

# Early forecasting of COVID-19 case progression with hematological and biochemical parameters of patients in Egypt

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**Abstract:** The coronavirus pandemic 2019 (COVID-19) is changing the world and reshape all aspects of life. Side by side to global efforts to develop potential vaccines and effective drugs against COVID-19, clinical parameters scanning the prognosis of COVID-19 infection are badly required to help the clinicians in premature management of COVID-19 cases before critical progression. The main objective of our study is to specify reliable biomarkers which differentially change upon case progression and clearly reflect the extent of lung lesions. Forty-one patients from Mansoura area, confirmed for COVID-19 infection were classified according to the diameter of lung lesions measured by lung computed tomography (CT) into mild and severe cases including 66% and 34% of all patients, respectively. COVID-19 patients were followed since hospital admission for comparative studies covering measured biochemical and hematological parameters. Based on the degree of severity, five different biomarkers mainly; D-dimer, lactate dehydrogenase (LDH), C-reactive protein (CRP), lymphocytes and ferritin were found to clearly oscillate in response to COVID-19 infection and upon case transition from mild to severe. In our study, significantly higher levels of almost all the biomarkers except lymphocyte count, were detected in patients having severe complications of COVID-19 infection in contrast with non-severe patients.

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

## INTRODUCTION

COVID-19 is a pulmonary infection caused by the severe acute respiratory syndrome virus (SARS-CoV-2), a newly emerged corona virus, that was initially manifested in Wuhan city in China in December 2019 (Zhu *et al.*, 2019; Chen *et al.*, 2020). COVID-19 has been identified as a respiratory virus; however clinical data reported that COVID-19 can also attack other organs, such as gastrointestinal tract, liver, and nervous system and induce multiple organ failure (Liu *et al.*, 2020; Yang *et al.*, 2020). The clinical symptoms of COVID-19 infection exhibit some interference with many other acute respiratory infections, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS) (Huang *et al.*, 2020). The typical symptoms of COVID-19 include dry cough (76%), fatigue (44%) and fever (98%). Atypical symptoms may also comprise diarrhea (3%), headache (8%), expectoration, and hemoptysis. Moreover, COVID-19 infection may adversely affect chemosensory function, leading to loss of smell and taste, however, it frequently appears within 2 to 4 weeks after infection (Yan *et al.*, 2020). Interestingly, some confirmed patients were

identified as asymptomatic (Rodriguez-Morales *et al.*, 2020), almost recovered after 1 week exhibiting a low fever, mild fatigue, or other mild symptoms, with no pneumonia (Huang *et al.*, 2020). Another common abnormality could be also seen in chest CT images (e.g., bilateral multiple lobular and sub-segmental areas of consolidation), which were observed in 98% of COVID-19 patients (Huang *et al.*, 2020). Early diagnosis is the most rate-limiting step in the clinical outcome of the pandemic and the treatment strategy. In the same respect, biochemical markers, specifically associated with COVID-19 infection represent a high clinical impact for early diagnosis. In addition, the clinical diagnosis of COVID-19 mainly depends on the detection of virus nucleic acid by polymerase chain reaction (PCR); however, some factors including viral level and methodology of sample collection influence the PCR results. False-negative results may be also obtained in many studies, identifying variable laboratory detection data of the same COVID-19 patients (Chan *et al.*, 2019; Huang *et al.*, 2020). In this study, samples collected on admission to quarantine hospitals in Mansoura governorate Egypt were examined in a highly equipped private lab for hematological and other biochemical characters testing. In addition, laboratory and clinical data

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of COVID-19 patients were analyzed and compared to provide a clear protocol for early and differential diagnosis and evaluation of COVID-19 degree of severity based on cardinal hematology and inflammatory parameters to categorize cases with a pessimist prognosis and rapid intervention to reinforce diagnosis accuracy and clinical management. Variable laboratory findings were compared among the two groups of patients to purify five clear parameters that are tightly linked to case severity. D-dimer, LDH, CRP and ferritin dramatically go up in severe cases on the other hand lymphocytopenia clearly reflects poor prognosis of the COVID19-cases.

## MATERIALS AND METHODS

### *Data collection*

In the period between 20 November to 10 December 2020, a total of 41 patients, admitted to private clinics for check for COVID-19 infection in the villages around Mansoura City including: 41 patients (19 male and 22 female) with confirmed COVID-19 infection and classified as 66% mild and 34% severe cases were included in this study. Samples collected on admission were sent within 24 hours of admission for laboratory tests, in a highly equipped private lab for hematological and other biochemical characters testing. In early diagnosis of COVID-19, most patients were suffering from pneumonia, in addition to other symptoms including fever, headache, in-appetence, myalgia, shortness of breath chest distress, and fatigue. Positive infection was confirmed by lung CT scan examination and a positive viral nucleic acid test. According to, the diameter of the largest lung lesion and measured lung CT scan, patients were classified into non-severe and severe infection. This CT image scoring system was an adaptation of a method previously used to describe idiopathic pulmonary fibrosis and severe acute respiratory syndrome (SARS) (Rodriguez-Morales *et al.*, 2020). The experimental protocol conducted in this study was approved from the Research Ethics Committee of Delta University for Science and Technology, which is in accordance with the Code of Ethics of World Medical Association (Declaration of Helsinki involving use and handling of human subjects) under permit No.FPDU 18 (2020).

### *Laboratory testing*

All laboratory samples are typically processed within hour of receipt. Using automatic hematology analyzer, peripheral venous blood was collected for routine blood test. All biochemical and hematology parameters were tested using the following tools: LDH by Human diagnostics kit, D-dimer by Fia 8000 Getein Biotechnology, ferritin by Mindray CL-960I, lymphocytes by Diagen, D-cell 60 and CRP by Spinreact. Results were obtained via standard automated laboratory methods and using commercially available kits following to the manufacturer's protocols.

### *Data analysis and violin representations*

The common standards for the tested parameters were used to normalize the data. Violin plots were created using R version 4.0.1 with the package ggplot2 version 3.3.1 s(<https://cran.r-project.org/web/packages/ggplot2/citation.html>).

## STATISTICAL ANALYSIS

The statistical analysis was performed using the SPSS 22 software. T test was used to analyze the significance. Pearson correlation was used to analyze association between the variables. Roc curve was used to determine area under the curve. A value of  $p < 0.05$  was considered statistically significant.

## RESULTS

The symptoms of mild COVID-19 typically last about 7 to 10 days with fever and bone aches. People with moderate illness are more breathless and tend to have increased heart rates, however, cases with a severe form of the illness may develop pneumonia and extreme dyspnea.

### *COVID-19 patients' overview in term of Chest Radiographic Pattern*

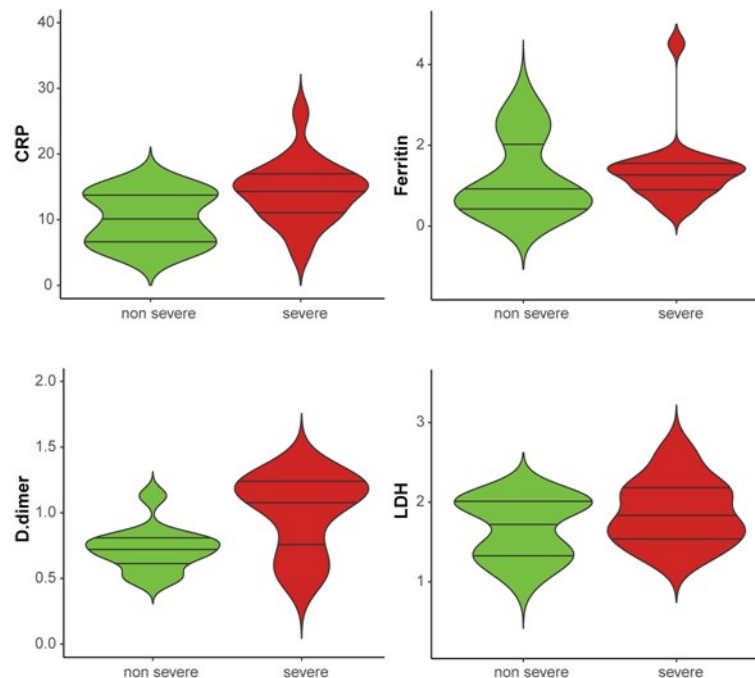
In this study, a total of 41 patients (19 male and 22 female) with confirmed COVID-19 infection by RT-qPCR and chest radiography were investigated. Patients were categorized according to chest radiographic pattern into mild representing 66% and severe representing 34% of cases. Chest x ray and CT scans performed for the patients on admission, uncovered reduced volumes of the lung, bilateral nodular opacities: small and round, ill-defined nodules of soft tissue density in mild cases while in severe cases, the opacities had become more confluent and denser, and bilateral ground glass opacification and ground glass opacification with consolidation in multiple lung segments with visible intralobular lines and interlobular septal thickening in bilateral lungs have been clearly detected. Collectively, these findings were proportional to the degree of severity of the infection where the diameter of the lung lesion on admission in the severe group was higher than those in the mild one.

### *Alterations of biochemical and hematological parameters coincide with the severity of COVID-19 infection*

In addition to chest radiographic pattern that represents a cutting edge for diagnosing and evaluating the severity of infection, biochemical and hematology parameters including CRP, D-dimer, LDH, Ferritin, and lymphocytes were tested to configure the correlation between these parameters and severity of infection. Interpretation and statistical analysis of laboratory data collected from patients of each category detected a positive significant

**Table 1:** Association between baseline variables and disease severity

Variables		Severe (no)		Non severe (no)		P value
Sex						
M		8	(17%)	11	(26.8%)	P=0.43
F		6	(14.6%)	16	(41.4%)	
CRP	< 100 mg/dL	2	(4.8%)	21	(51.2%)	P=0.000
	≥ 100 mg/dL	12	(29.3%)	6	(14.5%)	
Ferritin	< 350 ng/mL	3	(7.3%)	22	(53.6%)	P=0.004
	>350 ng/mL	11	(26.8%)	5	(12.2%)	
D-dimer	< 500	3	(7.3%)	17	(41.5%)	P=0.003
	> 500	11	(26.8%)	10	(24.4%)	
LDH	< 450	6	(14.6%)	15	(36.6%)	P=0.000
	> 450	8	(19.5%)	12	(29.3%)	
Lymphocyte	> 1 x10 <sup>3</sup> mm <sup>-3</sup>	4	(9.8%)	20	(48.8%)	P=0.000
	<1 x10 <sup>3</sup> mm <sup>-3</sup>	10	(24.4%)	5	(12.2%)	



**Fig. 1:** Overview of patient’s laboratory data. Violin plot showing blood parameters of 41 patients (19 male and 22 female) subdivided in 23 non-severe and 16 severe cases of SARS-CoV-2 infected individuals. The width of the violin plot corresponds to the number of data-points, while the lines represent the quantiles.

correlation of CRP with both D-dimer (R=0.4, p=0.008) and LDH (R=0.4, P=0.006) was detected. Similarly, Ferritin is significantly correlated with both D-dimer (R=0.56, P=0.001) and LDH (R=0.52, P=0.001). Furthermore, D dimer is significantly correlated with LDH (R=0.54, P=0.001). However, on other hand, CRP is negatively correlated with lymphocyte count (R=0.36, P=0.018). Interestingly, according to results obtained (table 1 and fig. 1).

There is a significant increase of all parameters in severe cases, in comparison with non-severe cases. In this study, binary logistic regression was implemented to validate

different factors as a predictive tool of COVID-19 severity. The results obtained, indicated three particular parameters CRP, ferritin and lymphocyte count which can significantly forecast the case progression when comparing sever to non-sever cases (table 2 and 3).

**Table 2:** Area under the curve of CRP and ferritin

	Area	P value
CRP	0.92	<0.001
Ferritin	0.89	<0.001

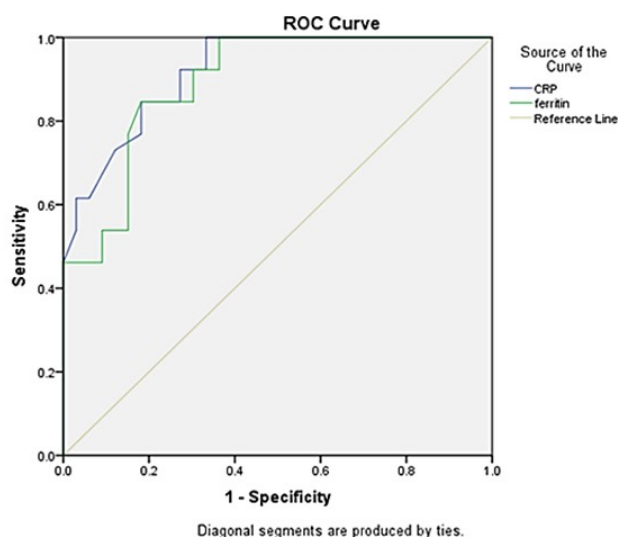
There is high sensitivity of both CRP and ferritin in detection of severe cases of COVID-19 in our patients.

**Table 3:** Binary logistic regression for factors predictive of COVID-19 severity

Variable	B	SE	P value	95%	
Sex	-0.96	0.89	0.28	0.177	0.460
CRP	0.077	0.035	0.026	0.855	0.984
Ferritin	0.007	0.003	0.037	0.816	0.940
D-dimer	0.009	0.005	0.102	0.701	0.886
LDH	0.003	0.010	0.749	0.638	0.885
Lymphocyte	-0.004	0.002	0.014	0.204	0.510

There is a significant association among COVID-19 severity and the variables in the study for CRP (p=0.02), ferritin (p=0.037) and lymphocyte count (p=0.014).

Taken all together, the five clinical parameters we distinguished in our study, show clear significance whether increasing or decreasing when compared to non-COVID-19 patients, however three particular parameters CRP, ferritin and lymphocyte count represent reliable and logistic measures that significantly forecast the case progression when comparing severe to non-severe cases, that is why those biomarkers should be considered at the first day of admission aside from symptoms and chest radiographic pattern to decide the proper therapeutic intervention and improve the clinical outcome.



**Fig. 2:** ROC curve for both ferritin and CRP.

## DISCUSSION

Different symptoms of COVID-19 infection are usually detected in infected patients, starting from asymptomatic features to a variety of symptoms such as severe pneumonia. In deadly severe cases, multiple organ damage including liver, heart and kidneys were detected, exhibiting similarity to other acute respiratory infections like SARS and MERS (Huang C *et al.*, 2020). In the early stage, abnormalities on chest imaging associated with COVID-19 infection usually appear as multiple small patch shadows, observed stromal changes and obvious lung exudate (Chung *et al.*, 2020), which then develops

into infiltrating shadows and multiple ground-glass shadows in both lungs (Pan *et al.*, 2020). Pathologically, CT scan offers a delayed application to differentiate mild from severe cases. For early diagnosis and severity assessment, more sensitive biomarkers are required in such tests. For instance, severe COVID-19 infections provoke a cytokine storm and maximize the release of inflammatory mediators (IL-6, IL-10 and TNF-) by macrophages leading to progressive damage to the lungs and other organs (Qin *et al.*, 2020). Consequently, monitoring of plasma inflammatory markers could precisely reflect the disease progress. In addition, it has been previously documented that pro-inflammatory cytokines may induce endothelial injury, initiate coagulation and prevent fibrinolysis in patients with severe sepsis (Bonaventura *et al.*, 2021). The pro-inflammatory cytokine storm has been reported in other infections caused by pathogenic corona viruses and recently has been recognized as the leading cause of death. Due to the uniqueness of COVID-19, prognostic markers are badly required to evaluate the clinical picture for patients admitted to the hospital relevant to the infection status. By tracking the dynamic profile of the laboratory findings, retrieved from patients with COVID-19 pneumonia, hematological parameters alterations were detected in patients infected with COVID-19 (Fan *et al.*, 2020; Zhou *et al.*, 2020; Tang *et al.*, 2020; Gao *et al.*, 2020). Some COVID-19 patients displayed abnormal blood picture on admission; decreased albumin and lymphocytes, in addition to increased CRP, LDH, and erythrocyte sedimentation rate (ESR). Other hematological markers, such as bilirubin and ferritin, consistently increase proportional to the severity of the disease (Wang *et al.*, 2019; Huang C *et al.*, 2020; Yan *et al.*, 2020).

LDH is an important marker for hemolysis that indicates the severity of COVID-19 infection. Moreover, the level of LDH increases more than twofold paralleling with a hemoglobin decrease (Zhou *et al.*, 2020). Interestingly, in the non-survivors, the neutrophil count, D-dimer, blood urea, and creatinine levels resumed to increase; though, the lymphocyte counts continued to decrease extensively till death.

The risk factors indicated the importance of considering laboratory findings as important as chest imaging patterns in practice regarding the disease severity (Pan *et al.*, 2020; Wang *et al.*, 2020). For example, compared to CT scans, CRP measurements represent a more reliable tool for earlier detection. CRP is a liver produced protein which serves as an early marker of infection and inflammation (Tan *et al.*, 2020). In addition, various diseased conditions have been directly linked with the CRP concentrations (Wang 2020 and Japa 2020). In the same way, as previously documented, CRP concentrations reflect the extent of the cardiac injury, in addition to the induction of acute kidney damage. Possibly for clearance of viral infections, immune system responded more vigorously by producing various immune molecules and production of CRP (Sadeghi-Haddad-Zavareh *et al.*, 2021). CRP has been validated as an important marker that could trace the pulmonary changes (Wang *et al.*, 2020). As previously detected, as a common response of the body to invading microorganisms, inflammation induced elevated CRP levels usually activate the complement, thus enhancing phagocytosis, which facilitates clearing of microbes. A rise in CRP levels are associated with an increase in disease severity (Gong *et al.*, 2020). As an important index for the diagnosis and assessment of severe pulmonary infectious diseases (Chalmers *et al.*, 2019), CRP levels were also implemented for early diagnosis of pneumonia (Warusevitane *et al.*, 2016), with increased levels in severe pneumonia (Matsumoto *et al.*, 2019), which is not affected by various factors including age, sex and physical condition (Bilgir *et al.*, 2015). In human blood, the normal concentration of CRP is less than 10 mg. However, a significant increase of CRP could be detected on average 20 to 50 mg/L in patients with COVID-19 (Chen *et al.*, 2020; Gao *et al.*, 2020; Mo *et al.*, 2020). CRP preferably binds to phosphocholine, expressed highly on the surface of damaged cells (Sproston and Ashworth, 2018). Interestingly, 10 fold higher levels of CRP could be found in patients who died from COVID-19, compared to the recovered patients (median 100 vs 9.6mg/L). In addition, average CRP concentrations of 39.4mg/L and 18.8mg/L are associated with more severe and mild symptoms respectively. In the current study, similar observation was detected where a significant increase in CRP levels exceeding 100mg/dL could be detected in severe cases compared to mild ones (P=0.000). LDH, an enzyme in glucose metabolism, associated with the lactate conversion to pyruvate, is usually increased in cases of tissue break down. In the current study, there is a significant increase of LDH in severe cases in comparison with non-severe ones (P=0.000). In various pathophysiological processes, in lung damage associated with viral infection, LDH secretion is triggered by necrosis of the cell membrane, as identified in pneumonia induced by SARS-CoV-2 (Han *et al.*, 2020). In addition, as previously documented,

convincing evidence has been found in diseased cases linking COVID-19 disease progress to the LDH levels measured (Liu *et al.*, 2020; Huang C *et al.*, 2020; Ferrari *et al.*, 2020). Furthermore, LDH levels can be also correlated with CT scans, indicating significantly higher levels in case of severe of pneumonia (Xiong *et al.*, 2020). For example, a multi-center study involving 1099 patients reported supporting evidence correlating extent of tissue damage and inflammation with increasing levels of LDH (Guan *et al.*, 2020). Some other studies indicate that LDH, a reliable marker of hemolysis has exhibited a remarkable efficiency in severe and mild cases classification of COVID-19 patients. More interestingly, an increase of LDH levels, in two-three folds, was found in parallel with hemoglobin decrease (Zhou *et al.*, 2020). Similarly, a relevant hypoferraemia has been reported in ICU patients, usually associated to severe hypoxemia-related respiratory insufficiency (Shah *et al.*, 2020). D-dimer is usually produced resulting from the cross-linked fibrin lyses during fibrin breakdown and act as a marker indicating the fibrinolytic activity. In addition, D-dimer, a major product of activation of the coagulation cascade (Zhang *et al.*, 2018), is usually found in critical patients or patients with sepsis. However, increased D-dimer levels have been rarely reported in both SARS and CAP patients. In contrast, in patients with COVID-19, D-dimer is significantly increased which could be implemented for disease prognosis (Gao *et al.*, 2020, Zhang *et al.*, 2020). Moreover, elevated levels of D-dimer are found in non-survivors compared to survivors (Tang *et al.*, 2020). The results obtained in our current study is consistent with the results obtained in the previous studies indicating a significant correlation identified of D-dimer levels and the diseased status (P=0.003). According to some studies, the alveolar haemostatic balance is shifted towards a prevalence of prothrombotic activity under inflammatory conditions (Koyama *et al.*, 2019).

Lymphocytopenia has been remarkably found to correlate with disease severity (Ruan *et al.*, 2020, Yang *et al.*, 2020). Previous studies reported obvious existence of lymphopenia in SARS patients with prevalence of 69.6%-54%. This reported lymphopenia could be attributed to two different possibilities, either due to direct suppression of bone marrow or to stimulation of an immune mediated destruction of lymphocytes (Zhao *et al.*, 2020). SARS-CoV-2 might also cross share mechanisms to induce lymphopenia with SARS virus giving priority to cytokine mediated lymphocyte destruction (Sarzi-Puttini *et al.*, 2020; Xie and Chen, 2020). A Similar observation was found in our current study, as lymphopenia was significantly detected in severe cases (P=0.000). In the same respect, an evidence of a relationship between lymphocytopenia and disease severity was previously found (Wagner *et al.*, 2020).

Serum ferritin is an inflammatory marker, which can be used as an indicator of iron status. It could be increased significantly due to inflammation in a variety of diseases such as ARDS, atherosclerosis and systemic lupus erythematosus. Hence, the serum ferritin level is proportional to severity of symptoms in patients with COVID-19. However, on the clinical level, hyperferritinemia is not highly considered as a valuable clinical signature, even though it has been involved in complications caused by other viral diseases such as dengue fever (Ji *et al.*, 2020). In COVID-19 infection, the alveolar cavity of the lung is overburdened with serous, fibrin exudate and clear membrane, in addition to profound congestion and edema (Xu *et al.*, 2020). In addition, laboratory data show apparent lower hemoglobin level and enhanced hyperferritinemia in non-surviving patient. Interestingly, these above results are in consistence with the results obtained in our study, as elevated levels were detected in severe compared to mild infections. Moreover, of all tested parameters, ferritin ( $p=0.03$ ) only could present a remarkable significant association among COVID-19 severity, which signify the role of ferritin among other variables. Sequestration of tissue iron uniquely leads to deposition of ferritin in the epithelium and immune cells of the lungs; this finding is probably a physiological reflex action to protect lung cells from air oxygen-driven oxidative stress and pathogens (Neves *et al.*, 2019). Hyperferritinemia may directly or indirectly induce a series of serious injuries to most organs during COVID-19, such as coagulopathies, hemochromatosis-like liver injury, macrophage activation syndrome and other ferroptosis-driven syndromes (Shoenfeld, 2020). Additionally, free circulating heme and ferritin over deposition typically damage endothelial cells and may contribute to vascular wall remodeling, creating a form of diffused endotheliitis (Varga *et al.*, 2020).

## CONCLUSION

Hospitalized patients with COVID-19 were characterized by substantial biochemical parameters examination, which are linked to lung lesions and disease severity. CRP levels could precisely trace the pulmonary changes associated with the severity of COVID-19 infection. LDH, D-dimer and lymphocytopenia could clearly correlate with the degree of lung damage, prothrombotic activity and other hematological alterations of COVID-19, while the serum ferritin level is proportional to severity of symptoms. CRP, serum ferritin, and lymphocytopenia particularly dictate the severity and predict future complications of the case. Collectively, these biomarkers may aid the clinician in the detection of severity that can improve the prognosis of ambulatory COVID-19 patients. Our findings not only sort COVID-19 cases according to the degree of severity, but also forecast the prognosis of the case.

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