EVALUATION OF THE ROLE OF D-DIMER, FERRITIN PARAMETERS IN THE PROGNOSIS OF COVID-19 PATIENTS

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ABSTRACT

Background: COVID-19 has spread worldwide from December 2019 to the present. Many biological markers have been used to predict poor outcomes, contributing to early detection and improving patient management.

Objective: To evaluate the role of D-dimer and Ferritin parameters in predicting the severity of COVID-19 patients.

Methods: Cross-sectional descriptive design combined with a prospective study on 293 patients with positive RT-PCR results for SARS-CoV-2 at Military Hospital 7A; Demographic characteristics, vaccination history, underlying disease, and laboratory parameters including D-dimer and ferritin were collected. Patients were divided into two groups based on disease severity: mild group (n=208), and severe group (n=85).

Results: The median age of the study population was 49 (34-62), with 50.9% were male patients. The severe COVID-19 group had significantly higher ferritin and d-dimer levels compared to the mild COVID-19 group. ROC curve analysis, serum Ferritin concentration ≥ 602.5 Microg/L predicted severe COVID-19 with a sensitivity of 68.2% and specificity of 90.9%.

Conclusion: Early Ferritin analysis in COVID-19 patients could effectively predict the severity of the disease.

Keywords: COVID-19, SARS-CoV2, D-dimer, Ferritin

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1. Introduction

Coronavirus Disease 2019 (COVID-19) is a dangerous infectious disease caused by Coronavirus-2 (SARS-CoV-2) that first appeared in Wuhan, China, quickly spreading worldwide, infecting hundreds of millions of people, and causing millions of deaths. Many biochemical indices have been investigated in studies to better understand the pathogenesis mechanism and assess the predictive role of disease severity. This leads to the development of better monitoring, treatment, and management protocols for COVID-19 patients.

Ferritin is an iron-storing protein in the body that has been demonstrated to play a crucial role in immune regulation and the pathogenesis mechanisms of inflammatory and autoimmune diseases. A study conducted on 5700 COVID-19 patients in the United States showed that elevated ferritin levels could predict impending inflammation reactions in COVID-19 or be related to viral spread in the body and affect iron metabolism processes[1]

Another study in Brazil involving 97 patients showed that Ferritin levels at a threshold of 1873 ng/ml had predictive value for mortality in hospitals with a sensitivity of 68.4% and specificity of 79.3%[2].

D-dimer is a good indicator of blood coagulation activation and fibrinolysis. Research by Berger et al. showed that COVID-19 patients with abnormal D-dimer tests were associated with an increased risk of progressing to severe COVID-19, acute kidney injury, thrombosis, and death[3].

We conducted this study to evaluate the roles of D-dimer and ferritin in predicting the severity of COVID-19 patients.

2. Subjects and methods

2.1. Study subjects: Patients aged 15 and above hospitalized at Military Hospital 7A who were prescribed D-dimer and ferritin blood tests from July 2021 to March 2022.

Inclusion criteria:

- Patients aged 15 and above who meet all of the following criteria:

- Diagnosed with COVID-19 by RT-PCR method for SARS-CoV-2.

- Patients prescribed to undergo D-dimer and/or ferritin testing.

- Consent to participate in the study (prospective).

Exclusion criteria:

- Presence of other infections.

- Previous use of anticoagulant drugs and/or history of deep vein thrombosis and/or pulmonary embolism.

2.2. Research method

Study design: Cross-sectional description combined with a prospective study.

Sampling technique: All patients meet the specified criteria within the study period.

Measurement technique: Ferritin testing was performed on the Beckman Coulter DxC700AU analyzer using reagents from Beckman Coulter. D-dimer testing was conducted on the Sysmex CA-660 analyzer using reagents from Siemens.

2.3. Study variables

- Demographic characteristics: age, gender, history of COVID-19 vaccination, underlying disease.

- Results of ferritin and d-dimer tests.

- COVID-19 subgrouping into two groups based on Ministry of Health guidelines:

• Mild COVID-19 group: when patients have all three of the following factors:

+ Patients have no clinical symptoms or nonspecific symptoms such as fever, dry cough, sore throat, stuffy nose, fatigue, headache, muscle aches, loss of taste, smell, diarrhea…

+ Respiratory rate < 20 breaths/ minute, SpO2 > 96% on room air.

+ Normal chest X-ray or minimal lung involvement.

• Severe COVID-19 group: when patients have the following factors:

+ Signs of pneumonia with dyspnea, rapid breathing ≥20 breaths/ minute and/or SpO2 ≤ 96% on room air.

+ Chest X-ray showing features of pneumonia.

2.4. Data entry and analysis

Data entry and analysis were performed using SPSS 22 software. A comparison of proportions of categorical variables and COVID-19 severity was conducted using the chi-square test or Fisher's Exact test. Comparison of means for two quantitative variables with normal distribution was done using an independent sample t-test, or Mann-Whitney U test for variables without normal distribution. Multivariable regression analysis to identify predictive factors influencing the severity of COVID-19. ROC curve analysis was used to find predictive threshold values affecting the severity of COVID-19, as well as sensitivity and specificity.

2.5. Ethics

The study was approved by the Ethics Committee in Biomedical Research Military Hospital 7A, No. 21/HĐĐĐ-BVQY7A on January 29, 2022.

3. Results

During the study period, we

enrolled 293 COVID-19 patients who met the inclusion criteria. Among them, 85 patients had severe COVID-19, accounting for 29.01% of the total (Chart 1).

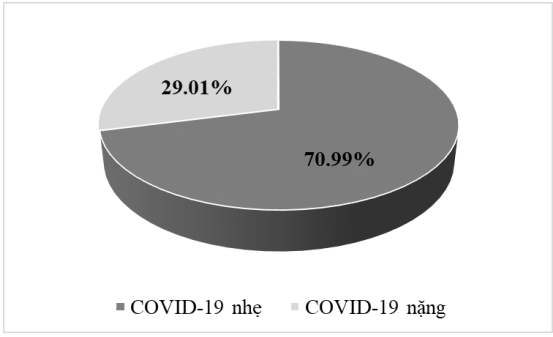


Chart 1: Distribution of COVID-19

Table 1: Demographic characteristics including age, gender, and history of COVID-19 vaccination

Characteristics	Study Population
Gender - Male (%)	50.9
Median age (Interquartile range - IQR)	49 (34-62)
Not vaccinated n (%)	56 (19.1)
1 injection n (%)	45 (15.4)
2 injections n (%)	171 (58.4)
3 injections n (%)	21 (7.2)

The gender ratio in the study was roughly equivalent, with a median age (IQR) of 49 (34-62). Among them, 19.1% of patients have not been vaccinated against COVID-19, and 65.6% of patients were fully vaccinated with two doses of vaccine.

Table 2: Characteristics of underlying disease

Underlying disease	Study population n (%)
Hypertension	99 (33.8)
Diabetes	62 (21.2)
Coronary Artery Disease	22 (7.5)
Heart Failure	20 (6.8)
Chronic Kidney Disease	20 (6.8)
Stroke	10 (3.4)
Chronic hepatitis	5 (1.7)
COPD	4 (1.4)
Cancer	3 (1.0)
Cirrhosis	2 (0.7)
Systemic Disease	1 (0.3)

The study recorded 121/293 patients having at least one underlying disease. Among them, hypertension, diabetes mellitus, coronary artery disease, and heart failure were the most common underlying diseases (Table 2).

The severe COVID-19 group had a significantly higher D-dimer test result of 1.547 (0.77–4.07) compared to the mild COVID-19 group's result of 0.36 (0.249-0.512) with $p<0.001$ (Table 3).

The severe COVID-19 group had a ferritin test result of 669 (493-692), significantly higher than the mild COVID-19 group's result of 225 (68-450) with $p<0.001$ (Table 4).

Table 3: Characteristics of D-dimer testing in the severe and mild COVID-19 groups (n=293)

Test	n=293 Median (IQR)	Group COVID-19 Median		p
		Mild (n1=208	*Severity (n2=85)*	
D-dimer *(ng/L)*	0.419 (0.300-1.081)	0.360 (0.249-0.512)	1.547 (0.770-4.070)	<0.001

Table 4: Characteristics of ferritin testing in the severe and mild COVID-19 groups (n=242)

Test	n=242 Median (IQR)	Group COVID-19 Median		p
		Mild	*Severity*	
Ferritin (Microg/L)	333 (127-610)	225 (68-450)	669 (493-692)	<0,001

4. Discussion

The gender ratio was equivalent in the study population. However, when analyzed within the severe COVID-19 group, males predominated (50/85 cases of severe COVID-19, accounting for 58.8%). Our results were consistent with many studies regarding gender disparities in severe illness and mortality. Research by author Petrilli CM in 5279 COVID-19 cases in New York City, USA, males were associated with a risk of hospitalization OR 2.8 95% CI (2.4-3.2), the risk of disease severe OR 1.5 (1.3-1.8), risk of death OR 1.3 (1.1-1.5)[1].

The median age of the study population was 49, with an IQR of 34-62, the oldest being 91 and the youngest 15. Our study population was younger compared to the study populations of authors Richardson and Nanshan (49 versus 63 and 55, respectively). Older age was associated with higher mortality rates. In the United States, 80% of deaths occurred in individuals aged 65 and older[4].

Our study found that only 65.6% of patients were fully vaccinated with two doses of COVID-19 vaccine. The low vaccination rate in the study population was due to the timing of the study, conducted from July 2021 to March 2022, when vaccines were just beginning to be widely deployed in the community in Vietnam.

Regarding the underlying disease characteristics: 121 patients had at least one underlying disease in the study. The majority had a history of hypertension (33.8%), type II diabetes mellitus (21.8%), coronary artery disease (7.5%), heart failure (6.8%), chronic kidney disease (6.8%), and prior stroke (3.4%). Our

study had a lower underlying disease rate compared to Richardson's study on hypertension (56.6%) and diabetes (33.8%), and was similar to Nanshan's study on cardiovascular disease (40%), chronic kidney disease (13%), and neurological disorders (1%)[3].

Although COVID-19 can affect any individual, having multiple comorbidities is a risk factor for severe illness. Many studies have shown that most severe cases have at least one underlying disease. A study in Italy found that among 355 deceased cases, the number of underlying diseases was 2.7, and only three patients had no underlying conditions.

In our study, we observed that patients with severe COVID-19 had higher levels of D-dimer compared to those with mild COVID-19, which was consistent with the findings of many other studies. Several scientists have demonstrated that coagulation disorders in COVID-19 patients silently drive disease progression to severe stages and lead to death. Deaths from COVID-19 were related mostly to hypercoagulability and increased risk of venous thromboembolism (VTE), leading to thrombotic inflammation.

Some studies have indicated that COVID-19 can cause thrombosis in both arteries and veins, with a pulmonary embolism (PE) rate of up to 25%. Disease phases such as cytokine storm, disseminated intravascular coagulation (DIC), immobilization, and secondary hypoxia due to excessive lung damage in COVID-19 can also lead to VTE.

Therefore, coagulation biomarkers such as D-dimer can indicate the severity of the disease, helping to classify and predict patients, and thereby determining appropriate treatment and monitoring methods. A general report of 100 studies by Seshadri showed that elevated D-dimer levels were associated with disease severity and thrombosis in COVID-19. D-dimer levels typically increased in the early stages of the disease, while other screening tests such as platelet count and prothrombin time were usually normal during this period.

The VTE screening activation threshold in COVID-19 patients was when D-dimer levels exceeded the 3-fold upper limit threshold. An increase of more than four times the normal value was considered a good predictor of mortality[5]. However, it is important to note that D-dimer levels increase with age and can also increase physiologically, such as during pregnancy or in certain other conditions like cancer, surgery, or other infections.

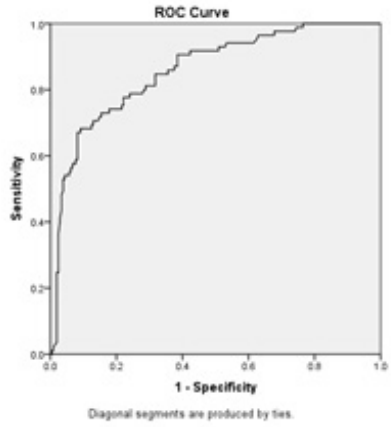
Elevated serum ferritin levels were associated with severe COVID-19 in our study, consistent with the findings of Cheng's study[6]. Ferritin levels increase in the serum during viral infections and may be a sign of viral replication. In the cytokine storm of COVID-19,

many proinflammatory cytokines were rapidly produced, including IL-6, TNF-α, IL-1β, IL-12, and IFN-γ, which stimulated hepatocytes, Kupffer cells, and macrophages to release ferritin

Additionally, ferritin was not only a consequence of excessive inflammation but also played a pathogenic role by binding to T-cell immune globulin and TIM-2, promoting the expression of proinflammatory mediators. Furthermore, some studies have shown that ferritin-activated macrophages secrete cytokines. Another aspect to consider was the role of iron, which was essential for viral replication and other processes including mitochondrial activity, ATP synthesis, RNA synthesis, and repair. For example, the RNA unwinding activity of SARS-CoV-2 during replication required ATP hydrolysis, for which iron was necessary.

Zhou et al. suggested that increased serum ferritin levels were associated with worse outcomes in COVID-19. Serum ferritin levels above 500 ng/mL predict mortality up to 58%[7]. Li et al. found that serum ferritin eventually returned to normal values compared to other inflammatory markers such as CRP[8], which may limit the effectiveness of using ferritin in assessing the risk of adverse outcomes.

ROC curve analysis revealed that a Ferritin value ≥ 602.5 Microg/L best predicts the severity of COVID-19 with sensitivity of 68.2% and specificity of 90.9%. Area under the curve (AUC) was 0.859, p<0.001; 95% CI = 0.812 – 0.906.



5. Conclusion

Elevated ferritin and D-dimer levels were associated with severe COVID-19. Specifically, ferritin ≥ 602 microg/L could effectively predict the severity of the disease with a sensitivity and specificity of 68.2%, 90.9%; AUC 0.859.

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