ARTICLE / INVESTIGACIÓN

Impact of inflammatory markers, dread diseases and cycle threshold (C_t) Values in COVID-19 progression

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Abstract: The link between the inflammatory marker and SARS-CoV-2 cycle threshold (C_t) with disease progression remains undefined, mainly in coronavirus disease-2019 (COVID-19). Therefore, this study aimed to identify several inflammatory markers (Ferritin, LDH, and D-dimer), and C_t values to predict outcomes in hospitalized COVID-19 Iraqi patients. A case study was performed on 426 patients to guess cutoff values of inflammatory markers that were detected by a real-time polymerase chain reaction (RT-PCR) and specific auto-analyzer instrument. Significantly increased levels of inflammatory markers in critical and severe patients compared with mild-moderate ($p < 0.001$). Compared with aging and disease severity, inflammatory markers and C_t values are significantly related to the aging and severity in critical and severe COVID-19 patients ($p < 0.001$). Finding the C_t value was negatively associated with Ferritin, LDH, and D-dimer ($p < 0.001$); moreover, inflammatory markers concentrations and Ct values were significantly higher during the first ten days. The Ct values correlate with some relevant clinical parameters of inflammation. Higher levels of D dimer, S. Ferritin and LDH were associated with older age and the severity of COVID-19. The area under the ROC curve indicates that serum ferritin was the highest and excellent predictor for disease severity.

Key words: Coronavirus disease 2019, Inflammation, D-dimer, Ferritin, Lactate dehydrogenase, Cycle threshold (C_t).

Introduction

Coronavirus (CoV) has been linked to outbreaks of severe disease in East Asia and the Middle East in the last two decades. SARS (severe acute respiratory syndrome) and Middle East respiratory syndrome (MERS) first appeared in 2002 and 2012, respectively[1]. In December 2019, a group of patients with unexplained pneumonia appeared in a seafood wholesale market in Wuhan, China, which was identified from a sequence-based analysis of isolates from the patients[2]. The first cases were spread more rapidly, and the epidemic has unevenly affected nearly all continents. The outbreaks of new type pneumonia add to evidence of the SARS-COV-2 (COVID-19) epidemic steadily increasing through person-to-person transmission and involving patients across all age groups and geographic areas[3,4]. One of the nations with the highest number is Iraq for cases of coronavirus disease (COVID-19)[5]. The first confirmed SARS-CoV-2 case was reported on February 24, 2020, from an Iranian student who had traveled from Iran. There has been an upsurge in instances since that time, whether imported or local[6]. COVID-19 has very important clinical manifestations, such as high rates of transmission and mild to critical clinical features, especially with more serious abnormalities found in the elderly and patients with comorbidities; however, young people without obvious underlying diseases may also have life-threatening complications, such as fulminant myocarditis and diffuse intravascular coagulopathy (DIC)[7, 8].

For patients with COVID-19, circulating inflammatory markers representing the immune system and inflammation have been considered a prognostic indicator. Assessing and analyzing several laboratory inflammatory biomarkers of PCR-positive COVID-19 patients, such as plasma D-dimer, serum ferritin, and serum LDH levels, might facilitate early aggressive treatment, thereby reducing mortality and improving hospital resource allocation. In Iraq, biomarkers also show increased D-dimer, Ferritin, LDH and another inflammatory marker in COVID-19 patients[9-11]. Therefore, the current study was conducted to guess the cutoff values of inflammatory markers (Ferritin, LDH, and D-dimer) and clarify their correlation with SARS- COV-2 C_t values and other clinical data variations and severity of the disease.

Materials and methods

Populations studied

The current study involved 426 COVID-19 patients admitted to the Al-Shifa center in Baghdad medical city from December 1, 2020, to the end of April 2021. The practical part of the study was accomplished in Baghdad National Central Public Health Laboratory (CPHL), aged between (18- >70) years old and of both sexes. Those patients included 123 cases with dread disease (83 with hematological disorder and cancer, 36 with renal failure and 4 with autoimmune disease). COVID-19 patients were grouped into mild-moderate (113), severe (231 included 43 hematological disorders and cancer and 15 renal failure) and critical (82 including 38 death cases, 38 hematological disorder and cancer, 21 renal failure and four autoimmune) according to the WHO classification severity. The physical disability of COVID-19 patients with mild-moderate symptoms, no

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evidence of hypoxia or pneumonia; moderate clinical signs of pneumonia (i.e., fever, cough, dyspnea, respiratory distress), but not severe pneumonia with medium oxygen saturation (SpO2) ≥ 90% in room air. For clinically significant signs of severe COVID-19 patients, pneumonia plus one of the following conditions: respiratory rate >30 breaths/minute, extreme breathing difficulty and SpO2 <90% in room air. Meanwhile, the critical condition of COVID-19 patients suffering from other complications such as fatal acute respiratory distress syndrome (ARDS), sepsis or septic shock, acute pulmonary embolism, acute coronary syndrome, acute stroke and delirium[12].

Laboratory tests

Nasopharyngeal (NP) or oropharyngeal (OP) swabs, together with 5 ml of blood samples, were collected from the study groups. Samples were collected from swabs directly put into viral transport media (VTM). A total of 200 µl of each (NP) or (OP) model was used for viral RNA extraction via the ExiprepTMPlus Viral DNA/RNA Kit (Bioneer, Korea). For detection of SARS-CoV-2 infection was performed on swabs samples by specific real-time, reverse transcription polymerase chain reaction (RT-PCR) according to the WHO-approved protocol published by AccuPower® SARS-COV-2 Multiplex Real-Time RT-PCR Kit, and detecting particular sequences in the E, N and RdRp genes. Blood samples were split into two tubes (Sodium Citrate tubes and Gel tubes):

The first part of the blood samples (Sodium Citrate tubes) was centrifuged for 20 minutes at 3500 rpm to obtain plasma which is used for the determination of plasma D-Dimer by using a specific automated protein analyzer (BIOSENCER STANDARD F200 analyzer) provided by (Suwonsi, Gyeonggi Co., Ltd. Korea 2020). plasma samples for all patients were applied to the instrument then the concentration of D-Dimer was automatically calculated.

The second part of the blood samples (Gel tube) was centrifuged for 10 minutes at 6000 rpm to obtain serum used to determine lactate dehydrogenase (LDH), and Ferritin. Serum concentrations of LDH were evaluated using electro-chemiluminescence immunoassay, Roche Cobas Integra 400 plus (Roche Diagnostics GmbH, Mannheim, Germany). At the same time, the Ferritin was assessed by using a miniVIDAS analyzer for the fluorescent enzymatic detection of β2-microglobulin (β2M) using the technique Enzyme Linked Fluorescent Assay (ELFA) (BioMerieux). Serum samples for all patients were applied to the instrument then the concentration of LDH and Ferritin was automatically calculated.

Statistical analysis

Using the statistical program, data were input, maintained, and evaluated, and variables were presented as mean, standard deviation, frequencies and percentages accordingly. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine if continuous variables were standard. The chi-square test was used to assess the association between categorical variables, as Fisher's exact test was used when the chi-square was inapplicable. To compare mean values of a variable/parameter across severity categories, non-parametric Kruskal-Wallis one-way ANOVA test was applied as an alternative test used when the variable did not follow the expected statistical distribution. Receiver operating characteristics curve (ROC) analysis is used to estimate the area under the curve (AUC), 95% confidence interval (CI), cutoff value, sensitivity and specificity to assess the validity of the significantly different parameters across the disease severity in the prediction of severe or critical disease. The AUC was calculated, and it is an indicator of the validity of a test; an AUC of <0.600 indicates failure of a test as a predictor, 0.600 to 0.700 is a sufficient predictor, 0.700 - 0.800 is good, 0.800 - 0.900 is very good and > 0.900-1.00 indicates excellent predictor test. The optimal cutoff point was identified using the Youden J statistic (also called the Youden Index), which records the effectiveness of a dichotomous diagnostic test. The higher index value indicates the better validity of a test Youden J statistic calculated as an alternative, J = Sensitivity + specificity – 1. The odds ratio (OR) and 95% confidence interval (CI) were determined using logistic regression analysis for two models; I (chronic disease) and II (dread disease). In this analysis, patients were distributed along with and without groups according to mean in without (≤ and > mean, respectively), and the without group was the reference category. Statistical significance was defined as the probability (p) ≤ 0.05. The analytical tool IBM SPSS Statistics 25.0 (Armonk, NY: IBM Corp.) and GraphPad Prism version 8.0.0 were used to perform these analyses.

Results

Baseline characteristics of COVID-19 infection

A total of 426 cases, with male 267(62.7%) and female 159 (37.3%) enrolled in this study. All patients diagnosed with COVID-19 using PCR technique with mild to moderate, severe and critical disease according to the WHO criteria for the classification of disease severity. The distribution of patients according to the severity of diseases it had been found that 113 (26.5 %) patients had mild-moderate disease, 231 (54.2 %) had severe, and 82 (19.3%) had the critical disease and required admission to RCU, including 38 (8.9 % inside the critically ill group) cases were with deterioration for death at admission as shown in Table 1.

The cross-tabulation of patients' age across severity of diseases revealed a statistically significant association between age and severity, younger age patients were more likely to have less severe disease than older ones, (p <0.001). Furthermore, the age of patients with critical disease appeared to be larger than those with severe and those with mild-moderate disease (p <0.001). The association between COVID-19 severity and certain comorbidities (chronic and dread disease) is shown in figure 1. We noticed that the highest prevalence of severe and critical diseases was seen among chronic disease patients (diabetic and hypertension) and dread disease (immunological, cancer, renal and liver disease) patients. Obviously, the prevalence of infection severity is increasing with some comorbidities to reach the highest significant association (p < 0.001).

The distribution of COVID-19 infections by duration from onset of disease to admission. Time from the disease's beginning to access ranged from 1 - 20 days. The first ten days of infection have a significant role (p < 0.001); we noticed that most severe and critical patients were admitted to the hospital in less than ten days from the onset of the disease, as shown in figure 2.

Biomarkers with SARS –COV-2 C_t value

The D-dimer levels, lactate dehydrogenase, and Ferritin showed significant correlations with C_t values of RT-

Age groups/year	Cases Frequency with Severity			Total
	mild-moderate	severe	Critical (dead)	
18-40	68 (60.18%)	92 (39.83%)	12 (1) (15.85%)	173
41-50	17 (15.04%)	59 (25.54%)	14 (8) (26.83%)	98
51-60	17 (15.04%)	52 (22.51%)	7 (16) (28.05%)	92
61-≥70	11 (9.74%)	28 (12.12%)	11 (13) (29.27%)	63
Total	113(26.5 %)	231(54.2 %)	44 (38) (19.3%)	426
Statistical analysis	Person Chi-Square= 45.94, df=15, p <**0.001**			

Table 1. The age breakdown of the patient population and the severity of the diseases.

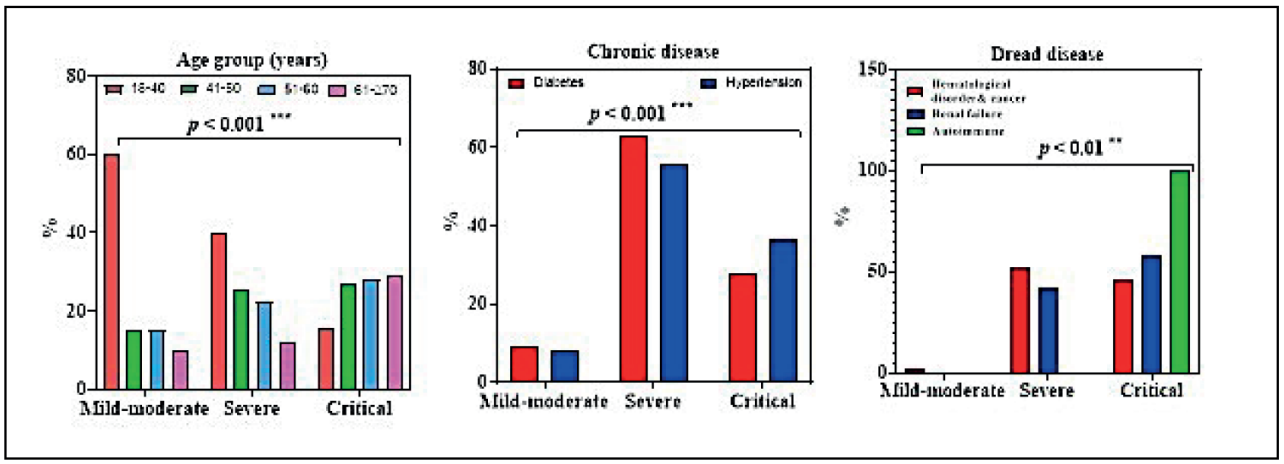

Figure 1. Frequency of severity groups (mild-moderate, severe and critical) of COVID-19 patients stratified to age groups, chronic and dread diseases. Two-tailed Chi-square test was used to compare frequencies.

PCR in COVID-19 patients (p >0.001), as shown in figure 3. Furthermore, the patient's age, severity, sex and duration of infection onset across inflammatory biomarkers (Ferritin, D-dimer and LDH) revealed an increase in the subversive biomarker values that are statistically significant (p <0.001).

Biomarkers with COVID-19 infection

Logistic regression analysis demonstrated that Biomarkers (Ferritin, D. dimer and LDH) were associated with an increased risk of developing COVID-19 whether the study was unadjusted or adjusted for chronic and dread disease. Still, these diseases do not consider an influential factor in increasing levels of biomarkers (Table 2).

To assess the validity of different inflammatory biomarkers in prediction of severity of disease, Receiver Operating Characteristics (ROC) Curve analysis was applied, which is a plot analysis for the true positive rate (sensitivity) against false positive rate (1- specificity), the area under the ROC curve (AUC) was calculated which is an indicator for the validity of a test in prediction of an outcome. As an interpretation, an AUC of less than 0.600 indicates failure of a test as a predictor, 0.600 to 0.700 is a sufficient predictor, 0.700-0.800 is good, 0.800 -0.900 outstanding and > 0.900-1.00 indicates excellent predictor test, according to these cutoff value of AUC, S. Ferritin, was excellent predictors of severe and critical disease with AUC 0.913, LDH and D-dimer were the stronger predictor with AUC of 0.871 and 0.860 respectively, (excellent predictor) (Figure 3).

Model†		OR	95% CI	p-value
Ferritin	I	1.2	1.01-1.5	**0.021**
	II	1.02	1.0-1.3	**0.036**
D. dimer	I	1.2	1.03-1.42	**0.025**
	II	1.06	1.001-1.38	**0.042**
LDH	I	1.03	1.0-1.3	**0.041**
	II	1.00	1.01-1.72	**0.022**

†: The reference category is > Mean; OR: Odds ratio; CI: Confidence interval; p: Probability (significant p-value is indicated in bold); I: chronic disease; II: dread disease.

Table 2. Logistic regression analysis of Ferritin, D. dimer and LDH in COVID-19 patients and chronic and dread disease stratified according to the mean of these biomarkers in cases without the desired condition.

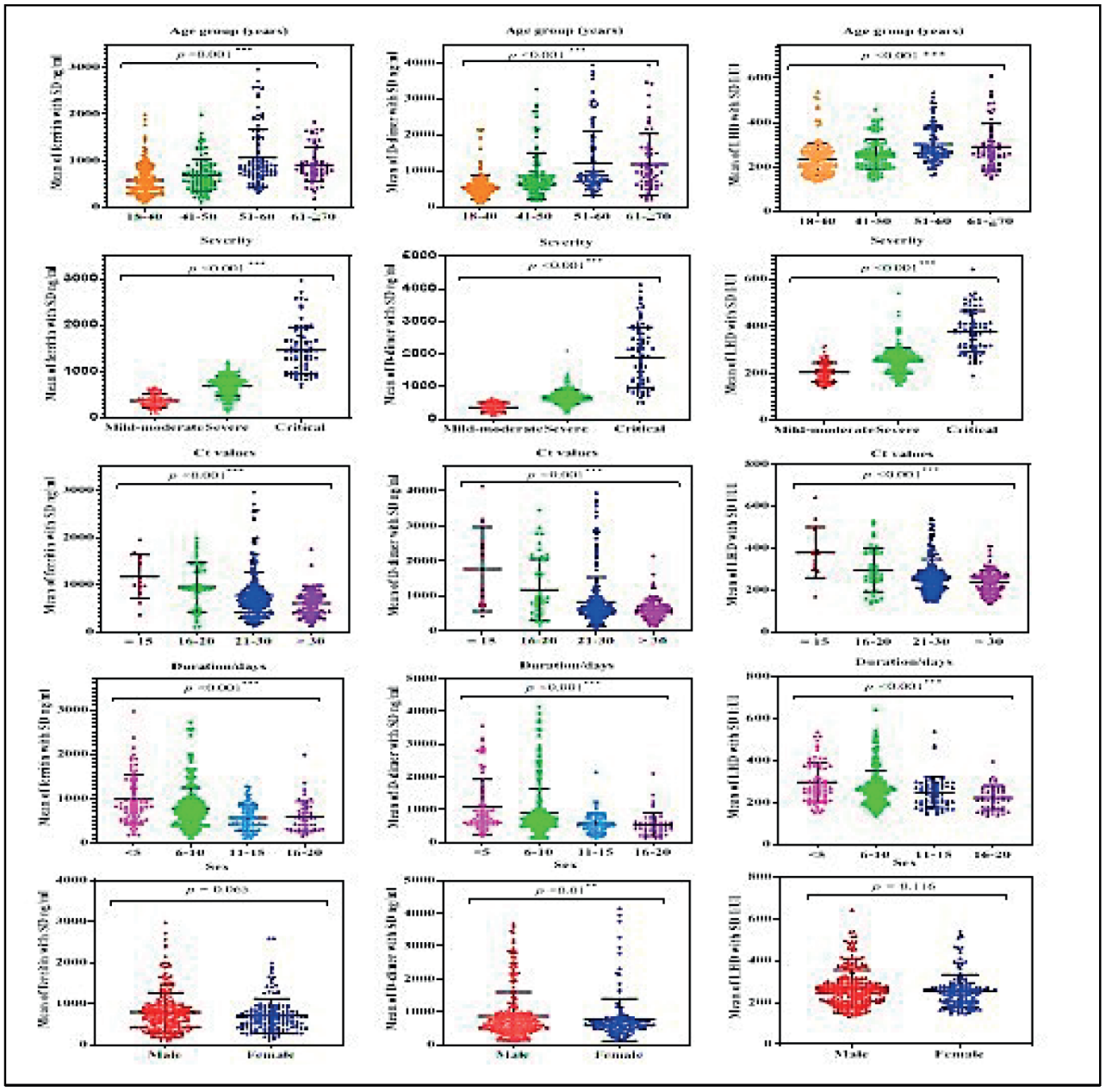

Figure 2. Scatter dot plot (ferritin, D-dimer and L-LDH) graphs of baseline characteristics of COVID–19 patients (age, severity, Ct values, sex, and duration of infection onset). Significant differences were assessed using the One-way ANOVA test (to compare between means).

Discussion

Covid-19 is a significant public health problem; with the number of cases reported daily rising exponentially, no estimate appears adequate for predicting the destruction this disease will cause in death and disability. Covid19 has a more extended incubation period, ranging from 2 to 15 days, and is more contagious than seasonal flu. Following infection, the patient may be asymptomatic or develop flu-like symptoms such as fatigue, myalgia, cough, shortness of breath, and fever[13]. However, some patients may have severe pneumonia or complications such as ARDS, myocarditis, septic shock, venous thromboembolism, and multiorgan failure. Inflammatory biomarker investigation plays an essential role in the management of COVID-19 as it helps not just in diagnosis but also in predicting the disease severity.

The current study aims to identify several inflammatory markers and cycle threshold (Ct) values that predict outcomes in hospitalized COVID-19 Iraqi patients and assess the relationship between the inflammatory markers level and cycle threshold (Ct) values with clinical categories in a diverse group of patients. We analyzed the effect of inflammatory markers and Ct value on COVID-19 disease severity and outcome among 426 COVID-19 patients who were admitted to Al-Shifa center in Baghdad medical city from December 1, 2020, to the end of April 2021. Early detection of inflammatory biomarkers of COVID-19 disease severity and death may assist in focused intervention and patient management. Among the 426 patients studied, 113 had a non-severe disease (26.5 % mild-moderate), the rest, 231 (54.2%), had a severe illness, and 82 (19.2 %) had critical including 38(8.9 %) death cases at admission. The role of gender and age were assessed in covid-19 hospitalized patients; we found that men with COVID-19 were 1.671 times higher than women (62.7 % vs. 37.3%). Elevated incidence of CO-

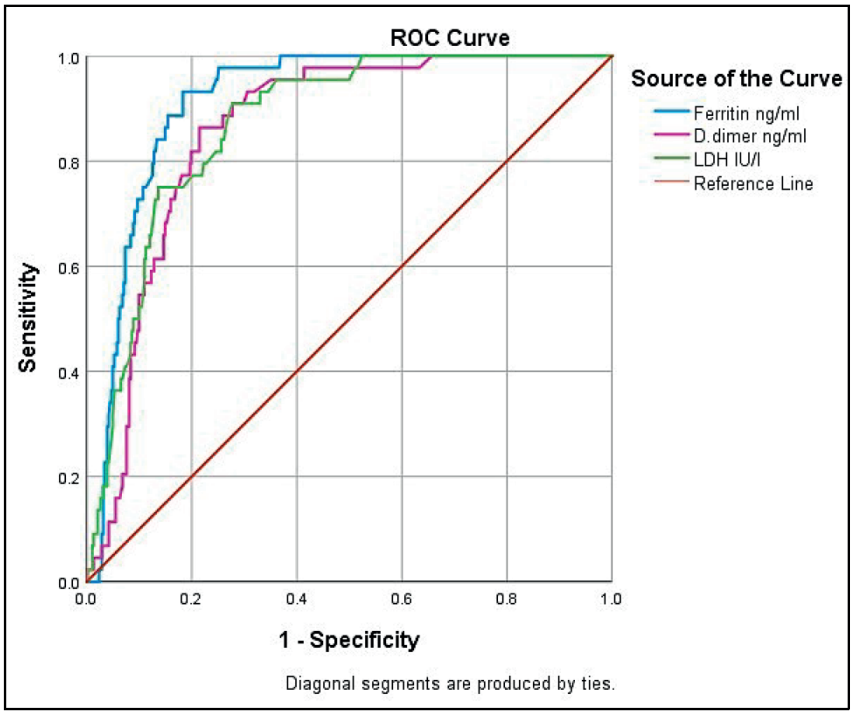

Figure 3. Receiver Operating Characteristics (ROC) curve for the validity of S. Ferritin, D. dimer and S.LDH in the prediction of severity of the disease. Ferritin: area under the curve (AUC) = 0.913; 95% confidence interval (CI) = 0.884 – 0.943; p-value < 0.001; cut–off value > 840.5 ng/ml); sensitivity = 90.9%; specificity = 78.3%. D. dimer: AUC = 0.860; 95% confidence interval (CI) = 0.817 – 0.903; p-value < 0.001; cut–off value > 736 ng/ml); sensitivity = 86.4%; specificity = 76%. S.LDH: AUC = 0.871; 95% confidence interval (CI) = 0.828 – 0.914; p-value < 0.001; cut–off value > 273.5 I/UI); sensitivity = 86.4%; specificity = 76%.

VID-19 in males as they are subjected more than females to certain risk factors, for example, higher expression of angiotensin-converting enzyme-2 (ACE 2; receptors for coronavirus) in males than females, sex-based immunological differences driven by sex hormone (sex-specific steroids) and the activity of X-linked genes, both of which modulate the innate and adaptive immune response to virus infection[14]. our results, in line with previous investigation studies, reported that men with COVID-19 infection were higher than women and reached (56%) in Italy, (52%) in Germany and Sweden, (57%) in Iran, and (51%) in Austria[15]. Differences in susceptibility and inflammation between males and females may be due to chromosomes; for example, the female X chromosome encodes several immune regulatory genes that result in reduced viral load levels. Toll-like receptor 7 (TLR7), higher in females than males, could enhance immune responses and boost the resistance to COVID-19[16].

Furthermore, gender behavior (lifestyle), i.e., higher levels of smoking and drinking among males, lead to less robust immune responses and more susceptibility to various viral infections than females[17].

On the contrary, another study by the Korean Society of Infectious Diseases in 2020 suggested that COVID-19 risk may be greater in females. These variations in COVID-19 gender incidence between studies likely have a complex explanation, including several biological, social, and economic variables[18]. Accordingly, we observed a statistically significant association between age and severity (p <0.001); the chance of acquiring severity was shown to be greater in those 50 years and older. Age is implicated to be related to the seriousness of COVID-19 and outcome in additional research conducted in China, the United States and Europe[7,19]. Similar results are also reported from studies conducted in our country[20-22]. Another study by Terpos et al. described older age and male gender as risk factors for severe disease and death in patients with COVID-19[23]. The reasons for this could be the increased possibility of a reduced immune defense mechanism and co-morbid illnesses, which make older people more susceptible to various diseases with severe progression and the worst outcome. Comorbidities such as diabetes, hypertension, and dread disease which are unequally distributed among men and women of different ages, may also impact the progression of the disease[24]. The most common comorbidities identified in COVID-19 patients at diagnosis are hypertension, Diabetes Mellitus and dread conditions (immunological, cancer, heart, renal and liver disease). In our study, we noticed that significant predictors of disease severity were seen among comorbidity patients compared to patients with no such comorbidities (p <0.001). Cheema et al. notice that SARS-COV-2 may contribute to an elevated risk of microvascular and macrovascular problems resulting from low-grade vascular inflammation (Vasculitis) in patients that suffered from diabetes mellitus[25]. Similar findings were observed in a study by Jin *et al.*, who noticed that in COVID-19 patients, Increased severity and death were correlated with older age and a significant number of comorbidities[26-28].

The inflammatory markers that are found to be significant determinants of disease outcome were Ferritin, lactate dehydrogenase (LDH) and D-dimer level. An increased level of this inflammatory biomarker indicates the body's stress as an indicator of systemic inflammation. When there is more stress, such as in severe and critical patient states, the level rises to an even higher level. As a result, this inflammatory biomarker indirectly indicates the body's stress level due to the disease's severity. Our study found COVID-19 patients with severe, critical and patients who died (inside the critically ill group) had higher levels of serum ferritin compared with mild to moderate disease; the differences were statistically significant (p <0.001). Ferritin is one of the inflammatory markers that must be present to identify hyperinflammatory syndrome (HI-S) in COVID-19 infection[29]. Systematic review and meta-analysis study done by Szarpak *et al.* and his colleague for 12 studies show a close association between ferritin levels and the state of the COVID-19 patient. Markedly increased ferritin levels were associated with a more severe patient condition, more intensive care unit exposure, and higher mortality[30]. Also, similar findings from studies conducted showed that COVID-19 association hyperinflammatory criteria (ferritin levels

>1500 µg/L) upon admission was linked to a higher fatality rate[29]. Indeed, serum ferritin is affected by hepcidin upregulation, which is stimulated by proinflammatory cytokines, particularly IL-6[31]. Ferritin is highly relevant because it is a mediator of immune dysregulation; it has been proposed that under extreme hyperferritinemia, Ferritin generates direct immunosuppressive and proinflammatory impacts, contributing to the cytokine storm shown in COVID patients 19[32]. Because hyperferritinemia causes regular cell death (RCD), iron oxides interact with serum coagulation cascade proteins. Coagulation disorders are relatively frequently encountered among COVID-19 patients, especially those with the severe disease[33]. The virus may also assault and destroy the hemoglobin, releasing iron from porphyrins and discharging it into the circulatory system, leading to iron overload[34]. furthermore, the activity of the SARS-CoV helicases for viral replication generally requires ATP hydrolysis, which involves the presence of iron. Iron overload complicates the prognosis of HBV and HCV viral infections, and iron supplementation increases mortality in HIV patients. SARS-CoV-2 most likely requires iron for viral RNA replication and function[31]. It's important to note that SARS-CoV-2 is thought to infect macrophages. As a result, elevated iron accumulation in macrophages is expected to boost viral replication. Viruses can also modify other iron-related proteins to speed up their reproduction and spread. Homeostatic iron regulator protein (HFE), a competition of TfR1 for binding to transferrin, is destroyed following binding by US2 protein in the context of human cytomegalovirus (HCMV) infection, resulting in cellular iron overload. The combination between Nef protein and HFE causes cellular iron overload in HIV-1-infected macrophages. TfR1 is also used as a receptor by various viruses during their invasion[35]. When there is a systemic iron overload, there is a higher in cellular oxidative stress, mitochondria dysfunction, cytokine release, a significant decline in cellular oxygen consumption, lipid peroxidation, and a change from aerobic (pyruvate) to anaerobic (lactate) metabolism via lactic dehydrogenase (LDH). This enzyme is stimulated in COVID-19[36]. D-dimer and LDH levels in our findings showed a significant rise across disease severity, with the highest level in critical and severe patients compared with mid-moderate ($p < 0.001$). Elevated D-dimer parameters in severe and critical COVID-19 patients have been linked to coagulation activation, dysregulated thrombin generation, impaired natural anticoagulants, and fibrinolysis[37]. Also, several critically ill patients have been reported to develop coagulopathy, antiphospholipid antibodies, and increased arterial and venous thrombotic events such as cerebral infarction[38]. More than 1,800 COVID-19 individuals were studied by Paliogiannis *et al.* line with our results, who found that plasma D-dimer concentrations in those with severe forms of the disease were significantly higher than those in patients with milder forms[39]. LDH is present in lung tissue and is one of the parts mainly affected by COVID-19, so elevated levels of LDH may result from lung tissue degradation. Our findings concur with previous research, which showed high levels of LDH were common in COVID-19 patients in the ICU and indicated a poor outcome[38].

Regarding SARS –CON-2 RNA cycle threshold values (C_T values), we found the lower C_T value was significantly correlated with disease severity and higher inflammatory marker. Among hospitalized patients, those with C_t values <25 had a higher level of Ferritin LDH, D-dimer and higher risk disease severity and mortality rate than patients with C_t values >30. Worsening inflammation demonstrates that a lower C_t value (higher viral RNA concentration) is associated with excessive inflammation, which is highly likely to be a key factor contributing to the induction of cytokine storms and disease progression. This may indicate that the nasopharyngeal or oropharyngeal SARS-CoV-2 lower C_t value directly impacts organ function. Our results are consistent with earlier research that reported the correlation between C_t value and markers of inflammation[32, 40]. In a study conducted by Zheng *et al.*, similar outcomes were seen. Chen *et al.* in their studies reported that low C_t value in samples from the upper respiratory tract in patients with the highly aggressive disease compared to those with mild illness and C_t value associated with an elevated risk of mortality; also, these studies reported the higher lactate dehydrogenase (LDH) is imported marker correlated with lower C_t values[40-42]. Liu *et al.* noticed that Ct values of severe patients with COVID-19 were statically lower compared to mild patients at admission, and the mean viral load of severe patients was 60 times that of mild patients 35. Regarding the duration (time) course of the variation in inflammatory biomarkers, in our results, the first days of infection have a significant role ($p < 0.001$) recorded in severity cases during the first 10 days; we noticed that most of the severe and critical patients were admitted to the hospital in less than ten days from the onset of disease (figure 2). We observed a gradual increase in Ferritin, D-dimer and LDH concentration during the first 10 days of the disease. This result is comparable with previous studies that reported a mean time from symptom onset to hospitalization of 2.62 days in Singapore, 4.41 days in Hong Kong and 5.14 days in the UK[43]. Other studies report means values of time to hospitalization ranging from 5 to 9.7 days[44,45].

Additionally, in the current study, there is no significant differences in serum ferritin and serum LDH ($p = 0.064$) and $p = 0.116$), respectively, between male and female, also D. dimer levels in men were significantly higher than in women (figure 2). Our results disagree with previous studies; for example, a study in Italy reported that serum ferritin and LDH in males are higher than in females[46]. This may be because COVID-19 appears to be determined by the combination of numerous genetic and demographic heterogeneity of the subjects and sex-depending factors. The X chromosome contains approximately 1,200 genes; these genes' differential expression may be partly responsible for the differences in coagulopathy and inflammatory response between males and females[47]. Serum ferritin, LDH, and D-dimer levels were positively correlated with the severity of COVID-19 in both sexes. According to our findings, the area under the ROC curve of serum Ferritin was the highest, with high sensitivity and specificity with AUC of 0.913, followed by the AUC of serum LDH and plasma D. dimer (AUC of 0.871 and 0.860, respectively). The ROC curve analysis confirmed that serum ferritin has excellent prognostic accuracy in males and females with severe clinical conditions (AUC 0.913).

Conclusions

COVID-19 is a widespread systemic infection that substantially impacts the body's immune system. Increased inflammatory biomarkers are a typical side effect of disease with COVID-19. SARS-COV-2 RNA CT value correlates with inflammation marker; it is also essential to consider

viral dynamics; as a result, a more exact assessment of transmissibility would include combining the CT value with the time of evolution (or time since contact in asymptomatic people) clinical course, disease severity, and immunosuppression. Ferritin was the best predictor of mortality, followed by LDH and D. dimer. These parameters should be carefully analyzed at the outset of the study to assist doctors in evaluating primitive risks, and moreover, nearby monitoring can probably reduce mortality. As a result, it is critical to continue conducting virological and immunological studies on this new coronavirus to fully understand the molecular process of viral replication and identify potential markers of disease progression and targets of therapeutic drugs that will allow COVID19 control.

Author Contributions

Thaer A. Abdul Hussein: Designing the experiment, collecting samples with clinical data, analyzing samples, and writing the manuscript. Hula Y. Fadhil: Designing the experiment, supervision, statistical analysis, writing-reviewing, and revision of the manuscript.

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Institutional Review Board Statement

The Ethics Committee of the Iraqi Ministry of Health and Environment and Department of Biology (College of Science, University of Baghdad) (Ref: CSEC/1120/0050) approved the study protocol and written consent was obtained from all participants for collection of blood along with nasopharyngeal swabs.

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Conflicts of Interest

The authors declare that there were no conflicts of interest.

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