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Plasma ICAM-1 level is highly associated with disease severity and predict the progression of COVID-19

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Abstract— **Background**: Inflammation and immune-mediated reactions are facilitated by the endothelial cell adhesion molecule intercellular adhesion molecule-1 (ICAM-1). In patients with corona virus disease 2019 (COVID-19), viral infection of endothelial cells brought on by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) can result in vascular alterations and boost the expression of ICAM-1, and may be utilized as a biomarker to assess disease severity. The purpose of this study was to determine how serum ICAM-1 levels affected the severity and prognosis of COVID-19. **Materials and Methods**: 120 patients with COVID-19 participated in the research. According to the severity of the condition, the COVID-19 patients were divided into three groups: critical disease (n = 23), severe disease (n = 37), and mild/moderate disease (n = 60), with 60 healthy volunteers working as the control group. Blood samples were taken as well as all of the patients' fundamental clinical and demographic information. **Results**: ICAM-1 levels were significantly higher in the all cases of patients with COVID-19 ($p<0.0001$). ICAM-1 levels were correlated with SpO_2, Lymphocyte, total cholesterol, HDL-C, and LDL-C($r = -0.639$, -0.549, -0.348, -0.582, and -0.500respectively; $p <0.01$)negatively, and correlated with SBP, WBCs, neutrophil, D-dimer, ferritin, CRP, triglyceride, and VLDL-C($r = 0.477$, 0.579, 0.475, 0.688, 0.741, 0.709, 0.739, and 0.739 respectively; $p<0.01$), whereas age $r = 0.179$ $p<0.05$ positively. A cutoff value of 298.665 ng/ml for ICAM-1 predicted severe COVID-19 with a sensitivity of 92.5% and a specificity of 91.7% (AUC: 0.982, 95% confidence interval 0.968–0.996; $p<0.0001$). **Conclusion**: Intercellular adhesion molecule-1 (ICAM-1) may be a valuable predictive biomarker for determining the severity of COVID-19.

Keywords: COVID-19, Severe COVID-19, Intercellular adhesion molecule-1 (ICAM-1).

Introduction

The severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) that caused the coronavirus disease 2019 (COVID-19) has infected millions of people worldwide. Clinically, it often manifests as mild flu-like symptoms, but in high-risk individuals, it can result in respiratory failure. The cytokine-driven vascular leaks in the lung alveolar-endothelial interface of COVID-19 promote lung damage; it is likely that the virus enters the systemic circulation by moving from the respiratory epithelium to the endothelium[1], making the lung

a significant organ target. Patients with COVID-19 have issues with many organs. In COVID-19, there is a significant prevalence of encephalopathy, respiratory failure, myocarditis, myocardial infarction, acute renal damage, and a hypercoagulable condition, allof which may be impacted by impaired endothelial function[1,2]. In fact, those with pre- existing comorbidities that entail endothelial dysfunction, such as diabetes mellitus, hypertension, and cardiovascular disease, have a worsening of the condition [3].

The pathophysiology and progression of several human vascular illnesses, such as liver disease, hypertension, diabetes, stroke, septic, and now COVID-19, are considered to be heavily influenced by endothelial activation and damage. The characteristics of COVID-19 patients include altered vascular permeability, inflammation, leucocyte buildup and extravasation, activation of procoagulant pathways, and alteration of the alveolar-capillary barrier. These characteristics are consistent with endothelial dysfunction[4,5]. It has also been hypothesized that underlying endothelial dysfunction contributes to the increased fatality rate and poor clinical outcomes associated with COVID-19 infections in older patients and those with concomitant diseases such diabetes, obesity, and hypertension[6].

The membrane of leukocytes and endothelial cells continually contains modest quantities of ICAM-1, also known as CD54. ICAM-1 is expressed by the vascular endothelium, macrophages, and lymphocytes and can be stimulated by IL-1 and TNF-α. A number of chronic inflammatory conditions include ICAM-1. ICAM-1 has been linked to lung inflammation and has been demonstrated to be elevated by cytokine production during inflammation of the respiratory epithelium[7].

Additionally, it has a direct role in viral inflammatory processes such rhinovirus infection of the lungs and the onset of systemic inflammation in newborn sepsis[8]. Previous research shown the value of this biomarker in predicting poorer outcomes, including mortality, in patients with "classical" acute respiratory distress syndrome (ARDS)[9–11].

A systemic inflammatory response brought on by COVID-19 involves the deregulation and incorrect expression of several inflammatory cytokines [12]. The production of several types of inflammatory mediators, including cytokines, chemokines, and adhesion molecules(ICAM-1), is necessary for the recruitment and activation of inflammatory cells[13].

Previous study[14] have found pathological evidence of widespread endothelial inflammations, direct viral infection of the intestinal epithelium, and venous thromboembolism. In order to maintain vascular homeostasis, endothelial cells manage inflammation, regulate platelet aggregation, and guard against thrombosis[15]. One key characteristic of COVID-19 has been found as endothelial cell dysfunction[16]. Therefore, it is important to look into COVID-19's expression of endothelium cell adhesion molecules.

Materials and Methods

This case control study of 180 subjects was conducted age 35 to 65 years. Between September and November 2021, 120 confirmed COVID-19 patients were admitted to Al-Amal Specialized Hospital for infectious diseases in an Najaf governorate, Iraq. Patients with COVID-19 were diagnosed based on positive quantitative RT-PCR and chest x-ray or chest computed tomography (CT) scan findings, with 60 healthy participants providing as a control

group with similar ages ranges to the patients. This study excluded participants with diabetes, liver illness, chronic renal disease, pulmonary disease, pregnant women, and smokers to prevent the impact of additional comorbidities. Before participating in this study, all controls and patients provided written informed permission.

The COVID-19 patients were divided into three groups upon admission to the hospital based on the clinical findings, respiration rates, oxygen saturation (SpO2) levels, and low-dose chest CT results. The classification's specifics are as follows:
Mild /Moderate illness:SpO2 94% on room air, mild clinical symptoms, mild respiratory symptoms, positive pneumonial signs on low-dose CT.
Severe illness: Those who fit one or more of the following descriptions:
mild clinical symptoms, mild respiratory symptoms, positive pneumonial findings on low-dose CT, and room air SpO2≥94%.
Severe illness: Those who meet any of the following criteria:
1. Respiratory rate >30 times per min;
2. SpO2 <94% at room air;
3.Lung infiltrates >50% on low-dose CT.

Critical disease: Acute respiratory distress syndrome (ARDS) patients may have septic shock, numerous organ failure, coagulation issues, and possibly pass away[17].

The research was carried out in accordance with Iraqi and international ethical and privacy rules, as well as the declaration of helsinki of the world medical association.

After an overnight fast, samples of venous blood were taken from both the patient and control groups. We used two tubes to collect blood samples. Prior to centrifuging 3 ml at 3000 Xg for 10 minutes to extract serum, allow the sample to clot at room temperature for 10 to 15 minutes. Following that, the serum samples were separated into tubes and stored in the refrigerator at -20°C until they were ready for analysis. The rest of the blood (2 ml) was used to calculate the complete blood count. Using Biolabo® kits from Maizy, France, the levels of serumtotal cholesterol, triglyceride, and HDL-cholesterol were measured spectrophotometrically. LDL-cholesterol was calculated by Friedwald formula[18]. Fluorescence immunoassay was used to determine serum ferritin, C-reactive protein, and D-dimer levels were measured by (ichroma^{TM}). An autohematology analyzer was used to determine the whole blood count (linear, Spain). We used Melsin Medical Co. (Jilin, China) ELISA kits to measure serum ICAM-1. Furthermore, the detection range of ICAM-1was 250–4000 ng/ml.

Statistical Analyses
The statistical studies were conducted using IBM SPSS Statistics 26 software. The analyses' findings were presented as mean standard deviation. The cutoff point for statistical significance was $p<0.05$. Using the student's t-test, two independent samples were compared. The Pearson's correlation analysis was used to assess the parametric variables. Analysis of variance (ANOVA) was employed in the study to examine any variations in scale variables between categories. To establish the cutoff value for ICAM-1, the receiver operating

characteristic (ROC) analysis approach was used. The area under curve (AUC) value was calculated using the ROC curve.

Results

The 120 patients enrolled in this study were categorized according to severity of COVID-19. Fifty patients had moderate disease, while remaining patients experienced either severe or critical illness (37 and 23 patients, respectively). The latter two groups of patients had a significantly higher mean age compared to patients with moderate disease (57.09±4.89, 50.66±2.57and 45.98±2.92years, respectively; $p < 0.05$). Distributions of BMI subgroups in the three disease severity groups showed no significant differences. Patients were also defined by the laboratory parameters listed in Table 1. Means of these parameters showed significant differences between the three disease severity groups except Hb. The mean serum ICAM-1levels of the patients with critical, severe and mild/moderate COVID-19 were 663.97±159.28, 540.23±125.29 and 449.06±128.23, respectively ($p<0.0001$).Pearson's correlation analysis was performed tocalculate correlation coefficients (r) between ICAM-1 and laboratory parameters in COVID-19 patients.ICAM-1 showed significant negative correlation withSpO_2,lymphocyte, total cholesterol, HDL-C, and LDL-C($r = -0.639, -0.549, -0.348, -0.582$, and -0.500respectively; $p < 0.01$),while it was significant positively correlated with, SBP, WBCs,neutrophil, D-dimer, ferritin, CRP,triglyceride, and VLDL-C($r = 0.477, 0.579, 0.475, 0.688, 0.741, 0.709, 0.739$, and 0.739respectively; $p<0.01$), whereas age $r = 0.179$ $p<0.05$(Table 2 and Figure 1).

ICAM-1 considerably rises in the critical group as compared to other groups(severe, moderate, and healthy control), as demonstrated in Figure 2.

By using ROC analysis, the effectiveness of ICAM-1 for predicting severe illness was assessed. ICAM-1's AUC was shown to be 0.982 (95% confidence interval: 0.968-0.996; $p<0.0001$). The sensitivity was determined to be 92.5%, while the specificity was determined to be 91.7% when the cutoff value for ICAM-1 in predicting severe illness was established to be 298.665 ng/ml (Figure 3).

Table 1. Comparison of the demographical and laboratory data of patients with COVID-19 and control groups.

Variables	COVID-19cases; n= 120			Healthy control (n=60)	p-value
	Critical (n=23)	Severe (n=37)	Mild/Moderate (n=60)		
Age (year)	57.09±4.89	50.66±2.57	45.98±2.92	49.99±5.78	0.05

Gender M/F	15/8	20/17	40/20	40/20	----
BMI (kg/m^2)	23.73±0.55	24.07±1.01	24.61±1.07	24.04±0.86	0.105
SBP (mmHg)	140.04±4.76	133.64±5.68	129.11±4.75	127.8±3.27	0.00
DBP (mmHg)	81.61±3.65	75.89±3.11	77.48±3.22	78.06±2.31	0.00
SpO_2	67.79±9.66	87.82±6.38	95.38±1.09	98.96±0.47	0.00
Hb (g/dl)	12.48±1.20	12.38±1.42	12.73±1.41	12.46±1.28	0.590
WBCs $\times 10^9/L$	13.47±1.05	11.86±1.14	10.06±1.47	8.78±0.99	0.000
Neutrophil $\times 10^9/L$	9.78±1.88	8.05±2.23	7.37±2.07	6.01±1.47	0.000
Lymphocyte $\times 10^9/L$	2.41±0.55	2.95±0.88	3.93±0.83	4.24±0.51	0.000
D-Dimer (ng/ml)	3873.76±870.17	3029.83±833.57	1125.28±400.82	304.81±123.72	0.000
Ferritin (ng/ml)	731.56±87.71	503.72±71.22	438.3±74.03	135.06±47.87	0.000
CRP (mg/L)	41.39±8.38	32.86±10.17	28.71±7.69	3.49±1.47	0.000

Total cholesterol (mg/dl)	156.34±10.09	166.26±10.12	170.90±14.17	174.22±12.99	0.000
Triglyceride (mg/dl)	284.15±11.44	281.11±8.77	232.91±23.29	134.81±9.53	0.000
HDL-C (mg/dl)	28.71±3.72	32.63±8.26	35.37±6.21	48.34±6.07	0.000
LDL-C (mg/dl)	70.81±10.71	77.41±12.37	88.94±16.60	98.92±12.16	0.000
VLDL-C (mg/dl)	56.83±2.28	56.22±1.75	46.58±4.65	26.96±1.91	0.000
ICAM-1 (ng/ml)	663.97±159.28	540.23±125.29	449.06±128.23	241.87±45.12	0.000

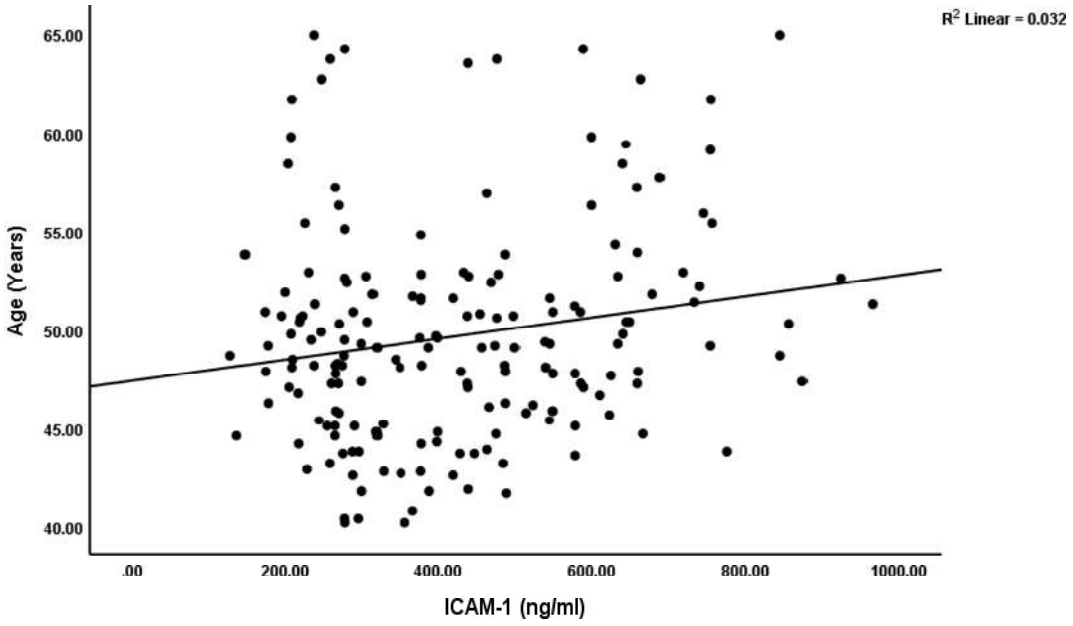
Abbreviations: M/F, Male/Female; BMI, body mass index; SBP, systolic blood pressure ; DBP, diastolic blood pressure ; SpO_2, saturation oxygen percentages ; Hb, hemoglobin; WBCs, white blood cells;
CRP, C-reactive protein; HDL-C, HighDensity Lipoprotein-Cholesterol; LDL-C, Low Density Lipoprotein-Cholesterol; VLDL-C, Very Low Density Lipoprotein-Cholesterol;ICAM-1, intercellular adhesionmolecule-1. Values are given as mean ± standard deviation.

Table2.The correlation between clinical parameters and serum ICAM-1 level in COVID-19 patients

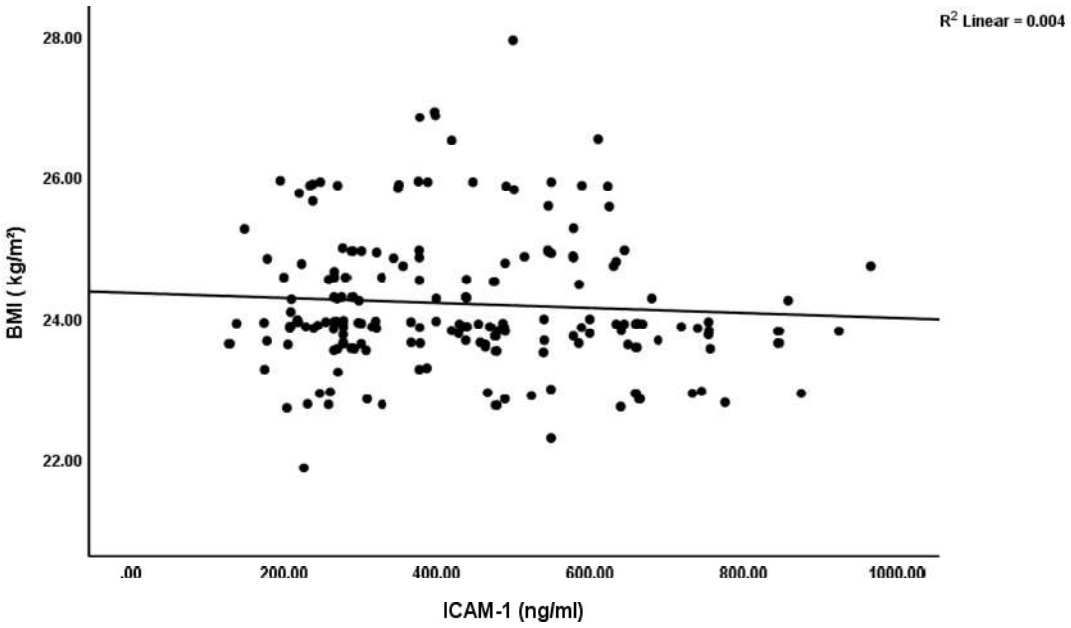
Variables	r
Age (year)	0.179*
BMI (kg/m^2)	-0.065

SBP (mmHg)	0.477**
DBP (mmHg)	0.033
SpO_2	-0.639**
Hb (g/dl)	-0.063
WBCs $\times 10^9$/L	0.579**
Neutrophil $\times 10^9$/L	0.475**
Lymphocyte $\times 10^9$/L	-0.549**
D-Dimer (ng/ml)	0.688**
Ferritin (ng/ml)	0.741**
CRP (mg/L)	0.709**
Total cholesterol (mg/dl)	-0.348**
Triglyceride (mg/dl)	0.739**
HDL-C (mg/dl)	-0.582**
LDL-C (mg/dl)	-0.500**
VLDL-C (mg/dl)	0.739**

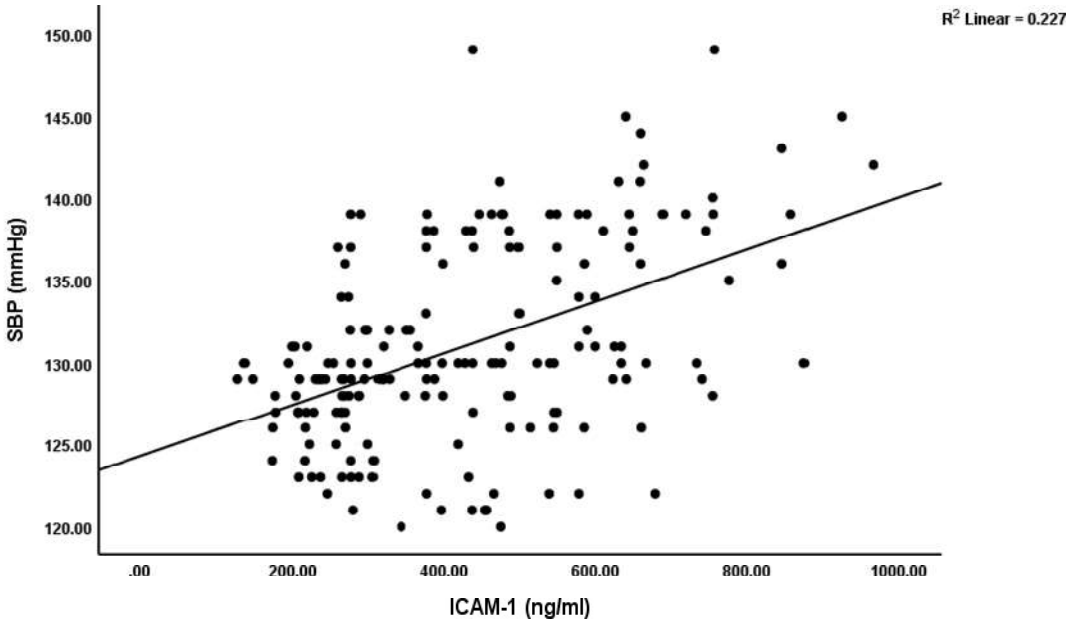
Abbreviations: BMI, body mass index; SBP, systolic blood pressure ; DBP, diastolic blood pressure ; SpO_2, saturation oxygen percentages ; Hb, hemoglobin; WBCs, white blood cells; CRP, C-reactive protein; HDL-C, HighDensity Lipoprotein-Cholesterol; LDL-C, Low Density Lipoprotein-Cholesterol; VLDL-C, Very Low Density Lipoprotein- Cholesterol; r, Pearson's correlation coefficient; *, $p<0.05$, and **, $p<0.01$.


R² Linear = 0.032
65.00
60.00
55.00
50.00
45.00
40.00
Age (Years)
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

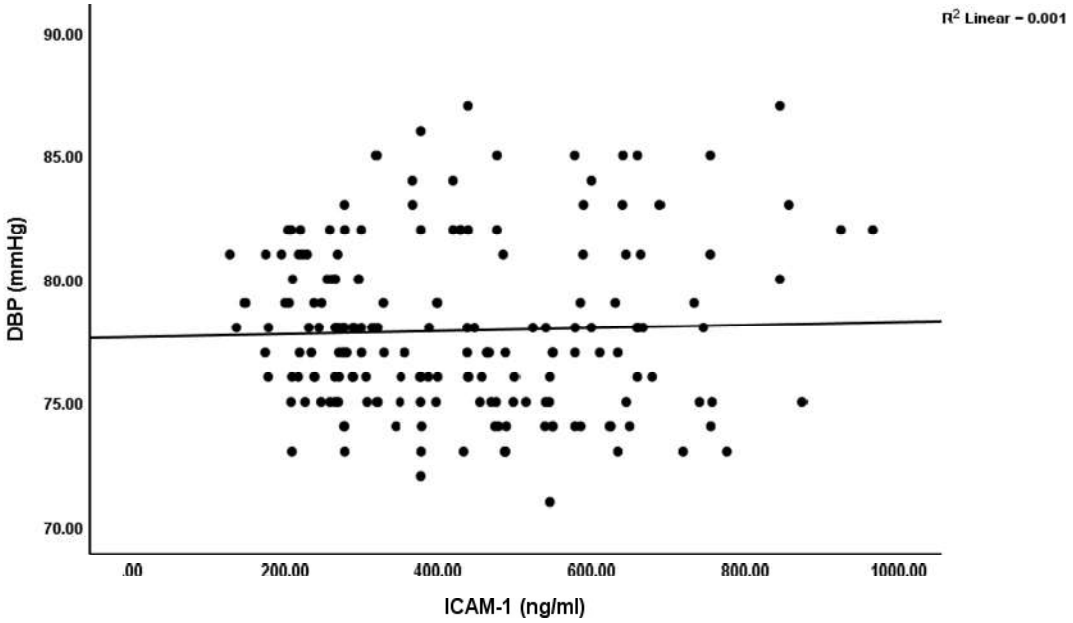
(A)


R² Linear = 0.004
28.00
26.00
24.00
22.00
BMI (kg/m²)
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

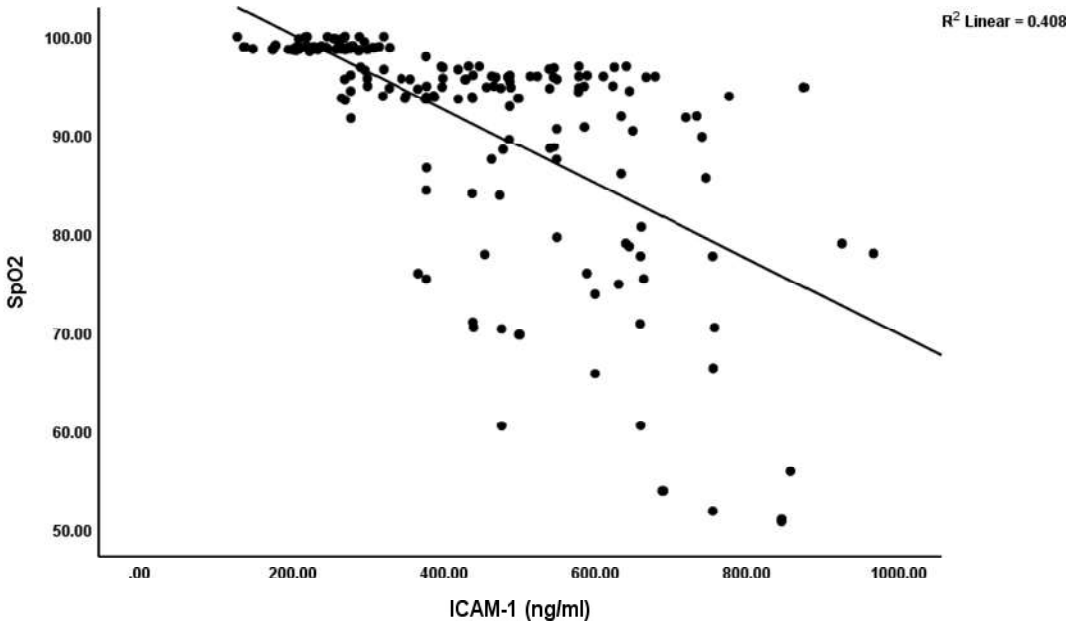
(B)


R² Linear = 0.227
150.00
145.00
140.00
135.00
130.00
125.00
120.00
SBP (mmHg)
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

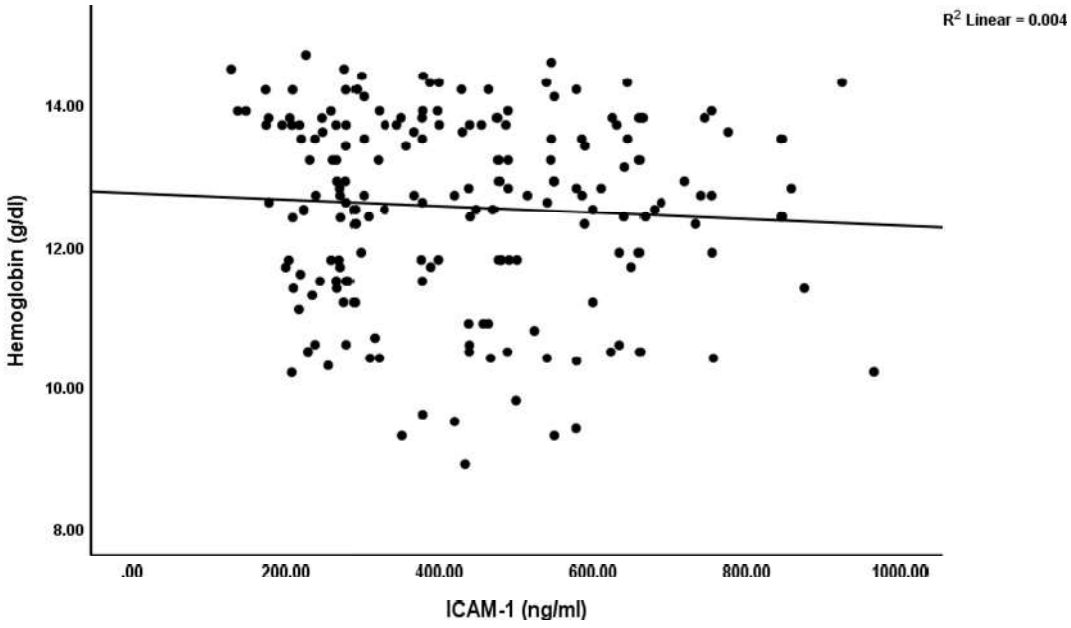
(C)


R² Linear = 0.001
90.00
85.00
80.00
75.00
70.00
DBP (mmHg)
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

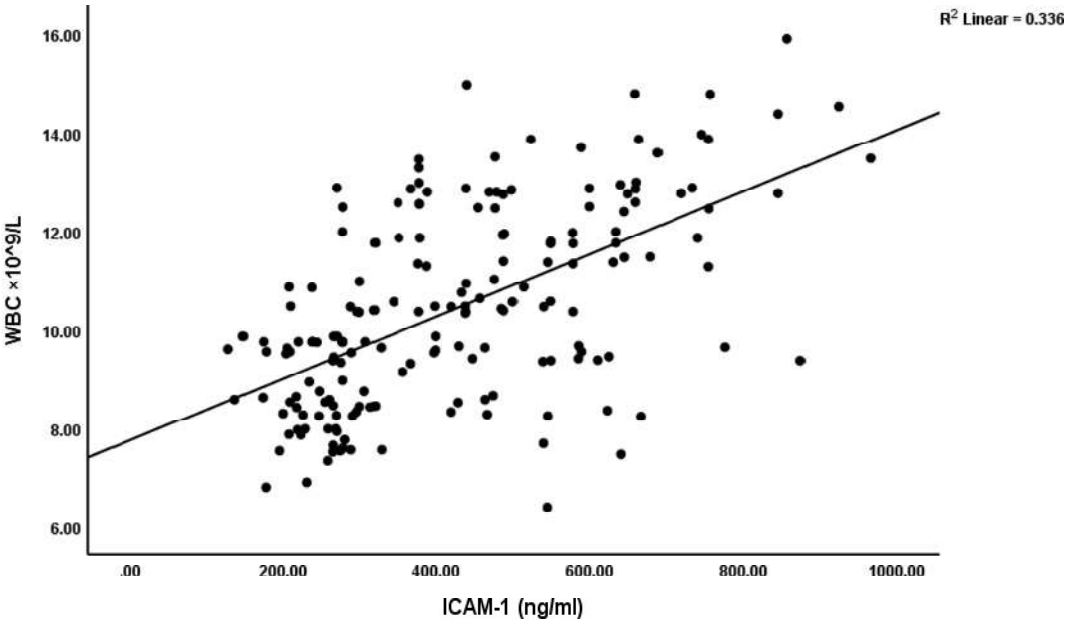
(D)


R² Linear = 0.408
SpO2
100.00
90.00
80.00
70.00
60.00
50.00
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

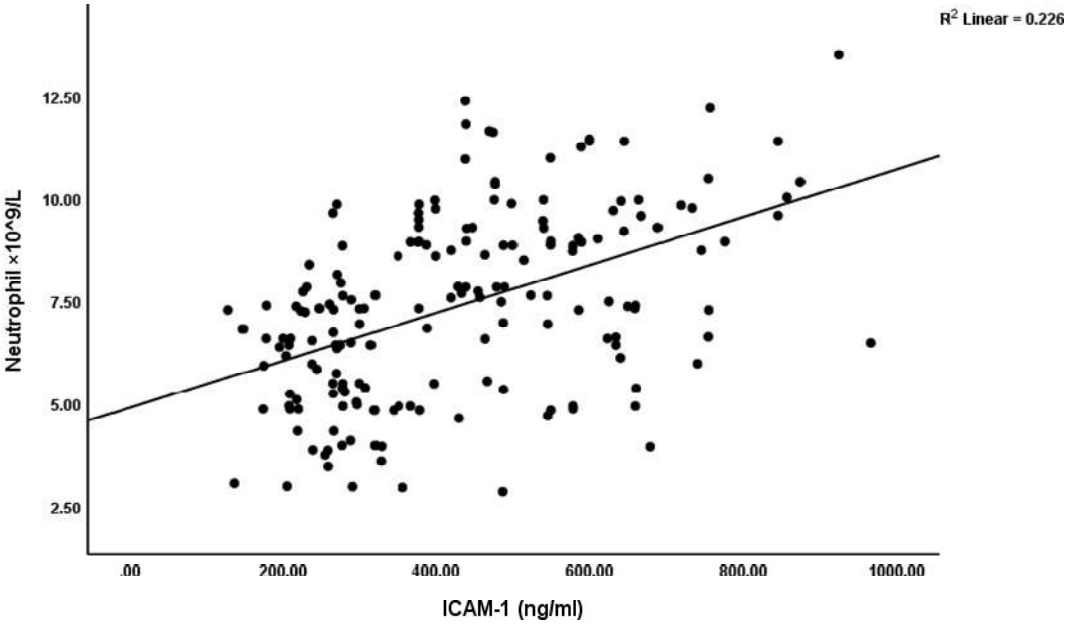
(E)


R² Linear = 0.004
Hemoglobin (g/dl)
14.00
12.00
10.00
8.00
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

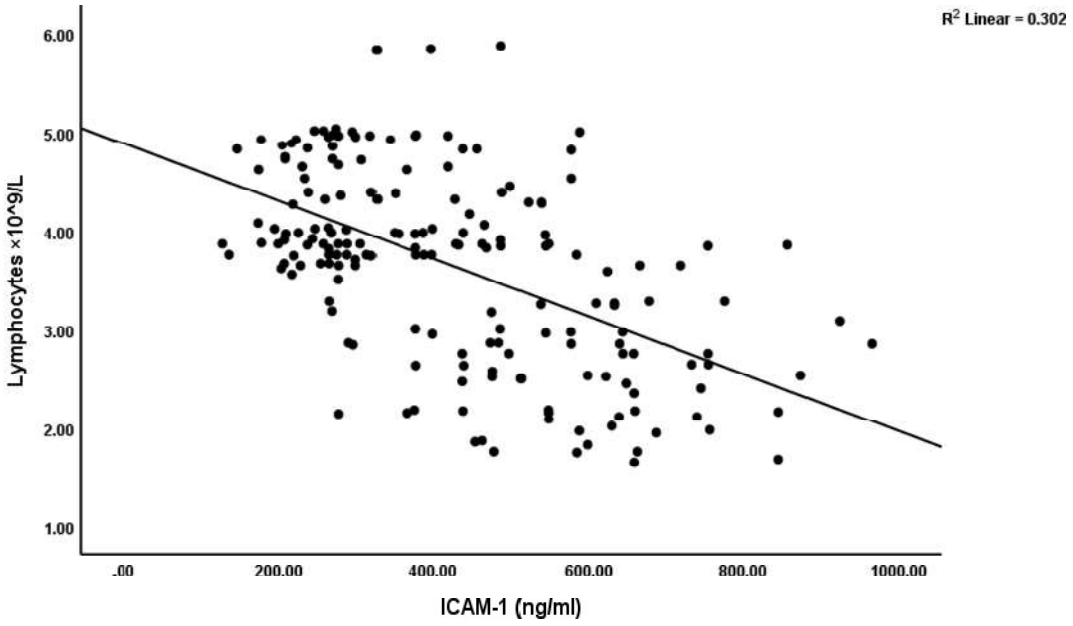
(F)


R² Linear = 0.336
16.00
14.00
12.00
10.00
8.00
6.00
WBC ×10^9/L
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

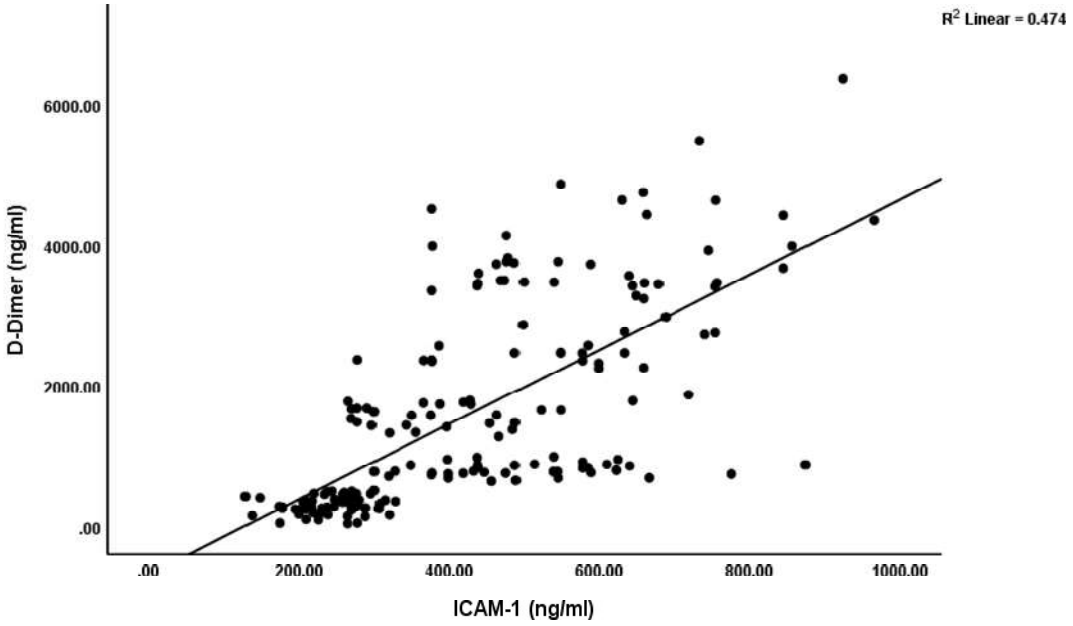
(G)


R² Linear = 0.226
12.50
10.00
7.50
5.00
2.50
Neutrophil ×10^9/L
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

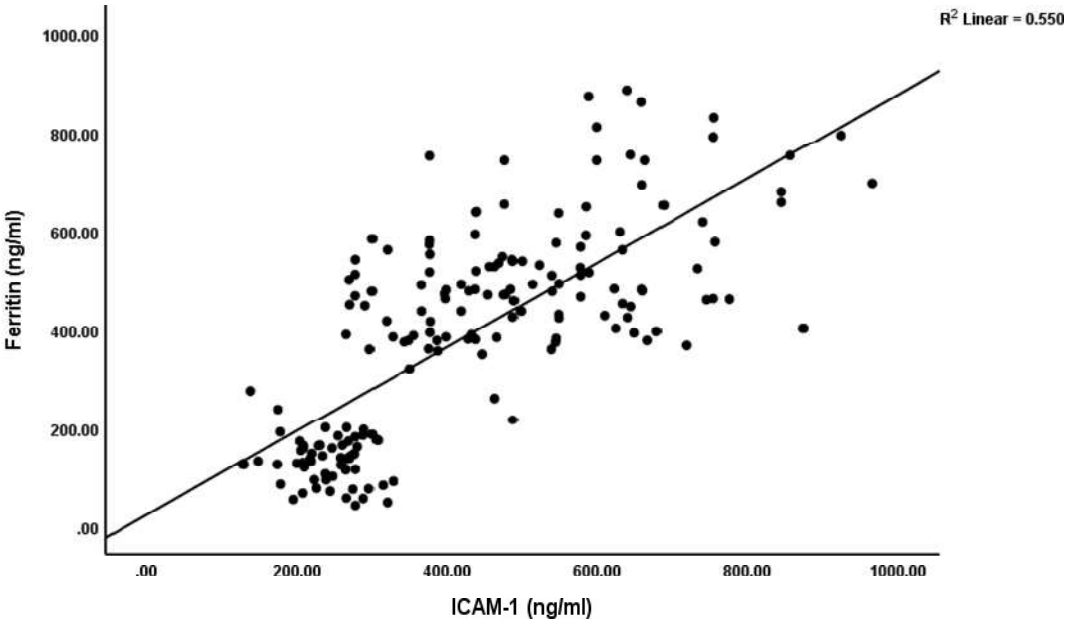
(H)


R² Linear = 0.302
Lymphocytes ×10^9/L
6.00
5.00
4.00
3.00
2.00
1.00
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

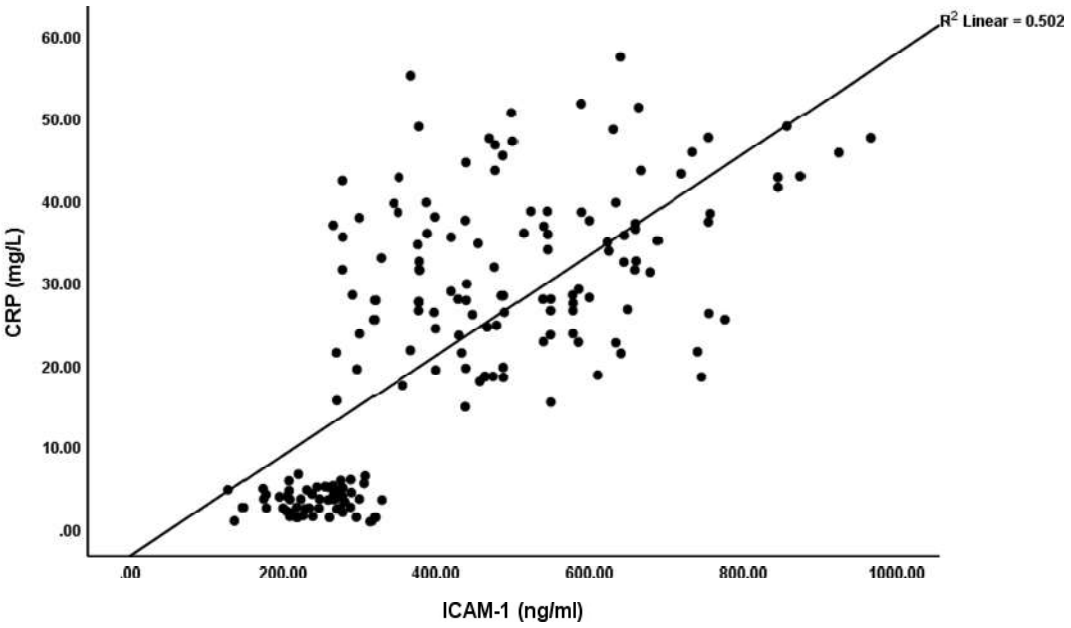
(I)


R² Linear = 0.474
D-Dimer (ng/ml)
6000.00
4000.00
2000.00
.00
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

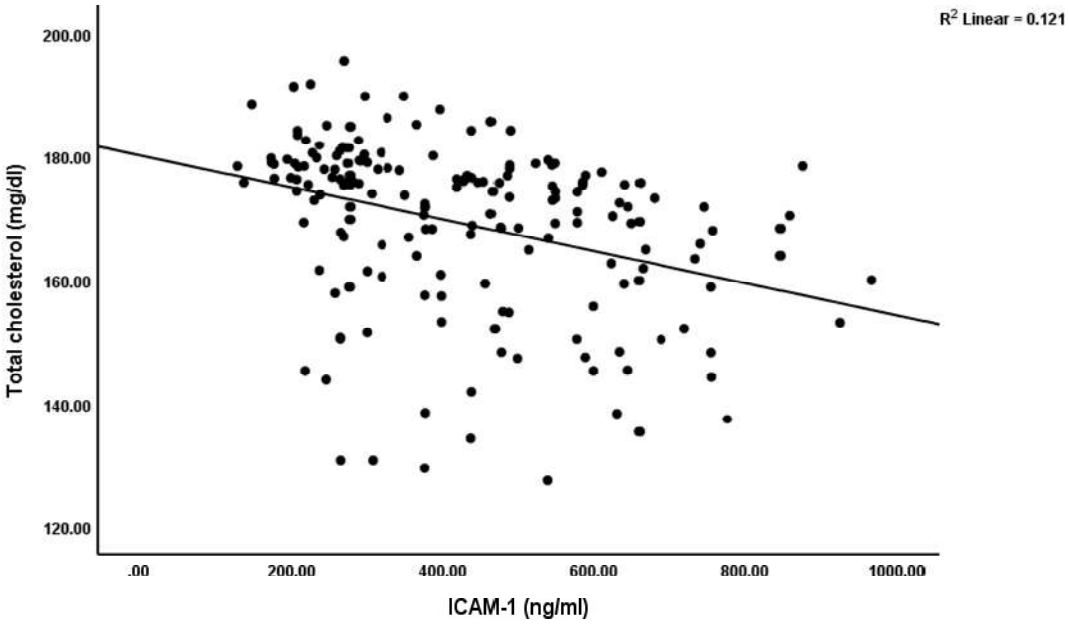
(J)


R² Linear = 0.550
Ferritin (ng/ml)
1000.00
800.00
600.00
400.00
200.00
.00
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

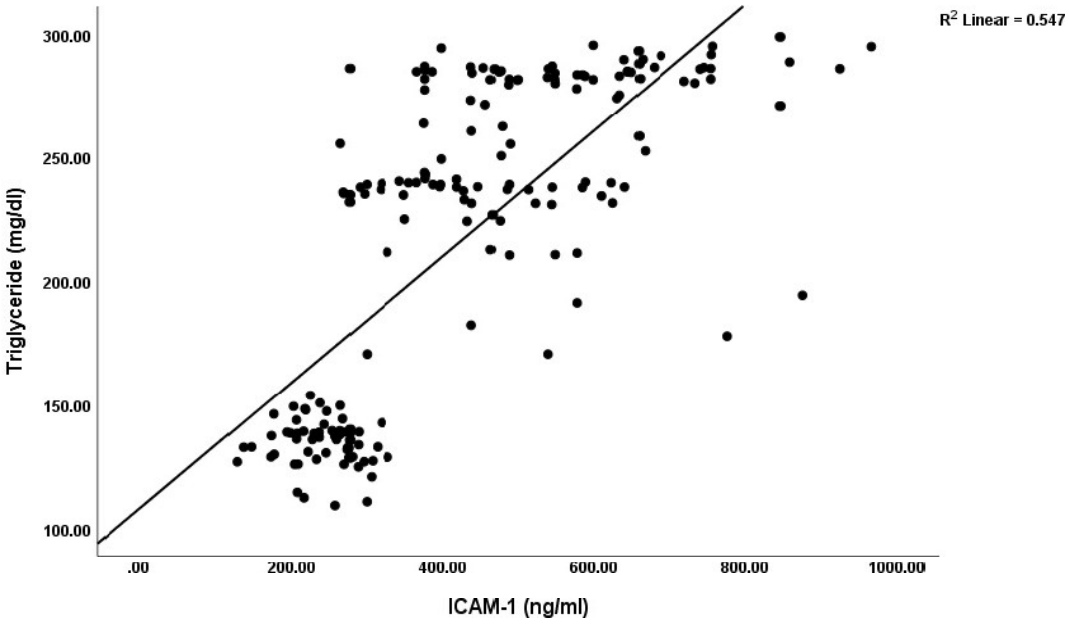
(K)


R² Linear = 0.502
CRP (mg/L)
60.00
50.00
40.00
30.00
20.00
10.00
.00
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

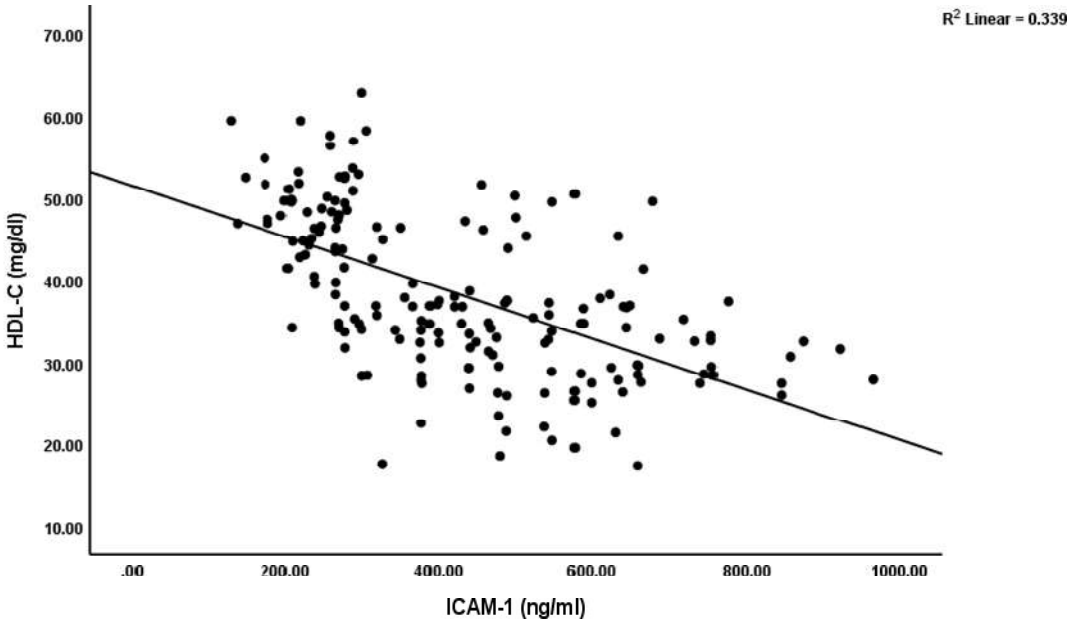
(L)


R² Linear = 0.121
Total cholesterol (mg/dl)
200.00
180.00
160.00
140.00
120.00
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

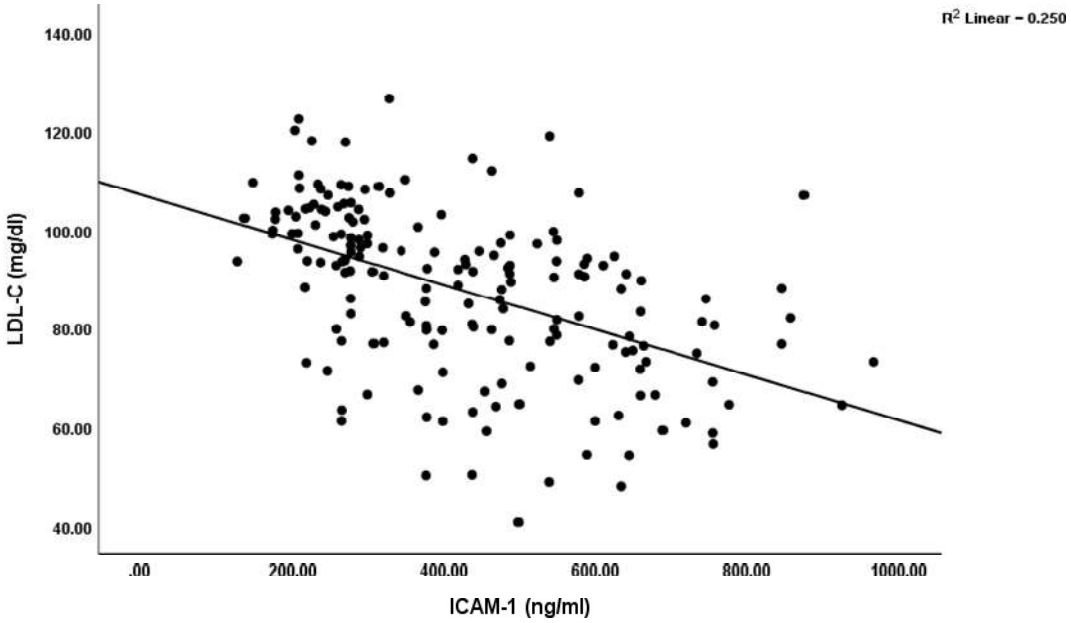
(M)


R² Linear = 0.547
Triglyceride (mg/dl)
300.00
250.00
200.00
150.00
100.00
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

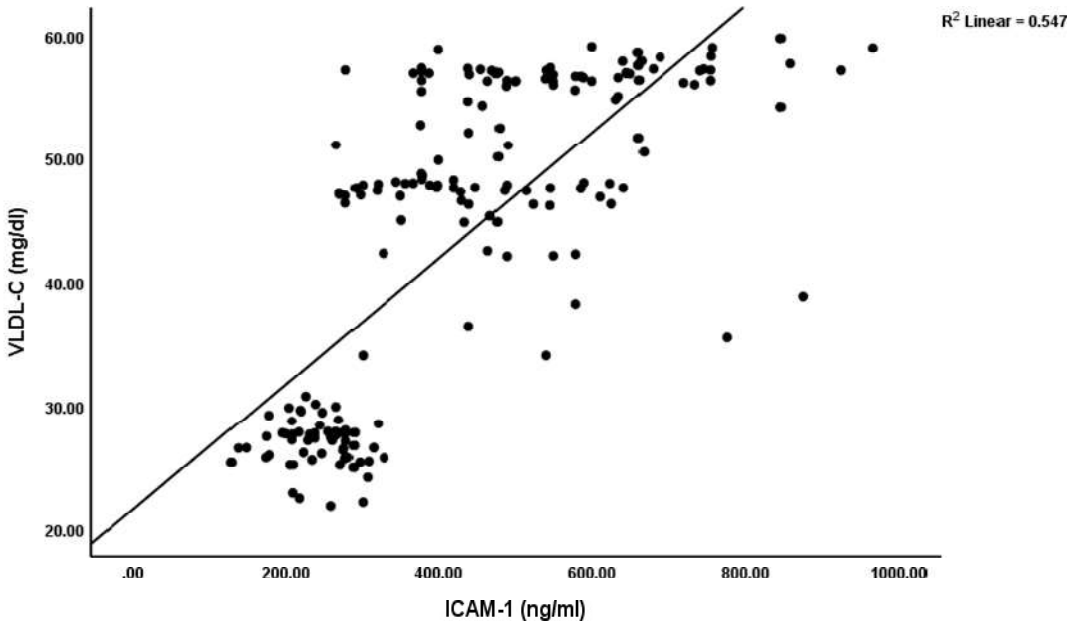
(N)


R² Linear = 0.339
70.00
60.00
50.00
40.00
30.00
20.00
10.00
HDL-C (mg/dl)
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

(O)


R² Linear = 0.250
140.00
120.00
100.00
80.00
60.00
40.00
LDL-C (mg/dl)
.00
200.00
400.00
600.00
800.00
1000.00
ICAM-1 (ng/ml)

(P)



(Q)

Figure 1. Correlation between serum ICAM-1 levels and (A) Age, (B) BMI, (C) SBP (D) DBP (E) SpO_2, (F) Hemoglobin, (G) WBCs (H), Neutrophil (I) Lymphocytes, (J) D-Dimer , (K) Ferritin, (L) CRP, (M) Total cholesterol, (N) Triglyceride , (O) HDL-C, (P) LDL-C, and (Q) VLDL-C.

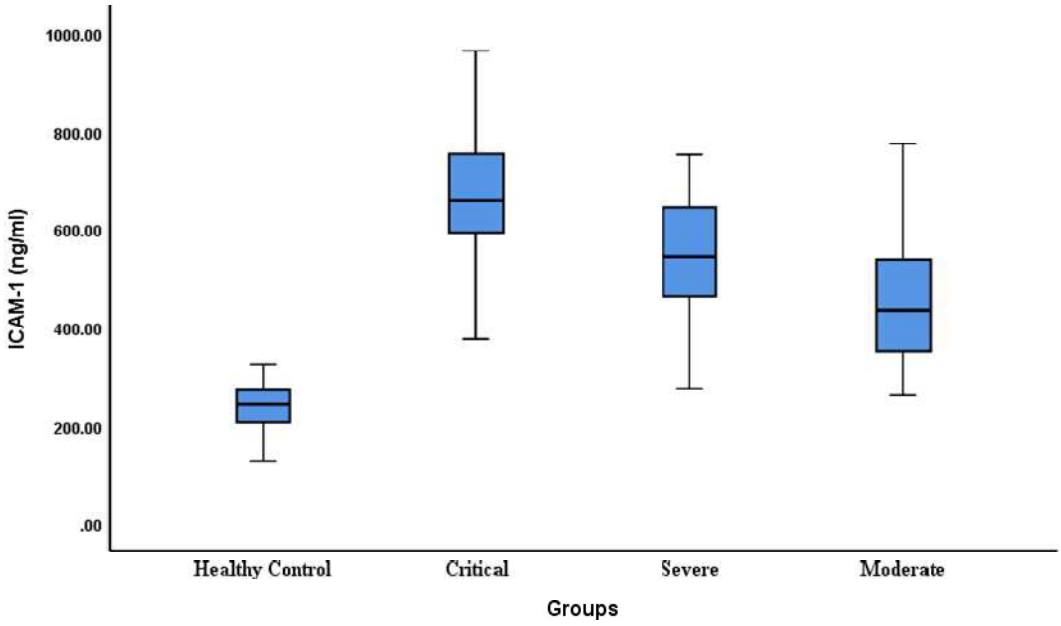


Figure 2. Comparison between groups (COVID-19 cases and healthy control) of ICAM-1 level.

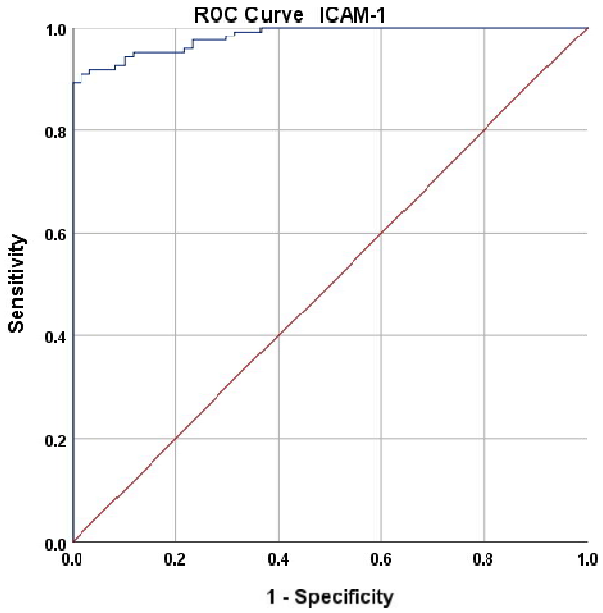


Figure 3. Receiver operating characteristic curve analysis of ICAM-1 for diagnosis of COVID-19.

Discussion

In this study, we determined that ICAM-1 levels was elevated in all cases patients with COVID-19. ICAM-1, levels was positively correlated with neutrophil, CRP, D-dimer and ferritin but negatively correlated with the Lymphocyte, SpO_2, total cholesterol, HDL-C, and LDL-C.It is hypothesized that vascular endothelial cells express adhesion molecules more often when infected with SARS-CoV-2. ICAM-1 overexpression is often caused by a variety of biological stressors, including oxidative stress, inflammation, and bacterial or viral infection[19–21]. In pathologic circumstances, matrix metalloproteinases break adhesion molecules bound in endothelial cell membranes and release them into the blood[22]. Numerous investigations shown that COVID-19 patients with severe illness have extremely higher levels of soluble ICAM-1[23,24].

Since the number of CD45+ cells in the lungs of COVID-19 patients increased it is possible to hypothesize that during SARS-CoV-2 infection, endothelial cells upregulate adhesion molecules in order to draw immune cells from the blood, and that this expression is then downregulated once immune cells have infiltrated the lungs. ICAM-1 may be downregulated on nearby endothelial cells as a result of endothelial microparticles released by stimulated endothelial cells[25]. Additionally, COVID-19 patients had abnormally high levels of plasma matrix metalloproteinase and enzymatic activity, which suggested that endothelial cells' membrane-bound adhesion molecules had been massively cleaved[26–28].

Notably, individuals with COVID-19 have been shown to have higher pla ma levels of adhesion molecules, particularly in severe instances, such as ICAM-1[24]. When compared to

healthy patients, Li et al. found that mild and severe COVID-19 cases had higher blood levels of VCAM-1 and ICAM-1[29] [61]. According to Kessel et al. research's, individuals with COVID-19 had higher blood levels of ICAM-1 than those with either macrophage activation syndrome or secondary hemophagocytic lymphohistiocytosis[30]. Plasma ICAM-1 levels in COVID-19-related acute respiratory distress syndrome non-survivors were reported to be greater than in survivors[31].

Leukocyte migration through endothelial cells is a critical phase of the immunological response [32]. ICAM-1 has been widely researched in relation to non-COVID-19 ICU outcome; ICAM-1 production has been demonstrated to be linked with higher mortality[33,34]. ICAM-1 regulates the strong adherence of neutrophils on the endothelium. The increased expression of endothelial cell adhesion molecules is associated with the severity of COVID-19 illness and may be a factor in coagulation dysfunction, according to research that linked blood levels of ICAM-1 and other molecules to patients' severity of the disease in ward settings [24].

In addition, a retrospective analysis of 39 patients with COVID-19 and 32 controls in China revealed that the former had considerably higher levels of ICAM-1 as well as other endothelial adhesion molecules, which may be a factor in coagulopathy [24]. Platelet activation, hypercoagulability, and high von Willebrand factor levels all appear to contribute to the coagulopathy associated with COVID-19 [23,35]. Therefore, the severity of COVID-19 may be influenced by an initial inflammatory process followed by a hypercoagulable condition.

In conclusion, our research shows that increased ICAM-1 levels are correlated with COVID-19 severity and act as an important prognostic indicator of disease.

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Declaration of Interests

The authors declare no conflict of interests

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