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Research Article

Enhanced Diagnostic Accuracy In COVID-19 Through Ferritin, D-Dimer, And Interferon-Induced Transmembrane Protein 3 (Rs12252) Analysis.

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Abstract

Background of the study: COVID-19, caused by the SARS-CoV-2 virus, has emerged as a global health crisis with significant morbidity and mortality. Identifying reliable biomarkers for the diagnosis and evaluation of disease severity is crucial. Ferritin and D-Dimer have shown potential as diagnostic markers, and genetic variations like interferon-induced transmembrane protein 3 (IFITM3-rs12252) could further enhance diagnostic accuracy. Understanding the role of these biomarkers could improve patient management and outcomes.
This study aimed to evaluate the diagnostic potential of Ferritin, D-Dimer, and IFITM3 (rs12252) levels in COVID-19 patients compared to controls, thereby enhancing the identification and assessment of disease severity.
Methods: A case-control study was conducted, involving 300 COVID-19 patients and 100 age- and sex-matched controls. Ferritin, D-Dimer, and IFITM3 (rs12252) levels were measured. Statistical analyses, including Ordinal Logistic Regression and ROC curves, were used to evaluate the diagnostic potential of these biomarkers.
The study was conducted as collaboration between teams from private and governmental hospitals in KSA as shown in affiliations of authors in a period from December 2023 to October 2024
Results: The study revealed significant diagnostic implications of Ferritin, D-Dimer, and IFITM3 (rs12252) in COVID-19 patients. Ferritin levels were notably higher in patients compared to controls, with a high sensitivity and specificity (94.9%, 97.03% at >42 mg/L). D-Dimer also demonstrated significant differences, though with lower sensitivity and specificity (71.34%, 62.38% at >150 mg/L). Crucially, combining Ferritin and D-Dimer with IFITM3 markedly enhanced the diagnostic accuracy, raising the AUC from 0.985 and 0.766 to 0.992 (P <0.001, 95% C.I = 0.981 – 1.000). These findings underscore the robust potential of these biomarkers in effectively diagnosing and evaluating COVID-19 severity.
Conclusion: Our study indicates that Ferritin, D-Dimer, and IFITM3 (rs12252) are potent biomarkers for COVID-19 diagnosis and severity assessment. Elevated Ferritin levels and D-Dimer, combined with IFITM3, significantly improve diagnostic accuracy. These findings support the use of these biomarkers in clinical settings for reliable and accurate identification and evaluation of COVID-19 severity, thus facilitating better patient management and treatment strategies.

Keywords : D-dimer, Ferritin, IFITM3 (rs12252), COVID-19, SARS-CoV2, interferon-induced transmembrane protein 3.

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INTRODUCTION

The unprecedented global impact of the COVID-19 pandemic has illuminated critical gaps in our diagnostic and prognostic capabilities. As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to exert significant morbidity and mortality worldwide, there exists a compelling necessity for sensitive and specific diagnostic tools not only to identify infected individuals but also to stratify disease severity and predict the need for intensive care unit (ICU) admission (Li et al., 2020; Sethuraman et al., 2020). Early and accurate detection of patients at risk of severe outcomes is paramount to optimizing clinical management and allocating healthcare resources effectively (Hachim et al., 2020).

Current diagnostic parameters, including nucleic acid amplification tests, confirm infection but offer limited prognostic information regarding disease progression (Butler-Laporte et al., 2021). Consequently, attention has turned to identifying biomarkers that can reliably predict disease severity and outcomes. Among these, D-dimer, C-reactive protein (CRP), and serum ferritin have emerged as potential predictive parameters due to their association with the pathophysiological processes of COVID-19 (Abdullah & Ali, 2022).

D-dimer, a fibrin degradation product, is indicative of thrombin generation and fibrinolysis (Lippi et al., 2023). Elevated D-dimer levels have been consistently observed in patients with severe COVID-19 and are associated with an increased risk of thrombotic events, including venous thromboembolism and disseminated intravascular coagulation (Park et al., 2024). The hypercoagulable state induced by SARS-CoV-2 infection underscores the utility of D-dimer as a marker for disease severity and prognosis (Jorjafki et al., 2024).

CRP, an acute-phase reactant synthesized by hepatocytes in response to interleukin-6 and other pro-inflammatory cytokines, reflects systemic inflammation (Agrawal & Wu, 2024). Elevated CRP levels correlate with increased disease severity (Ehler et al., 2024), pulmonary involvement (Folorunso et al., 2024), and adverse outcomes in COVID-19 patients (Sadeghi Mofrad et al., 2024). As a readily available laboratory parameter, CRP serves as a useful but non-specific indicator of the inflammatory response elicited by the infection (Chrostek et al., 2024).

Serum ferritin, an iron storage protein, functions as both an acute-phase reactant and an immunomodulatory molecule (Alsanory et al., 2024). Hyperferritinemia in COVID-19 patients is indicative of a hyperinflammatory state, often referred to as a “cytokine storm,” which is characterized by excessive cytokine release leading to multiorgan failure and mortality (EL-Molla et al., 2024). Elevated ferritin levels have been associated with severe clinical manifestations and poor prognosis (Kadhim et al., 2024).

Despite the prognostic value of D-dimer, CRP, and serum ferritin, these biomarkers individually lack sufficient specificity and sensitivity to serve as definitive predictive tools (Abdel-Ghany et al., 2024; Hanafi et al., 2024). Their levels can be influenced by a myriad of factors, including comorbid conditions such as malignancy, cardiovascular disease, and other inflammatory or infectious processes (Abdel-Ghany et al., 2024). This lack of specificity limits their utility in accurately identifying patients who will progress to severe disease or require ICU admission.

To enhance diagnostic accuracy, there is a growing interest in exploring genetic factors that may influence individual susceptibility to SARS-CoV-2 infection and disease severity. The interferon-induced transmembrane protein 3 (IFITM3) gene has gained attention due to its critical role in the innate immune response against viral infections (Xie et al., 2024). IFITM3 restricts the entry and replication of a broad range of viruses by altering cellular membranes and impeding viral fusion (Ren, Wang, et al., 2024).

The rs12252 single nucleotide polymorphism (SNP) within the IFITM3 gene results in a truncated form of the protein (Ren, Lin, et al., 2024), potentially diminishing its antiviral efficacy (Ren, Lin, et al., 2024). Studies have identified an association between the IFITM3 rs12252-C variant and increased susceptibility to severe influenza infection (Zakaria et al., 2024). Recent investigations suggest a similar relationship may exist between IFITM3 rs12252-G variant polymorphism and COVID-19 severity (Abdelaziz et al., 2024; Elessawy et al., 2024), proposing that individuals harboring the variant allele might be predisposed to more severe disease outcomes due to compromised antiviral defenses.Integrating IFITM3 rs12252 genotyping into diagnostic protocols offers a promising avenue for improving risk stratification in COVID-19 patients. As a stand-alone test, IFITM3 rs12252 genotyping could identify individuals at heightened risk for severe infection, warranting closer clinical monitoring and early intervention (Riabokon et al., 2024). Furthermore, combining genetic analysis with established biomarkers like D-dimer, CRP, and serum ferritin may enhance predictive accuracy (Kotsev et al., 2021). This multimodal approach acknowledges the multifactorial nature of COVID-19 pathogenesis, encompassing both host genetic factors and physiological responses to infection.

The potential of IFITM3 rs12252 polymorphism as a predictive marker is particularly significant given the limited specificity of current biomarkers. Genetic testing is inherently unaffected by external variables that influence protein expression levels, providing a stable and reliable indicator of susceptibility (Alghamdi et al., 2021). In populations with a higher prevalence of the variant allele, such as certain ethnic groups, the incorporation of IFITM3 genotyping could substantially impact clinical outcomes through personalized medicine (Nikoloudis et al., 2020).

METHODS

Study design

The aim of the current study was to assess the association between IFITM3 gene polymorphism (rs12252 variant), ferritin levels, D-dimer, and lactate dehydrogenase (LDH) on the risk of COVID-19 infection, its severity, and outcomes among the studied population. These parameters are critical in diagnosing and measuring COVID-19 severity, providing valuable insights into the disease's progression and patient prognosis.

Subjects

This study involved a total of 400 participants, comprising 300 COVID-19 patients confirmed positive via RT-PCR and 100 healthy controls confirmed negative for SARS-CoV-2. Eligible subjects were adults aged 18 years or older. Newly diagnosed SARS-CoV-2 patients were included before any treatment commenced to eliminate confounding factors that therapies might introduce to biochemical marker levels. Control subjects were verified negative for SARS-CoV-2 via RT-PCR to establish a clear baseline for comparison. Exclusion criteria encompassed individuals under 18 years of age, those with negative RT-PCR results, and patients suffering from other acute illnesses, ensuring the study's focus remained on COVID-19 infection and its specific impacts on D-dimer, LDH, serum ferritin levels, and IFITM3 gene polymorphism.

Procedures

All participants, both cases and controls, underwent comprehensive assessments including detailed history taking, thorough clinical examinations, chest x-rays, and abdominal ultrasounds to evaluate organ involvement and detect any complications associated with COVID-19. Diagnosis of SARS-CoV-2 infection was confirmed through RT-PCR testing, with positive results identifying patients and negative results designating the healthy control group.

Patients were categorized into mild, moderate, and severe subgroups based on clinical findings, following the classification criteria outlined in the COVID-19 Clinical Management Living Guidance (World Health Organization, 2021). This stratification allowed for the correlation of biochemical markers and genetic variations with disease severity.

Laboratory investigations were meticulously performed, with a specific emphasis on:

- D-Dimer Test: Elevated D-dimer levels are indicative of coagulation abnormalities and have been associated with an increased risk of thrombosis in COVID-19 patients.
- Lactate Dehydrogenase (LDH): LDH is an enzyme released during tissue damage. Increased LDH levels in COVID-19 patients correlate with cellular injury and are often associated with more severe disease presentations.
- Serum Ferritin: As an acute-phase reactant, serum ferritin levels rise in response to systemic inflammation. Elevated ferritin levels in COVID-19 patients have been linked to hyperinflammatory states and cytokine storms, which are critical factors in disease severity and mortality.

In addition to these parameters, a complete blood count (CBC) and C-reactive protein (CRP) levels were assessed to provide a comprehensive picture of each patient's inflammatory status.

IFITM3 Gene Polymorphism Analysis

The study highlighted the analysis of the IFITM3 (Interferon-Induced Transmembrane Protein 3) gene polymorphism, specifically the rs12252 variant. IFITM3 plays a significant role in the innate immune response against viral infections, including SARS-CoV-2. Variations in this gene may affect the protein's ability to restrict viral entry and replication within host cells.

Statistical analysis

Data analysis was conducted using IBM SPSS software version 22.0. Various statistical tests were employed, including Chi-square, Fisher Exact, Kolmogorov-Smirnov, Shapiro-Wilk, one-way ANOVA, Mann-Whitney, and Kruskal-Wallis. Qualitative data were presented as numbers and percentages, while quantitative data were described using means, standard deviations, or medians and interquartile ranges (IQRs). The significance level for assessing the results was set at $P < 0.05$. Additional analyses included Hardy-Weinberg equilibrium testing for population genetics and logistic regression for calculating odds ratios and confidence intervals.

RESULTS

Demography and group characteristics of the study

This study included 300 COVID-19 patients confirmed by RT-PCR for SARS-COV-2 and 100 age- and sex-matched control subjects confirmed negative for COVID-19. There was no significant difference between the case and control group regarding age and sex. However, the two groups showed significant differences regarding the hematological parameters (**Table 1**)

Table 1. Comparison between the different studied groups according to demographic data and hematological indices.

	DISEASE SEVERITY			CONTROL	TEST OF SIG. (P)
	Mild	Moderate	Severe		
MALE	(40%)	(20%)	(40%)	(60%)	χ2=2.588
FEMALE	(50%)	(20%)	(30%)	(40%)	p=0.460
AGE (YEARS)					
MEAN ± SD.	41.5 ± 13.9	49.2 ± 16.4	52.4 ± 14.9	46.1 ± 14.5	H=17.012
MEDIAN (MIN. – MAX.)	45.5 (34 – 61)	47.5 (17 – 80)	58# (38 – 77)	42 (20 – 70)	p=0.051
P0	0.052	0.082	0.098		
HB (G/DL)					
MEAN ± SD.	12.3# ± 1.6	12.8 ± 1.8	12# ± 2	13.3 ± 1.7	F=6.290*
MEDIAN (MIN. – MAX.)	12.2 (7 – 15.4)	12.8 (7 – 16)	11.7 (7 – 15.3)	13.2(10.5 –16.3)	p<0.001*
P0	0.006*	0.434	0.002*		
RBCS (10^6/UL)					
MEAN ± SD.	4.7 ± 0.6	5.2 ± 1.9	4.4 ± 0.7	5.1 ± 0.4	H=42.27*
MEDIAN (MIN. – MAX.)	4.7# (2.5 – 6.4)	4.9# (2.5 – 14.8)	4.4# (2.5 – 5.6)	5.1 (4.2 – 5.9)	p<0.001*
P0	<0.001*	0.009*	<0.001*		
HCT (%)					
MEAN ± SD.	37.5 ± 5.6	38 ± 8.2	39.6 ± 6.4	42.8 ± 3.8	H=38.414
MEDIAN (MIN. – MAX.)	37# (20.3 – 46)	41# (4.5 – 47)	42# (20.3 – 47)	43 (37 – 50)	p<0.001*
P0	<0.001*	<0.001*	0.010*		
PLT (10^3/UL)					
MEAN ± SD.	234.3 ± 66.8	221.7 ± 96.1	189.5 ± 85.5	306.5 ± 84.4	H=60.536
MEDIAN (MIN. – MAX.)	217.5(107–383)	219.5#(22 –569)	180# (32 – 402)	320 (157 – 450)	p=<0.001
P0	<0.001*	<0.001*	<0.001*		
LYMPHOCYTES (10^3/UL)					
MEAN ± SD.	25.9 ± 11.8	19.1 ± 9.6	13 ± 6.3	30.8 ± 8.1	H=101.00
MEDIAN (MIN. – MAX.)	25# (7 – 65)	17# (5.6 –45.5)	13# (4 – 22)	30 (20 – 46)	p<0.001*
P0	0.001*	<0.001*	<0.001*		
NEUTROPHILS (10^3/UL)					
MEAN ± SD.	62.9 ± 13.9	47.9 ± 19.8	66.6 ± 21	61.7 ± 9.2	H=35.23*
MEDIAN (MIN. – MAX.)	65.7 (20.3 –88)	42# (20 – 90)	72 (33.4 – 91)	65 (44 – 73)	p<0.001*
P0	0.583	<0.001*	0.128		

IQR: Inter quartile range; SD: Standard deviation; χ2: Chi-square test

F: F for One-way ANOVA test, Pairwise comparison bet. each 2 groups was done using a Post Hoc Test (Tukey)

H: H for Kruskal Wallis test, Pairwise comparison bet. Each 2 groups was done using a Post Hoc Test (Dunn's for multiple comparisons test).

p: p-value for comparing between the different studied groups

p0: p-value for comparing between Control and each other group

p1: p-value for comparing between Mild and Moderate

p2: p-value for comparing between Mild and Severe

p3: p-value for comparing between Moderate and Severe

*: Statistically significant at p ≤ 0.05 #: Significant with Control

There were highly significant differences among the studied subgroups of patients categorized according to disease severity (mild, moderate, severe) with respect to symptoms such as fever, headache, and muscle ache, as well as outcomes like ICU admission, with a p-value less than 0.001. Hypertension comorbidity showed significant differences among mild, moderate, and severe patients. However, diabetes mellitus, bronchial asthma, and heart disease did not show statistically significant differences among the studied subgroups of patients, with a p-value greater than 0.05 (**Table 2**).

Table 2. Comparison between the different studied groups according to different clinical presentations.

	Disease severity			*Test of Sig.*	*P*
	Mild	**Moderate**	**Severe**		
Symptoms					
Fever	(62.1%)	(91.9%)	(100.0%)	χ2=28.826*	<0.001*
Cough	(81.0%)	(79.0%)	(97.3%)	χ2=6.410*	0.041*
Sore throat	(20.7%)	(19.4%)	(29.7%)	χ2=1.576	0.455
Smell lost	(60.3%)	(41.9%)	(40.5%)	χ2=5.266	0.072
Taste loss	(31.0%)	(25.8%)	(18.9%)	χ2=1.724	0.422
Headache	(17.2%)	(67.7%)	(78.4%)	χ2=44.508*	<0.001*
Muscle ache	(19.0%)	(67.7%)	(62.2%)	χ2=32.214*	<0.001*
Diarrhea	(6.9%)	(8.1%)	(29.7%)	χ2=12.609*	0.002*
Comorbidity					
Heart disease	(5.2%)	(16.1%)	(21.6%)	χ2=5.946	0.051
Bronchial asthma	(5.2%)	(3.2%)	(13.5%)	FET=3.818	0.151
Hypertension	(8.6%)	(32.3%)	(35.1%)	χ2=12.280*	0.002*
DM	(15.5%)	(17.7%)	(13.5%)	χ2=0.321	0.852
Outcome					
Mortality	(0.0%)	(8.1%)	(16.2%)	FET=9.876*	0.004*
ICU admission	(3.4%)	(17.7%)	(67.6%)	FET=50.135	<0.001*

χ2: Chi-square test; FET: Fisher Exact test
p: p-value for comparing between the different studied groups
*: Statistically significant at p ≤ 0.05

Ferritin and D-Dimer levels

Data analysis showed a significant difference between patients and the control group regarding Ferritin and D. Dimer, The mean ± SD for both Ferritin (343.9 ± 291.8 mg/L; 19.9 ± 9.9 mg/L; P value<0.001) and D-Dimer (544 ± 583.5ng/ml;141.9 ± 59.1 ng/ml; P value < 0.001) levels were significantly higher in patients compared to the control (**Table 3**).

Table 3. Comparison between the two studied groups according to Ferritin and D-Dimer.

	Patients(n = 300)	**Control(n = 100)**	**U**	**p**
Ferritin (mg/L)				
Mean ± SD.	343.9 ± 291.8	19.9 ± 9.9	236.00*	<0.001*
Median (Min. – Max.)	215 (9 – 1050)	18 (2 – 45)		
D-Dimer (ng/ml)				
Mean ± SD.	544 ± 583.5	141.9 ± 59.1	3707.00*	<0.001*
Median (Min. – Max.)	300 (50 – 3500)	120 (50 – 250)		

SD: Standard deviation; U: Mann-Whitney test
p: p-value for comparing between the two studied groups
*: Statistically significant at p ≤ 0.05

CRP, LDH, Ferritin, and D-Dimer, and COVID-19 severity

There were statistically significant differences between the control group and each of the patient subgroups in CRP, LDH, Ferritin, and D-Dimer levels (p ≤ 0.001). Additionally, there was a significant difference between the mild and moderate patient subgroups in CRP levels, as well as between the mild and severe patient subgroups in CRP and Ferritin levels (p ≤ 0.001). A significant difference was also observed between the moderate and severe patient subgroups in Ferritin levels only (p ≤ 0.05) (**Table 4**).

Table 4. Comparison between the different studied groups according to laboratory parameters.

	Disease severity			*Control*	*Sig. (p)*
	Mild	**Moderate**	**Severe**		
CRP (mg/L)					
Mean ± SD.	23.7 ± 23.1	102 ± 100.8	126.9 ± 69	2.6 ± 1.3	p<0.001
Median (Min. – Max.)	13.8# (0.6 – 97)	68# (3 – 528)	114(29 –348.8)	2.4 (0.5 – 5.2)	
p0	<0.001*	<0.001*	<0.001*		
LDH (mg/L)					
Mean ± SD.	361.7 ± 148.8	437 ± 251.7	509.9 ± 252.7	285.3 ± 46.8	p<0.001
Median (Min. – Max.)	336.5#(200–890)	346.5#(53–1500)	391# (216 – 890)	271 (217 – 391)	
p0	<0.001*	<0.001*	<0.001*		
Ferritin (mg/L)					
Mean ± SD.	153.1 ± 137.6	351.6 ± 254	630 ± 294.7	19.9 ± 9.9	p<0.001
Median (Min. – Max.)	112# (9 – 671)	257.5# (23 –923)	651# (100–1050)	18 (2 – 45)	
p0	<0.001*	<0.001*	<0.001*		
D-Dimer (ng/ml)					
Mean ± SD.	298.3 ± 196	565.6 ± 567.6	892.8 ± 803.5	141.9 ± 59.1	p<0.001
Median (Min. – Max.)	200# (50 – 790)	270# (50 – 2150)	530# (80 – 3500)	120 (50 – 250)	
p0	<0.001*	<0.001*	<0.001*		

SD: Standard deviation
H: H for Kruskal Wallis test, pairwise comparison bet. each 2 groups were done using a Post Hoc Test (Dunn's for multiple comparisons test)
p: p-value for comparing between the different studied groups
p0: p-value for comparing between Control and each other group
p1: p-value for comparing between Mild and Moderate
p2: p-value for comparing between Mild and Severe
p3: p-value for comparing between Moderate and Severe
*: Statistically significant at p ≤ 0.05
#: Significant with Control

Diagnostic performance of Ferritin, D-Dimer, and IFITM3 (rs12252) polymorphism

Prediction of disease activity: ROC curve analysis for Ferritin, D-dimer, and their combination with IFITM3 (rs12252) was conducted to distinguish between COVID-19 patients and healthy controls. Ferritin showed a sensitivity of 94.9% and specificity of 97.03% at a cutoff >42 mg/L. D-dimer showed a sensitivity of 71.34% and specificity of 62.38% at a cutoff >150 mg/L. The AUC increased significantly from 0.985 (Ferritin) and 0.766 (D-dimer) to 0.992 when combined with IFITM3 (P <0.001, 95% C.I = 0.981 – 1.000) (**Table 5**)

Table 5. Diagnostic performance for Ferritin, D-dimer, and Combination with IFITM3 (rs12252) to discriminate COVID-19 infection patients (n = 157) from control (n = 101).

Parameter	**AUC**	**p**	**95% C.I**	**Cut off#**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Ferritin	0.985	<0.001*	0.971 – 0.999	>42	94.90	97.03	98.0	92.5
D-Dimer	0.766	<0.001*	0.710 – 0.822	>150	71.34	62.38	74.7	58.3
Combination	0.992	<0.001*	0.981 – 1.000	–	98.09	99.01	99.4	97.1

AUC: Area Under a Curve; p-value: Probability value; CI: Confidence Intervals; NPV: Negative predictive value; PPV: Positive predictive value; *: Statistically significant at p ≤ 0.05; #Cut off was chosen according to Youden index; Combination: Ferritin + D-dimer + IFITM3 (rs12252)

Prediction of disease severity: The data analysis shows the prognostic performance of Ferritin, D-dimer, and their combination with IFITM3 (rs12252) in predicting COVID-19 severity. ROC curve analysis revealed that Ferritin had 83.78% sensitivity and 70.0% specificity at a cut-off >261 mg/L, while D-dimer had 62.16% sensitivity and 58.33% specificity at a cut-off >355 ng/mL. The AUC increased from 0.832 for Ferritin and 0.656 for D-dimer to 0.909 when combined with IFITM3 (P <0.001, 95% C.I = 0.957–0.861) (**Table 6**)

Table 6. Prognostic performance for Ferritin, D-dimer, and Combination with IFITM3 (rs12252).

Parameter	AUC	p	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
Ferritin	0.832	<0.001*	0.755 – 0.909	>261	83.78	70.0	46.3	93.3
D-Dimer	0.656	0.004*	0.545 – 0.767	>355	62.16	58.33	31.5	83.3
Combination	0.909	<0.001*	0.861 – 0.957	–	91.89	80.83	59.6	97.0

AUC: Area Under a Curve; p value: Probability value; CI: Confidence Intervals; NPV: Negative predictive value; PPV: Positive predictive value; *: Statistically significant at p ≤ 0.05; #Cut off was chosen according to Youden index; Combination: Ferritin + D-Dimer + IFITM3 (rs12252)

Risk factors predictors of mortality in COVID-19 infection

A univariate logistic regression analysis was conducted to determine the potential risk factors for mortality in patients with the G/A (rs12252) IFITM3 gene mutation. The heterozygote (AG) and homozygote (GG) genotypes were found to be significantly independent predictors of mortality (OR=18.077; 95% CI: 2.251 – 145.18; P = 0.006) (**Table 7**).

Table 7. Univariate logistic regression analysis for prediction of mortality (n = 11 vs. 146).

	p	OR (LL – UL 95%C.I)
CRP	0.410	1.003 (0.996 – 1.009)
LDH	0.148	0.997 (0.992 – 1.001)
Ferritin	0.595	1.001 (0.999 – 1.003)
D-Dimer	0.289	1.000 (1.000 – 1.001)
IFITM3 (rs12252) [AG + GG]	0.006*	18.077 (2.251 – 145.18)

OR: Odds ratio; C.I: Confidence interval; LL: Lower limit; UL: Upper Limit; *: Statistically significant at p ≤ 0.05

Predictors for the diagnosis of COVID-19 infection

The multivariate logistic regression analysis was conducted to identify independent predictors of the diagnosis of COVID-19 infection activity among the studied cohort. The variables included in the final model were C-reactive protein (CRP), lactate dehydrogenase (LDH), serum ferritin, D-dimer levels, and the IFITM3 (rs12252) gene polymorphism [AG + GG genotype]. The objective was to adjust for potential confounders and determine which factors have a significant association with the development of disease infection when considered simultaneously. In the final model, the significant predictors were the CRP, serum Ferritin, and D-Dimer while the non-significant predictors were LDH and IFITM3 (rs12252) gene polymorphism (AG+GG) (OR: 8.801; 95% CI: 0.186 – 416.239; P value=0.269) (**Table 8**).

Table 8. Univariate and Multivariate logistic regression analysis for the parameters affected by the infection of COVID-19 (n = 157 vs. 101).

	Univariate		#Multivariate	
	p	OR (LL – UL 95%C.I)	p	OR (LL – UL 95%C.I)
Female	0.595	1.147 (0.691 – 1.905)		
Age (years)	0.455	1.006 (0.990 – 1.023)		
CRP	<0.001*	2.135 (1.591 – 2.865)	0.017*	3.900 (1.270 – 11.974)
LDH	<0.001*	1.009 (1.005 – 1.013)	0.104	1.030 (0.994 – 1.068)
Ferritin$	<0.001*	4.182 (2.449 – 7.141)	0.006*	4.603 (1.540 – 13.757)
D-Dimer$	<0.001*	1.087 (1.052 – 1.122)	0.028*	1.235 (1.023 – 1.491)
IFITM3 (rs12252) [AG + GG]	<0.001*	4.840 (2.446 – 9.577)	0.269	8.801 (0.186 – 416.239)

Hosmer and Leme show Test (χ^2=0.102; p=1.000); OR: Odds ratio; C.I: Confidence interval; LL: Lower limit; UL: Upper Limit; #: All variables with p<0.05 were included in the multivariate analysis; *: Statistically significant at p ≤ 0.05; $: for each 10.

Predictors of the severity of COVID-19 disease

The multivariate logistic regression analysis aimed to identify independent predictors of COVID-19 infection severity: mild, moderate, and severe. The parameters included in the model were CRP, LDH, serum ferritin, D-dimer levels, and the IFITM3 (rs12252) gene polymorphism [AG + GG genotype]. The goal was to adjust for potential confounders and determine which factors were significantly associated with disease severity when considered together. The final model showed that CRP, serum Ferritin, and IFITM3 (rs12252) Polymorphism [AG + GG] (OR: 10.478; 95% CI: 3.466 – 31.676; P value <0.001) while LDH and D-Dimer levels were not significant predictors (when combined with other parameters) (**Table 9**)

Table 9. Univariate and Multivariate logistic regression analysis for the parameters affected by disease severity.

	Univariate		#Multivariate	
	p	OR (LL – UL 95%C.I)	p	OR (LL – UL 95%C.I)
CRP	<0.001*	1.008 (1.004 – 1.013)	0.031*	1.007 (1.001 – 1.013)
LDH	0.013*	1.002 (1.000 – 1.004)	0.495	0.999 (0.997 – 1.002)
Ferritin$	<0.001*	1.048 (1.032 – 1.065)	<0.001*	1.044 (1.024 – 1.066)
D-Dimer$	<0.001*	1.012 (1.006 – 1.019)	0.148	1.007 (0.998 – 1.016)
[AG + GG]	<0.001*	9.557 (3.967 – 23.025)	<0.001*	10.478 (3.466 – 31.676)

Hosmer and Lemeshow Test ((2=2.481; p=0.963); OR: Odd`s ratio; C.I: Confidence interval; LL: Lower limit; UL: Upper Limit; #: All variables with p<0.05 were included in the multivariate; *: Statistically significant at p ≤ 0.05; $: for each 10.

Predictors for ICU admission

The multivariate logistic regression analysis aimed to identify independent predictors of hospital admission among COVID-19 patients. The parameters included in the model were CRP, LDH, serum ferritin, D-dimer levels, and the IFITM3 (rs12252) gene polymorphism [AG + GG genotype]. The goal was to adjust for potential confounders and determine which factors were significantly associated with hospital admission when considered together. While D-Dimer test, IFITM3 (rs12252) Polymorphism [AG + GG] (OR: 144.34;95% CI: 18.084 – 1152.1; P value<0.001), the CRP, LDH, and serum ferritin levels were not significantly predictors for ICU admission (**Table 10**).

Table 10. Univariate and Multivariate logistic regression analysis for the risk factors for ICU admission (n = 38 vs. 119).

	Univariate		#Multivariate	
	p	OR (LL – UL 95%C.I)	p	OR (LL – UL 95%C.I)
CRP	0.083	1.004 (1.000 – 1.008)		
LDH	0.197	1.001 (0.999 – 1.003)		
Ferritin$	0.005*	1.018 (1.005 – 1.030)	0.717	1.003 (0.986 – 1.021)
D-Dimer$	0.001*	1.011 (1.005 – 1.017)	0.027*	1.011 (1.001 – 1.022)
[AG + GG]	<0.001*	139.12(18.187–1064.21)	<0.001*	144.34(18.084–1152.1)

Hosmer and Lemeshow Test (χ^2=2.409; p=0.966); OR: Odd`s ratio; CI: Confidence interval; LL: Lower limit; UL: Upper Limit; #: All variables with p<0.05 was included in the multivariate; *: Statistically significant at p ≤ 0.05; $: for each 10.

DISCUSSION

This study comprehensively evaluated the associations between biochemical markers and the IFITM3 (rs12252) gene polymorphism in COVID-19 patients compared to healthy controls, focusing on their predictive values for infection, disease severity, hospital admission, and outcomes. The findings demonstrated significant elevations in ferritin and D-dimer levels among COVID-19 patients, indicating their strong association with infection and its severity.

Elevated ferritin levels reflect a hyperinflammatory state characteristic of severe COVID-19. Increased D-dimer levels indicate coagulation abnormalities and a heightened risk of thrombotic complications due to endothelial dysfunction and cytokine storms induced by SARS-CoV-2. The significant differences in C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer levels between patient subgroups and controls underscore the progressive escalation of inflammatory and tissue damage markers with disease severity.

The results of the ROC curve analysis and multivariate logistic regression highlight significant findings regarding the predictive accuracy of Ferritin, D-dimer, and the IFITM3 (rs12252) polymorphism in detecting COVID-19 patients vs healthy. The ROC curve analysis revealed that Ferritin serves as a robust predictor of COVID-19 disease activity, achieving a sensitivity of 94.9% and a specificity of 97.03% at a threshold exceeding 42 mg/L. Conversely, D-dimer exhibited a lower predictive capability with a cutoff value above 150 ng/mL. However, when Ferritin and D-dimer were combined with the IFITM3 (rs12252) polymorphism, the predictive accuracy markedly improved, reflected by an increase in sensitivity to 98.09% and specificity to 99.01%. This underscores the enhanced diagnostic precision provided by integrating genetic markers with biochemical parameters for identifying individuals susceptible to COVID-19.

Furthermore, in assessing the severity of COVID-19, the ROC analysis demonstrated that Ferritin retained strong predictive power, with a sensitivity of 83.78% and a specificity of 70% at levels greater than 261 mg/L. On the other hand, D-dimer showed diminished predictive accuracy at a threshold above 355 ng/mL. The integration of Ferritin with the IFITM3 (rs12252) polymorphism significantly elevated the predictive accuracy, achieving a sensitivity of 92% and specificity of 81%. These

findings suggest that the IFITM3 (rs12252) polymorphism is a potent marker for differentiating severe cases from mild and moderate ones, thus emphasizing its utility in stratifying patients based on disease severity and identifying those at heightened risk for severe outcomes.

The IFITM3 (rs12252) polymorphism also emerged as a significant independent predictor of mortality. Carriers of the AG and GG genotypes had a substantially increased risk of death, emphasizing the influence of host genetic factors on patient outcomes. This underscores the crucial role of IFITM3 in the innate immune response and its significant impact on the clinical course of COVID-19.

In predicting disease severity, the combined use of ferritin, D-dimer, and the IFITM3 polymorphism yielded higher predictive accuracy than any single marker alone. Ferritin remained a strong predictor, correlating with the hyperinflammatory state associated with severe disease. The addition of the IFITM3 polymorphism enhanced prognostic value, suggesting that genetic susceptibility significantly contributes to disease progression and is critical in identifying patients at risk of developing severe symptoms.

Interestingly, in predicting the diagnosis of COVID-19 infection activity among the studied cohort, multivariate analysis revealed that CRP, ferritin, and D-dimer levels were significant independent predictors, while the IFITM3 polymorphism did not retain significance after adjusting for these variables. This indicates that while the polymorphism is a strong predictor of disease severity, ICU admission, and mortality, it may not independently predict susceptibility to infection when acute-phase reactants are considered. The acute inflammatory response may overshadow genetic influences during the initial phase of infection.

In assessing predictors for intensive care unit (ICU) admission, the multivariate analysis revealed that elevated D-dimer levels and the IFITM3 (rs12252) polymorphism were significant independent predictors among COVID-19 patients. Specifically, individuals with the AG or GG genotype of the IFITM3 polymorphism exhibited a markedly increased likelihood of requiring ICU care. In contrast, CRP, LDH, and ferritin levels were not significant predictors for ICU admission when considered alongside the genetic factor. This finding underscores the profound impact of genetic predisposition on the progression to critical illness necessitating intensive care, highlighting the IFITM3 polymorphism as a potent indicator of severe disease escalation.

The study highlighted the pivotal role of ferritin and D-dimer as significant biomarkers associated with COVID-19 infection, severity, and the necessity for ICU admission. More importantly, the IFITM3 (rs12252) polymorphism served as a potent predictor of disease severity, ICU admission, and mortality. Its strong association with critical outcomes underscored the profound impact of genetic factors on disease trajectory. The integration of this genetic marker with biochemical parameters enhanced diagnostic and prognostic capabilities, supporting its potential use in clinical practice for risk stratification and personalized patient management. These findings advocated for the incorporation of genetic testing alongside standard laboratory assessments to improve outcomes for patients afflicted by COVID-19.

Numerous studies have underscored the predictive significance of IFITM3 single nucleotide polymorphisms (SNPs), particularly rs12252, in determining mortality among COVID-19 patients. According to a case-control study by Abdelaziz et al. (2024), the rs12252 allele (G) of IFITM3-SNP was significantly more prevalent in deceased patients than in those who recovered (Abdelaziz et al., 2024). Additionally, a study conducted in Saudi Arabia demonstrated that patients with the AG/GG genotypes exhibited significantly lower plasma levels of IFNγ compared to those with the AA genotype, thereby associating the rs12252-G allele with increased mortality (Alghamdi et al., 2021). Similarly, a cross-sectional study in Egypt reported a higher frequency of the heterozygous AG genotype among deceased participants (32.0%) in comparison to those who had recovered (Elessawy et al., 2024). Furthermore, research by Ahmadi et al. (2022) revealed that the minor allele frequency of IFITM3 rs12252 (C) was significantly more common in deceased patients than in those who had improved (Ahmadi et al., 2022).

Our study, consistent with existing literature, found that the IFITM3 (rs12252) polymorphism is a significant independent predictor of mortality. Individuals with AG and GG genotypes had a higher risk of death, highlighting the role of host genetics in patient outcomes. Therefore, IFITM3 SNPs play a crucial role in the immune response and are a promising predictor of mortality in patients suffering from COVID-19 infection.

The interferon-induced transmembrane protein 3 (IFITM3) rs12252 single nucleotide polymorphism (SNP) has been implicated in the severity of viral infections. Studies by Zhang et al. (2013) and Wellington et al. (2019) demonstrated that individuals carrying the rs12252 variant faced significantly higher risks of severe influenza, including a six-fold increase in severity, early hypercytokinemia, and increased mortality (Wellington et al., 2019; Zhang et al., 2013). A pooled analysis by Li et al. (2022) further established a relationship between this polymorphism and COVID-19 susceptibility across various genetic models (Li et al., 2022), underscoring its critical role in disease severity.

Ethnic variations in IFITM3 rs12252 allele frequencies suggest differential susceptibility among populations. The 1000 Genomes Project (Auton et al., 2015) reported that the G-variant allele frequency is highest in East Asian populations (0.528), moderate in African populations (0.26), and lower in European (0.04), Hispanic American (0.17), and South Asian (0.14) populations. Nikoloudis et al. (2020) found a

strong correlation (r = 0.9687, p = 0.0003) between specific IFITM3 haplotypes and COVID-19 mortality rates among ethnic groups in England, suggesting that genetic variations associated with ethnicity may influence disease outcomes.

Our study aligns with these findings by demonstrating that incorporating the IFITM3 rs12252 polymorphism with ferritin and D-dimer levels enhances predictive accuracy for COVID-19 severity beyond any single marker. While Elessawy et al. (2024) reported no significant association in an Egyptian cohort (Elessawy et al., 2024), our results underscore the polymorphism's prognostic value, indicating that genetic susceptibility contributes significantly to disease progression. Discrepancies may arise from population-specific genetic differences or methodological variations. Overall, our findings reinforce the importance of considering genetic factors, particularly IFITM3 SNPs, in identifying patients at heightened risk for severe COVID-19 symptoms.

Evidence from the literature emphasized the association between the IFITM3 rs12252 polymorphism and COVID-19 susceptibility, yielding mixed results. Zakaria et al. (2024) conducted a case-control study in Alexandria and found no significant association between the IFITM3 rs12252 polymorphism and COVID-19 susceptibility under homozygote, dominant, and recessive genetic models (Zakaria et al., 2024). In contrast, Gómez et al. (2021) reported that the rs12252 polymorphism was associated with an increased risk of COVID-19, highlighting its role in antiviral responses (Gómez et al., 2021). Similarly, Cuesta-Llavona et al. (2021) identified a common IFITM3 haplotype as a susceptibility factor for severe SARS-CoV-2 disease, emphasizing the gene's critical role in innate immunity and defense against viral infections (Cuesta-Llavona et al., 2021).

In our study, we observed that while the IFITM3 rs12252 polymorphism was a strong predictor of disease severity, intensive care unit (ICU) admission, and mortality, it did not independently predict susceptibility to COVID-19 infection when acute-phase reactants such as C-reactive protein (CRP), ferritin, and D-Dimer were considered. This finding aligns with the results of Zakaria et al. (2024), suggesting that the acute inflammatory response may overshadow genetic influences during the initial phase of infection. However, our results contrast with those of Gómez et al. (2021) and Cuesta-Llavona et al. (2021), who demonstrated a significant association between the IFITM3 rs12252 polymorphism and increased risk or severity of COVID-19. The discrepancies could be attributed to differences in study populations, the versatility of ethnicity-based genetic backgrounds (Auton et al., 2015), or the impact of inflammatory markers (Zakaria et al., 2024), underscoring the necessity for further research to elucidate the precise role of IFITM3 polymorphisms in COVID-19 susceptibility.

Growing evidence from the literature has highlighted the association between the IFITM3 single nucleotide polymorphism (SNP) rs12252 and the intensive care unit (ICU) admission. Abdelaziz et al. (2024) reported that the G allele of IFITM3 rs12252 was significantly more prevalent among ICU-admitted patients compared to non-ICU patients in a case-control study, suggesting a strong link between this genetic variant and severe disease outcomes (Abdelaziz et al., 2024). Similarly, Alghamdi et al. (2021) found that the rs12252-G allele was associated with hospital admission in a study conducted in the Kingdom of Saudi Arabia (Alghamdi et al., 2021), indicating that carriers of this allele may have a higher propensity for severe infection requiring hospitalization. In contrast, a cross-sectional study by Elessawy et al. (2024) in Egypt observed no significant association between the IFITM3 rs12252 SNP and ICU admission among COVID-19 patients, highlighting potential geographic or population-specific differences in genetic impact (Elessawy et al., 2024).

The findings of our study revealed that the IFITM3 rs12252 polymorphism was a significant independent predictor of ICU admission among COVID-19 patients. Individuals with the AG or GG genotype exhibited a markedly increased likelihood of requiring intensive care, aligning with the findings of Abdelaziz et al. (2024) and Alghamdi et al. (2021). Notably, this association remained significant even when elevated D-dimer levels were considered, while other biomarkers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin levels did not retain significance alongside the genetic factor. This underscores the profound impact of genetic predisposition on disease progression to critical illness necessitating intensive care. The discrepancy between our results and those of Elessawy et al. (2024) may be attributed to differences in study design, sample size, or genetic heterogeneity among populations. Given the here before evidence, our findings emphasize the IFITM3 rs12252 polymorphism as a potent indicator of severe COVID-19 escalation, reinforcing the notion that genetic factors play a critical role in determining patient outcomes.

CONCLUSION

This study elucidated the significant roles of ferritin and D-dimer as biomarkers for assessing COVID-19 infection, disease severity, and the necessity for ICU admission. Elevated levels of these markers were strongly associated with severe clinical outcomes, reflecting the underlying hyperinflammatory state and coagulation abnormalities characteristic of severe COVID-19 cases.

Our findings highlighted the IFITM3 (rs12252) gene polymorphism, specifically the AG and GG genotypes, as potent predictors of disease severity, ICU admission, and mortality. This genetic susceptibility significantly influenced patient outcomes, underscoring the critical role of host genetic factors in the progression of COVID-19. The incorporation of

IFITM3 genotyping alongside biochemical markers such as ferritin and D-dimer substantially enhanced diagnostic and prognostic accuracy.

The integration of these biomarkers into routine clinical assessments can improve risk stratification, enabling early identification of high-risk individuals. This facilitates prompt initiation of targeted therapies, optimized resource allocation, and personalized patient management. Additionally, these findings support the potential use of genetic testing in clinical practice to better predict disease trajectories and improve patient outcomes.

While our study aligns with existing literature on the utility of ferritin and D-dimer, it also introduces novel insights into the significance of the IFITM3 polymorphism in COVID-19. Variability in genetic impact across different populations underscores the need for further research with larger, ethnically diverse cohorts to validate these associations.

In summary, the combination of genetic and biochemical markers offers a comprehensive approach to understanding COVID-19 pathogenesis, enhancing diagnostic precision, and tailoring interventions to mitigate the burden of severe disease. Our study advocates for the incorporation of these markers into clinical protocols to elevate the standards of care and improve the prognosis for patients afflicted by COVID-19.

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Authors' Contributions

All authors contributed to the study, encompassing study conception and design, data collection, analysis and interpretation of results, draft manuscript, reviewed and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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