantly (OR: 1.03, P: <0.01, OR: 1.005, P: <0.01,OR: 1.02, P: <0.01 respectively) associated with the increased risk for COVID-19 infection. The correlation analysis highlights significant positive correlation of CRP with ferritin levels (r: 0.4, P: <0.01) and CRP with D-dimer levels (r: 0.3, P: <0.01) (Table 4). The ROC curve analysis (Figure 2) illustrates a cutoff value for CRP of 14.5 mg/L, with an AUC value of 0.7, the sensitivity and specificity were 50% and 77% respectively. Ferritin cutoff value was found to be 290 ng / mL and the AUC was 0.7 with sensitivity and a specificity of 49% and 96% respectively. LDH cutoff value was determined to be 278 U/L and the AUC value was 0.6 with sensitivity and a specificity of

| Variable | Univariable logistic regression | | Multivariable logistic regression | |
|---|---|---|---|---|
| | OR (95%CI) | P value | OR (95%CI) | P value |
| Age | 0.9 (0.7-1.3) | 0.96 | | |
| Gender | 1.0 (0.98-1.01) | 0.96 | | |
| CRP (mg/L) | 1.04 (1.03-1.06) | < 0.001 | 1.03 (1.01-1.04) | < 0.001 |
| Ferritin (ng/mL) | 1.005 (1.004-1.007) | < 0.001 | 1.005 (1.004-1.007) | < 0.001 |
| LDH (U/L) | 1.01 (1.01-1.02) | < 0.001 | 1.02 (1.01-1.02) | < 0.001 |
| D dimer (mg/L) | 1.6 (1.1-2.2) | 0.004 | 1.3 (0.9-1.8) | 0.07 |

**Table 3. Univariable and Multivariable logistic regression analysis of the study subjects. OR: odds ratio. CI: confidence interval. P value < 0.05 is considered statistically significant**

| | (r) P value | | | |
|---|---|---|---|---|
| | Age | CRP (mg/L) | Ferritin (ng/mL) | D-dimer (mg/L) |
| CRP (mg/L) | (-0.02) 0.49 | | | |
| Ferritin (ng/mL) | (-0.04) 0.27 | (0.45) < 0.001 | | |
| LDH (U/L) | (-.0.01) 0.66 | (0.07) 0.09 | (0.09) 0.02 | (-0.01) 0.76 |
| D dimer (mg/L) | (-0.01) 0.68 | (0.32) < 0.001 | (0.07) 0.06 | |

**Table 4. Correlation analysis of laboratory parameters in the 2 investigated groups. r: correlation coefficient. P value < 0.05 is considered statistically significant**

| | Cut off value | Youden index | AUC | 95%CI | P value | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|
| CRP (mg/L) | 14.5 | 0.33 | 0.71 | 0.67 - 0.75 | < 0.001 | 0.56 | 0.77 |
| Ferritin (ng/mL) | 290 | 0.46 | 0.73 | 0.69 - 0.77 | < 0.001 | 0.49 | 0.96 |
| LDH (U/L) | 278 | 0.31 | 0.69 | 0.65 - 0.73 | < 0.001 | 0.38 | 0.93 |
| D dimer (mg/L) | 0.5 | 0.15 | 0.56 | 0.51 - 0.61 | < 0.001 | 0.30 | 0.84 |

**Table 5. ROC curve analysis of the laboratory parameters in predicting positive COVID-19 cases. ROC: receiver operating characteristics. AUC: area under the curve. P value < 0.05 is considered statistically significant**

| | Youden index | AUC | 95%CI | P value | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| CRP + ferritin | 0.53 | 0.77 | 0.74-0.81 | < 0.001 | 55 | 97 |
| Ferritin + LDH | 0.53 | 0.83 | 0.80-0.86 | < 0.001 | 65 | 92 |
| CRP + LDH | 0.46 | 0.78 | 0.75-0.82 | < 0.001 | 56 | 98 |
| CRP + LDH + ferritin | 0.61 | 0.85 | 0.82-0.88 | < 0.001 | 73 | 88 |
| CRP + LDH + ferritin + D dimer | 0.62 | 0.85 | 0.82-0.88 | < 0.001 | 75 | 87 |

**Table 6. ROC curve analysis of combined parameters in predicting positive COVID-19 cases. ROC: receiver operating characteristics. AUC: area under the curve. P value < 0.05 is considered statistically significant**

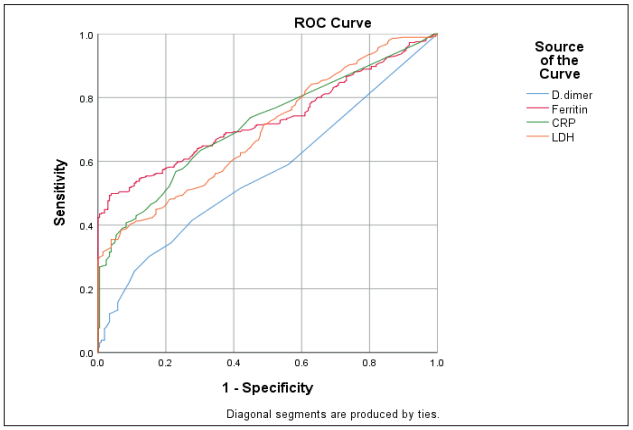


**Figure 2. Receiver operating characteristic curve for CRP, LDH, ferritin and D-dimer in predicting COVID-19 positive cases**

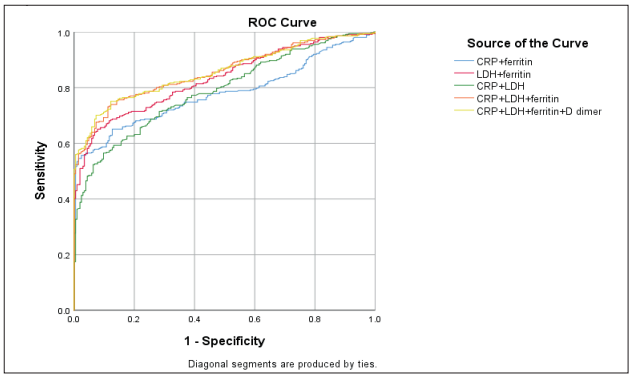


**Figure 3. Receiver operating characteristic curve for combined parameters (CRP, LDH, ferritin, D dimer) in predicting COVID-19 positive cases**

30% and 93% respectively. The D-dimer cutoff value was estimated to be 0.5 mg/L and the AUC value was 0.5 with 30% sensitivity and 84% specificity (Table 5). When we combine the parameters, CRP + ferritin; AUC:0.77 with 55% sensitivity and 97% specificity, Ferritin + LDH; AUC: 0.83 with 65% sensitivity and 92% specificity, CRP + LDH; AUC: 0.78 with 56% sensitivity and 98% specificity, CRP + LDH + ferritin; AUC: 0.85, with 73% sensitivity and 88% specificity, CRP + LDH + ferritin + D dimer; AUC:0.8575%-sensitivity and 87% specificity (Table 6, Figure 3).

## 5. DISCUSSION

The pandemic of COVID-19 has become a global catastrophe, characterized with elevated rate of complications and mortality and even economic impact. Thus, an urgent need is essential for cost effective and convenient indicators to simplify the diagnostic process and evaluate the disease severity. Numerous studies have identified raised levels of several serum or plasma biochemical constituents, including inflammatory parameters inCOVID-19 patients (15-17). In SARS and MERS patients, elevated serumpro-inflammatory cytokines has been reported in severe conditions compared to the mild and moderate cases (18, 19).

In our study, we pursed to assess the diagnostic accuracy of certain laboratory biomarkers (CRP, LDH, ferritin and D-dimer) in diagnosing of COVID-19 cases. It's one of the first studies that describe these findings in Arab population especially Iraq and the first one that uses combined markers to predict the diagnosis of COVID-19.

Our findings of CRP, LDH, ferritin and D-dimer levels revealed significant increases in those who were tested COVID-19 positive with RT-PCR when compared with those who were tested negative. A previous study in Italy (20) reported that CRP and LDH are significantly increased in those who were COVID-19 positive and these tests could be used as alternatives to RT-PCR for identifying COVID-19-positive patients. Another studies reported that CRP, LDH, ferritin and D-dimer were used to evaluate the severity of the disease and a high level are associated with poor outcome and mortality (21, 22).

Results of the multivariate logistic regression analysis have explored that CRP,LDH and ferritin are associated with increased risk of COVID-19 infection while, D-dimer did not do so, possibly because most of the cases that included in the study are outpatients without severe presentations. A recent metanalysis (23) demonstrated that high levels of CRP, ferritin and D-dimer are associated with poor outcome in COVID-19. Spearman correlation analysis showed that CRP and ferritin were positively correlated, this finding also reported by Lui *et al* (22). The specificity and sensitivity of CRP, LDH, ferritin and D-dimer estimations in suspected COVID-19 patients have been determined with the ROC method, the cutoff value for each marker in predicting the presence of COVID-19 infection has also been estimated.

The AUC for CRP, LDH and ferritin were about 0.7. Mardani et al. (24) reported an AUC of 0.8 for CRP and LDH which equals to our result (0.7). We found that ferritin and LDH had the highest specificity among these parameters (0.96 and 0.93 respectively) but unfortunately low sensitivity (0.49 and 0.38 respectively). We determined a cutoff value of 290 ng/mL for ferritin, a close value (304 ng/mL) was reported by Tular Onur *et al.* (25). For LDH, our cutoff value was found to be 278 mg/dL, this value was similar to the result (277 mg/dL) reported by Li *et al.* (26). For CRP, a cutoff value of 14 mg/L was observed to be concomitant with a specificity of 0.77and a sensitivity of 0.56, these findings in line with those reported by Cheng *et al.* (27).

Although there is no general agreement on a cutoff value to determine the severity of COVID-19, a recent meta-analysis (23) has shown that the majority of studies suggested a value of ≥10 mg/L cutoff for CRP and 0.5 mg/L for D-dimer. CRP may not only be used as a prognostic marker, but also to monitor the disease improvement (23).

COVID-19 patients with markedly increased D-dimer levels may require hospitalization, despite the severity of clinical presentation (28-38). The diagnosis of COVID-19 depends on high cost techniques like RT-PCR and CT imaging.

However, in a country like Iraq with a high rate of poverty and limited medical resources we can consider these routine low cost and available laboratory tests (CRP, LDH and ferritin) to predict the diagnosis of COVID-19 before proceeding to the high cost techniques, and combination of these markers cause improvement in sensitivity of analysis, so combination of (CRP, LDH and ferritin ±D dimer).

**Limitation of the study**

It is useful to mention the limitations of the current study. First, hospitalized patients were not recruited in the present investigation. Second, the severity of the disease was undefined in relevance to the laboratory parameter changes; third, we not include other laboratory markers such as procalcitonin, interleukins and hematological markers.

## 6. CONCLUSION

Combination of routine laboratory biomarkers (CRP, LDH and ferritin ±D dimer) can be used to predict the diagnosis of COVID-19 with an accepted sensitivity and specificity before proceeding to definitive diagnosis by RT-PCR.

- **Ethical approval**: This study was conducted according to the World Medical Association Declaration of Helsinki. It's approved by the Ethical committee at Kufa University. Informed consent was obtained from participants after elaborating the plan of the study.
- **Author's contribution**: Material preparation, data collection, and analysis were performed by A.N.K. who is the co-corresponding author. F.H.N written the first draft of the manuscript and also helped to revise the manuscript .M.K.H. designed the study, and took responsibility for the integrity of data and the accuracy of data analysis; A.A.A provided the administrative, technical and material support; All authors read and approved the final manuscript.
- **Conflicts of interest**: The authors declare that they have no conflicts of interest.
- **Financial support and sponsorship**: None.

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