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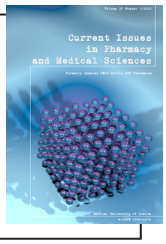

Serum of Interferon Lambda-1 level as a protein biomarker for the diagnosis of COVID-19 severity

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ABSTRACT

SARS-CoV-2, which mostly affects the respiratory system, is the agent that causes COVID-19. The virus enters human cells through the ACE2 receptor, which is expressed on the surface of many different types of cells in the body. Once inside the cell, the virus begins to replicate and spread throughout the body. Interferon Lambda-1, also known as IFN-λ1, is a type of cytokine that is secreted by the immune system of the body in response to viral infections.

Objective to evaluate if serum levels of Interferon Lambda-1 are associated with how severe the COVID-19 infection is, so as to determine if this cytokine may be considered as a disease marker.

This study was undertaken as a case control, using a study population of one hundred and twenty COVID-19 patients (79 males, 41 females). The COVID-19 patients were divided into three groups based on the severity of the illness: critical disease (n=30), severe disease (n=30), and mild/moderate disease (n=60), with (n=60) healthy volunteers as the control group (35 males, 25 females). Between January 2022 and May 2022, the patients were collected from Al-Amal hospitals and the AL-Shefaa center in AL- Najaf City, Iraq. Basic patient clinical and demographic data was obtained, along with blood samples. Enzyme-linked immunosorbent tests (ELISA) were used to measure the blood's concentration of interferon lambda-1. Total cholesterol, triglycerides and high density lipoprotein content were measured by colorimetric methods. Ichroma was tested for serum ferritin and D-dimer, while CBC was obtained via Swelab to ascertain if interferon Lambda-1 levels are related to the severity of the disease.

Interferon Lambda-1 levels in the patient group were determined to be higher, particularly in cases with mild to moderate (64.19±18.77) pg/mL (P=0.0001), severe (236.51±63.65) pg/mL (P=0.0001), and critical (465.61±62.16) pg/mL (P=0.0001) cases, as compared to healthy controls (41.72±12.92) pg/mL groups, respectively. Our results showed a significant negative correlation between SPO2%, Lymphocyte, HDL, TC and Hb (p.value=0.001) levels in the group of COVID-19 patients. TG, VLDL-C, neutrophils, WBCs, platelets, the N/L ratio, D-dimer, CRP and ferritin all have a significant positive correlation (p.value=0.001) with Interferon Lambda-1 in the COVID-19 patients group. A cutoff value of 50.50 (ng/mL) with a sensitivity of 82.5% and a specificity of 80.9% (AUC: 0.910, 95% CI 0.870-0.950; p<0.0001) for Interferon Lambda-1 predicted severe COVID-19.

In comparison to the mild/moderate patient group and healthy controls, we found that severe and critical COVID-19 patients had considerably greater serum Interferon Lambda-1 concentrations. This could be a useful sign of the disease's severity. In order

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to prevent the onset of pulmonary inflammation, high blood Interferon Lambda-1 concentrations in the early stages of COVID-19 should be continuously monitored. Our work also revealed that Interferon Lambda-1 was highly associated with COVID-19 severity. We believe that Interferon Lambda-1 may be a valuable biomarker in determining the severity of the disease in COVID-19 patients.

INTRODUCTION

The novel coronavirus was given the name SARS-CoV-2 due to its 80% similarity to the severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), which caused acute respiratory distress syndrome (ARDS) and significant mortality between 2002 and 2003 (2019–nCoV) (1). Presently, it is commonly acknowledged that ARDS can cause COVID-19 respiratory symptoms that range from barely noticeable, to severely hypoxic (2). The data from Wuhan described above shows that there was only a 9-day gap between the onset of symptoms and the onset of ARDS, indicating that the respiratory symptoms could progress quickly (3). Acute shortness of breath, fever, muscle soreness and loss of taste and smell are just a few of the moderate symptoms that COVID-19 can produce (4). This illness may also be lethal. Elderly individuals have higher mortality rates, according to epidemiological studies (5) and children have a substantially lower incidence [6,7].

Interleukin (IL)-29, commonly known as interferon (IFN)-λ1, is a recent addition to the IFN- or Type III IFN family. The three members of the Type III IFN family are IFN-1 (IL-29), IFN-2 (IL28A), and IFN-3 (IL-28B). IFN-λ1has been demonstrated to play a substantial role in the pathogenesis of various autoimmune and inflammatory illnesses, including systemic sclerosis, rheumatoid arthritis and systemic lupus erythematosus [8,9].

These cytokines are part of the antiviral family of cytokines, which includes type I IFNs and members of the IL-10 family. Two tyrosin kinases, Janus kinase 1 and tyrosine kinase 2, are activated as a result of IFN-λ1-mediated signaling through a receptor complex containing IL-28R1 and IL-10R2, which enables phosphorylation and activation of STAT1 and STAT2 [10,11]. Although various immune cells, including dendritic cells, macrophages and Th17 cells, are cellular sources of IFN-λ1, it is mostly produced in epithelial tissues [12,13]. IFN-λ1 is increased in cells that are infected with viruses and plays a crucial part in the host's defense against microorganisms. In numerous tumors, such as lung cancer, esophageal.

IFN-λ1 is increased in cells that are infected with viruses and plays a crucial part in the host's defense against microorganisms. In numerous tumors, such as lung cancer, esophageal, carcinomas and colorectal cancer [14], IFN-λ1 has an anticancer impact. IFN-λ1 also has antiviral and antitumor properties, and it modulates the immune system in allergic asthma and rheumatoid arthritis cases [15,16]. Lipids are important in the spread of viral infection, being the stuctural foundations of cellular and viral membranes [17,18]. Viruses alter host cells to create lipids for their envelopes by attacking lipid synthesis and signaling [19,20].

Since lipids play a crucial role in membrane fusion, envelopment and transformation during viral replication, chemicals that affect lipids like cholesterol and sphingolipids may be specifically targeted to prevent viral reproduction [21]. Viruses must enter and depart the host cell through the membrane because they reproduce inside the host cell [17,22]. Lipids have a range of functions in viral invasion, including acting as entry cofactors, fusion cofactors, and direct and indirect viral receptors [19,23].

MATERIALS AND METHODS

One hundred twenty individuals (79 men and 41 women) with COVID-19 participated in the case-control study that was undertaken for this research. The COVID-19 patients were divided into three groups based on the severity of the illness: critical/death cases (n=30), severe disease (n=30), and mild/moderate disease. (n=60), with (n=60) healthy volunteers as the control group (35 males, 25 females). Between January 2022 and May 2022, the Al-Amal hospitals and the AL-Shefaa facility in Al-Najaf City, Iraq, provided the patients. All of the patients' fundamental clinical and demographic data were collected, along with blood samples. They were diagnosed quantitatively by RT-PCR and chest X-ray or CT scan at 7-12 days from the onset of symptoms. All were all older than 20 years old. The patients were gathered at the time of admission for the COVID-19 study, and Murray scores were used to evaluate the severity of the condition (24). The period from January 2022 to May 2022 was used for sample collecting.

Patients with a history of vasculitis connective tissue disease who were currently on long-term treatment with oral corticosteroids, IL-6 antagonists or TNF antagonists, were not included in the study. Those with chronic diseases such as diabetes, cardiovascular disease, infection and inflammation were also excluded from the study. Moroever, patients with cancer, kidney disorders, smokers and thyroid problems were not enrolled in the study. In addition, any patient who received anti-COVID vaccination in the past six months or less, as well as any patient under the age of 20, was also ineligible.

Five mL of samples of venous blood were taken from patients and controls. It was divided into two tubes to separate the blood samples. The first 3 mL was allowed to clot at room temperature for 10-15 minutes prior to serum being obtained by centrifugation at (3000 rpm) for 10 minutes. Serum samples were then divided into tubes and kept at -20°C until the time of analysis. The second tube contained 2 mL of blood with the anticoagulant EDTA for the purpose of complete blood count (CBC) measurement, which was obtained via an automatic hematology analyzer (Swelab Alpha, Swedish in origin).

To measure serum ferritin and dimer levels, a Fluorescent Immunoassay (FIA) was used. To measure interferon (IFN)-λ1, an Enzyme-linked immune sorbent assays (ELISA) were employed to detect the concentration levels in the serum sample. Finally, ichroma TM technology was

applied to measure the levels of CRP in the serum sample.

Patient were assessed to have mild to moderate COVID-19 because of high fever, respiratory symptoms, as well as radiological indicators of pneumonia. Patients were classified as having severe COVID-19 if any of the following changes were found in their patients:

1. Respiratory rate of more than 30 times per minute.
2. Oxygen saturation being less than 94 % SpO2 at room temperature.
3. Lung leakage greater than 50% as indicated via low-dose computed tomography.
4. Admission of the patient to the intensive care unit for the purpose of using mechanical ventilation due to the collapse of the patient's respiratory system [25].

Critical Illness: Patients with acute respiratory distress syndrome (ARDS), septic shock, multi-organ failure and coagulation problems. In addition, any patient who had passed away during the course of the study was not counted as having survived their illness. This inquiry study was given its stamp of approval by the local medical ethics committee, as well as by each participant individually and collectively before the study began. The patients were asked to fill out registration forms, after which a list containing their names was given to them.

Table 1. Demographic and clinical characteristics of the patient's categories and control groups

Parameters	Control Group Mean±SD N=60	Patient Groups			P. value			
		Mild/ Moderate Mean±SD N=55	Severe Mean±SD N=35	Critical Mean±SD N=30				
No.	60	60	30	30				
No. M/F	35/25	22/38	20/10	21/9				
Age (Years)	37.61 ±10.96	38.26 ±11.27	40.86 ±11.72	41.96 ±10.28	A0.014	B0.023	C0.573	D0.036
Height (m)	1.70 ±0.10	1.68 ±0.09	1.67 ±0.07	1.71 ±0.08	A0.121	B0.086	C0.941	D0.185
Weight (kg)	73.36 ±10.45	75.81 ±9.57	78.16 ±11.46	73.86 ±12.03	A0.119	B0.413	C0.324	D0.128
BMI (kg/m²)	25.54 ±4.84	27.19 ±4.40	27.97 ±4.26	25.26 ±3.66	A0.091	B0.051	C 0.435	D0.068
SBP (mmHg)	128.75 ±5.51	129.50 ±14.11	135.12 ± 16.40	138.75 ±12.20	A0.03	B0.01	C0.01	D0.001
DBP (mmHg)	79.86 ± 4.10	78.30 ±7.40	77.53 ±8.32	81.30 ±15.43	A0.01	B0.01	C0.11	D0.01
SPO2%	98.8 ±0.75	93 ±0.52	87.32 ±6.55	71 ±10.32	A0.001	B0.001	C0.01	D0.001
Hb (g/dL)	12.77 ±1.36	12.86 ±1.33	12.13 ±1.38	12.56 ±1.03	A0.208	B0.304	C0.014	D0.431
T-WBC ×109/L	8.65 ±0.96	10.12 ±1.32	12.02 ±0.66	13.30 ±1.01	A0.0001	B0.0001	C0.0001	D0.0001
Neut.×109/L	5.89 ±1.54	7.44 ±1.77	8.78 ±1.94	9.49 ±1.78	A0.114	B0.0001	C0.001	D0.0001
Lym.×109/L	3.93 ±0.55	3.65 ±0.80	3.07 ±0.72	2.21 ±0.66	A0.0001	B0.0001	C0.0001	D0.0001
NLR	1.53 ±0.47	2.15 ±0.76	3.04 ±1.05	4.64 ±1.54	A0.0001	B0.0001	C0.0001	D0.0001
PLT×109/L	297.25 ±35.55	241. ±37.07	277.23 ±46.78	296.83 ±36.91	A0.049	B0.0001	C0.0001	D0.0001
D-dimer (ng/mL)	306.70 ±115.87	1121.28 ±404.43	2513.81 ±401.65	3883.63 ±891.92	A0.0001	B0.0001	C0.0001	D0.0001
Ferritin (ng/mL)	147.06 ±53.68	435.56 ±83.45	475.93 ±65.91	846.43 ±66.45	A0.0001	B0.0001	C0.514	D0.0001
CRP (ng/mL)	3.33 ±1.46	24.26 ±5.64	58.87 ±8.21	74.21 ±6.44	A0.0001	B0.0001	C0.0001	D0.0001
TG (mg/dL)	132.50 ±8.39	231.31 ±22.12	269.54 ±18.46	279.87 ±13.59	A0.017	B0.0001	C0.0001	D0.0001
TC (mg/dL)	171.1 ±12.897	169.35 ±14.29	161.95 ±9.79	157.86 ±27.64	A0.328	B0.002	C0.046	D0.0068
HDL.C (mg/dL)	46.95 ±6.41	34.60 ±6.15	34.26 ±9.51	29.13 ±4.96	A0.004	B0.0001	C0.825	D0.0001
VLDL.C (mg/dL)	26.96 ±1.67	46.26 ±4.42	53.91 ±3.69	55.01 ±6.42	A0.291	B0.0001	C0.0001	D0.0001
LDL.C (mg/dL)	97.64 ±12.46	88.48 ±16.11	73.77 ±13.25	67.54 ±12.76	A0.092	B0.0001	C0.0001	D0.0001
Interferon λ-1 (pg/mL)	41.72 ±12.92	64.19 ±18.77	236.51 ±63.65	465.61 ±62.16	A0.0001	B0.0001	C0.0001	D0.0001

Data represented as: Mean±SD – standard deviation, SBP – Systolic blood, Pressure, DBP diastolic blood pressure SPO2% – Oxygen saturation percentage, Hb – hemoglobin, WBC – White blood cell, LYM – lymphocyte, Neut – neutrophil, NLR – neutrophil/ lymphocyte ratio, PLT – Platelet; CRP – C-reactive protein, TG – triglyceride, HDL.C – High density lipoprotein cholesterol, TC – total cholesterol, LDL.C – low density lipoprotein cholesterol, VLDL.C – Very Low Density Lipoprotein cholesterol. A=p. value (Critical×Severe), B=p.value (Critical×Moderate), C=p.value (Severe×Moderate), and D=(All COVID-19 patients×healthy control)

Statistical Analyses

An IBM SPSS 26 program was used to conduct statistical studies. The mean and standard deviation of the analysis' results were determined. The threshold for statistical significance was $p<0.05$. Two independent samples were compared via Student's t-test. For the purpose of evaluating the parametric variables, we employed the Pearson's correlation cofficient method, while analysis of variance (ANOVA) was implemented in the study to examine any changes in the scale variables between groups. To determine the cut-off value of the interferon (IFN)-λ1, An approach called receiver operating characteristic (ROC) analysis was applied. The ROC curve was used to compute the area under the curve (AUC) value.

RESULTS

The severity of COVID-19 was used to classify each of the 120 patients who participated in this study. As stated in Table 1, sixty healthy individuals served as a control, and one hundred and twenty as a patients.

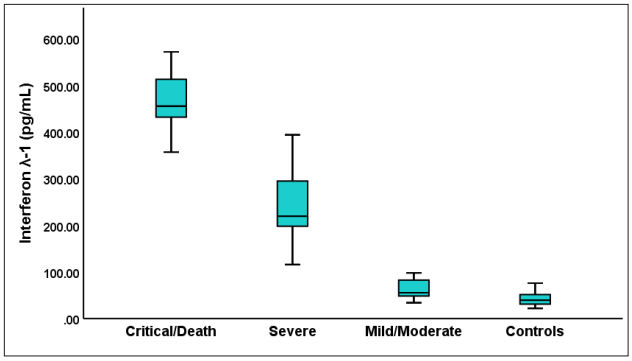


Figure 1. Comparison of Interferon λ-1 level between categories of COVID-19 patients groups and control group

As indicated in Table 1, the mean age in the group of patients (Critical) has significant difference as compared with healthy group (55.96±10.28, 47.61±10.96 years, respectively; p=0.05). There were no statistically significant variations in the BMI subgroup distributions, however, among the three disease severity categories. Statistically significant

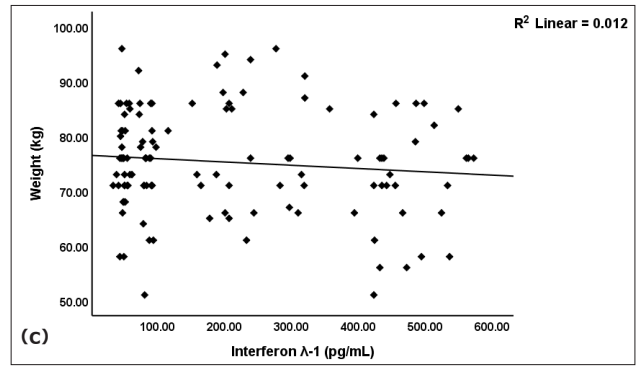
changes in the means of the laboratory measures reported in Table 1 between the three groups of illness severity were seen for all, save Hb. Comparison of patients with mild/moderate, severe, and critical test findings were comparable with controls in the data of serum Interferon-λ1 levels (41.72±12.92, 64.19±18.77, 236.51±63.65, 465.61±62.16, respectively), ferritin (147.06±53.68, 435.56±83.45, 475.93±65.91, 846.43±66.45, respectively), D-dimer (306.70±115.87, 1121.28±404.43, 2513.81±401.65, 3883.63±891.92, respectively) and CRP (3.33±1.46, 24.26±5.64, 58.87±8.21, 74.21±6.44, respectively).

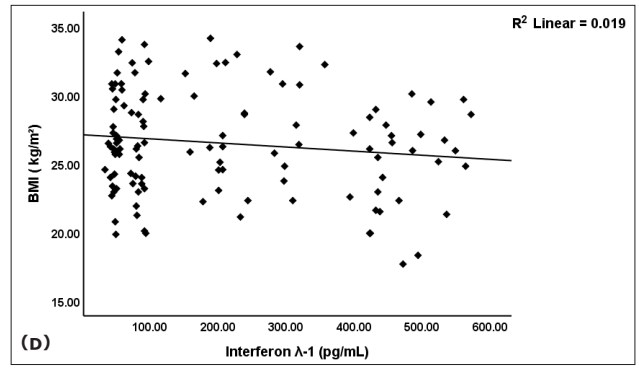
Table 2 and Figure 2 show that a significant negative correlation was obtained between Weight, BMI, SBP, DBP, SPO2, Hb., Lymphocyte,TC, HDL.C, and LDL.C levels in the COVID-19 patients group. At the same time, a significant positive correlation was obtained between Age, Height, T.WBCs, Neutrophil, NLR, Platelet, D-dimer, Ferritin, CRP, TG and VLDL.C levels, with Interferon -λ1 levels in the COVID-19 patients group.

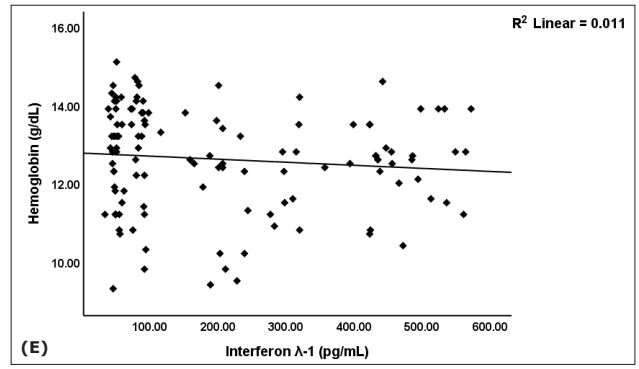
Table 2. Correlation analysis between serum Interferon λ-1 with biochemical parameters in COVID-19 patients

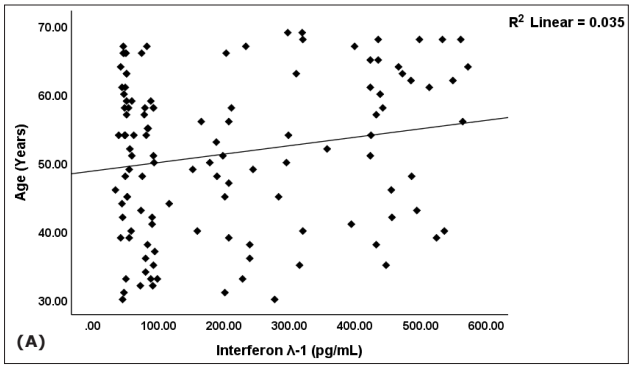
Variables	r	p-value	Variables	r	p-value
Age (Years)	0.187	0.05	Platelet ×109/L	0.460	0.01
Height (m)	0.153	NS	D- Dimer (ng/mL)	0.943	0.01
Weight (kg)	-0.109	NS	Ferritin (ng/mL)	0.760	0.01
BMI (kg/m²)	-0.137	NS	CRP (mg/L)	0.899	0.01
Hb (g/dL)	-0.104	NS	TG (mg/dL)	0.673	0.01
T-WBCs×109/L	0.746	0.01	TC (mg/dL)	-0.437	0.01
Neutrophil×109/L	0.407	0.01	HDL-C (mg/dL)	-0.325	0.01
Lymphocyte×109/L	0.600	0.01	LDL-C (mg/dL)	-0.461	0.01
NLR	0.654	0.01	VLDL-C (mg/dL)	0.651	0.01

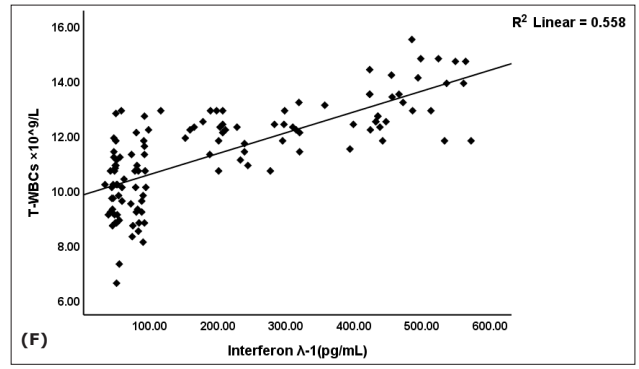
r=Pearson's correlation coefficient, NS – Non-significant

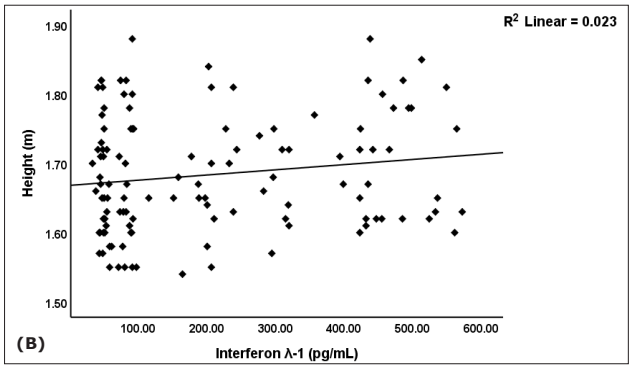


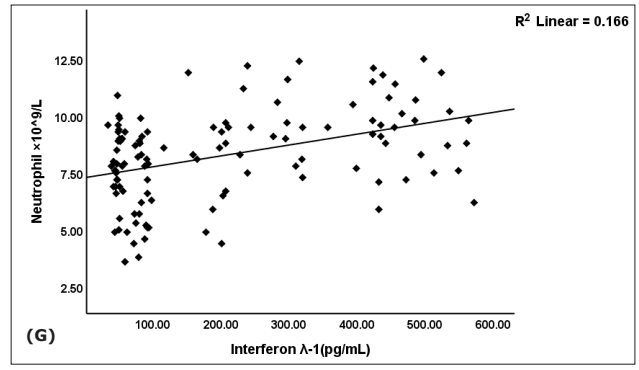


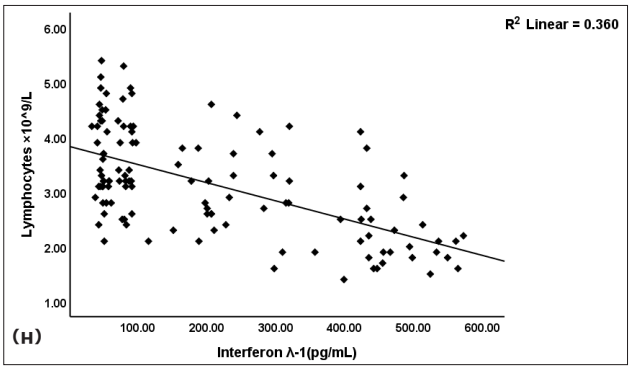


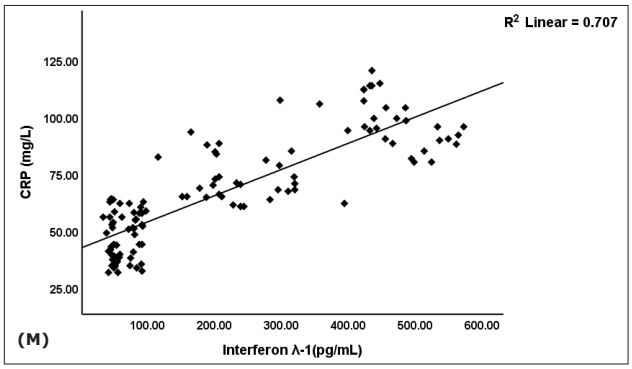


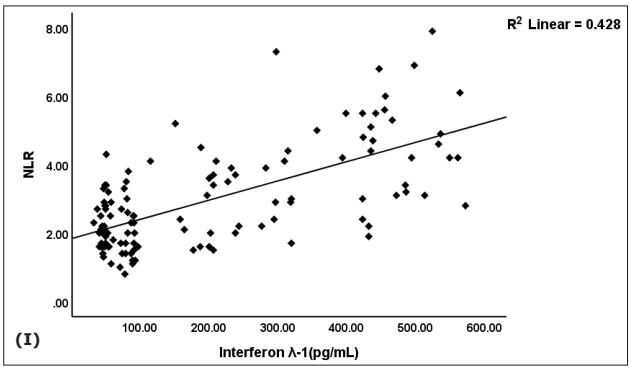


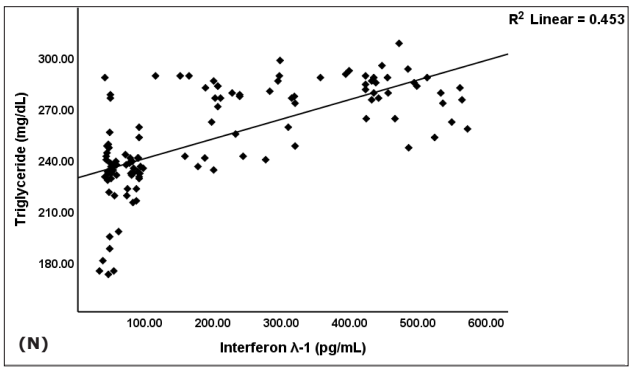


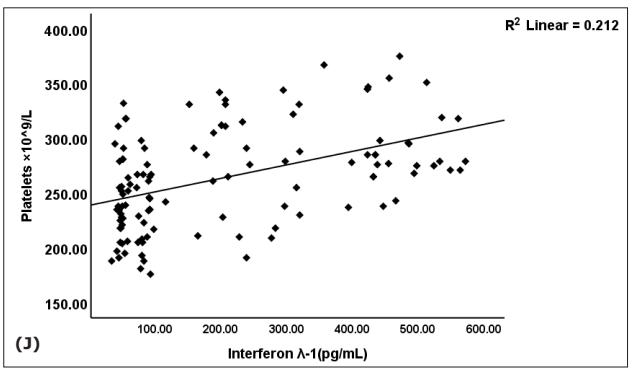


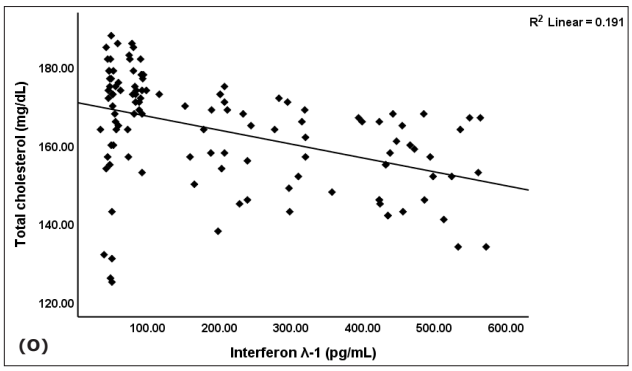

R² Linear = 0.360
Lymphocytes ×10^9/L
6.00
5.00
4.00
3.00
2.00
1.00
100.00
200.00
300.00
400.00
500.00
600.00
Interferon λ-1(pg/mL)
(H)

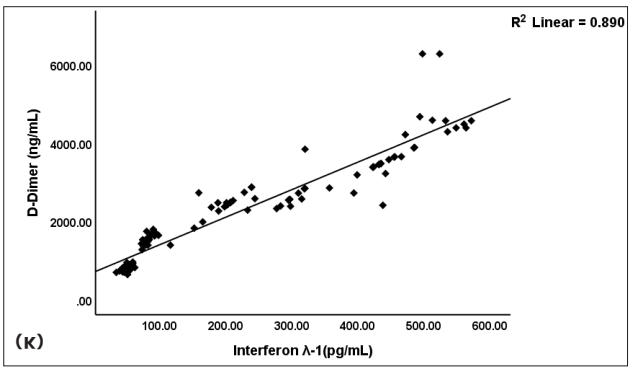

R² Linear = 0.707
CRP (mg/L)
125.00
100.00
75.00
50.00
25.00
100.00
200.00
300.00
400.00
500.00
600.00
Interferon λ-1(pg/mL)
(M)

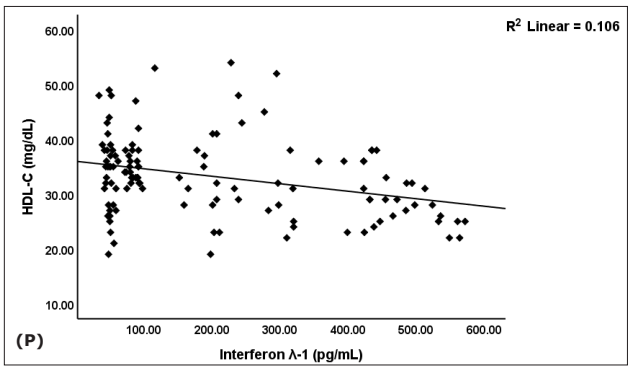

R² Linear = 0.428
NLR
8.00
6.00
4.00
2.00
.00
100.00
200.00
300.00
400.00
500.00
600.00
Interferon λ-1(pg/mL)
(I)

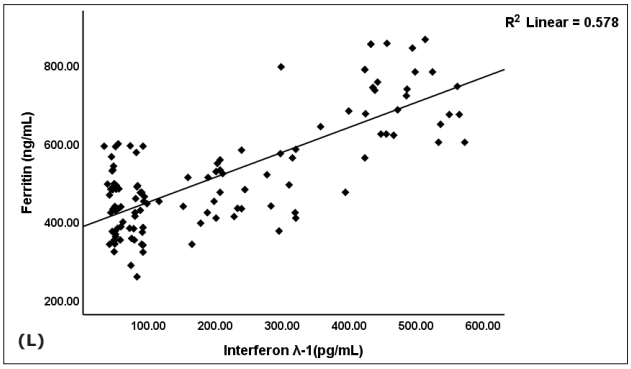

R² Linear = 0.453
Triglyceride (mg/dL)
300.00
270.00
240.00
210.00
180.00
100.00
200.00
300.00
400.00
500.00
600.00
Interferon λ-1 (pg/mL)
(N)

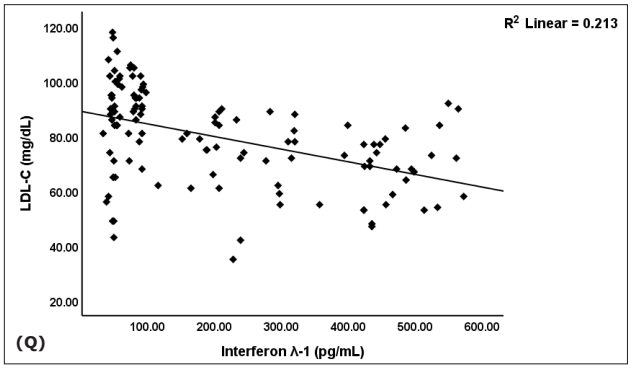

R² Linear = 0.212
Platelets ×10^9/L
400.00
350.00
300.00
250.00
200.00
150.00
100.00
200.00
300.00
400.00
500.00
600.00
Interferon λ-1(pg/mL)
(J)


R² Linear = 0.191
Total cholesterol (mg/dL)
180.00
160.00
140.00
120.00
100.00
200.00
300.00
400.00
500.00
600.00
Interferon λ-1 (pg/mL)
(O)


R² Linear = 0.890
D-Dimer (ng/mL)
6000.00
4000.00
2000.00
.00
100.00
200.00
300.00
400.00
500.00
600.00
Interferon λ-1(pg/mL)
(K)


R² Linear = 0.106
HDL-C (mg/dL)
60.00
50.00
40.00
30.00
20.00
10.00
100.00
200.00
300.00
400.00
500.00
600.00
Interferon λ-1 (pg/mL)
(P)


R² Linear = 0.578
Ferritin (ng/mL)
800.00
600.00
400.00
200.00
100.00
200.00
300.00
400.00
500.00
600.00
Interferon λ-1(pg/mL)
(L)


R² Linear = 0.213
LDL-C (mg/dL)
120.00
100.00
80.00
60.00
40.00
20.00
100.00
200.00
300.00
400.00
500.00
600.00
Interferon λ-1 (pg/mL)
(Q)

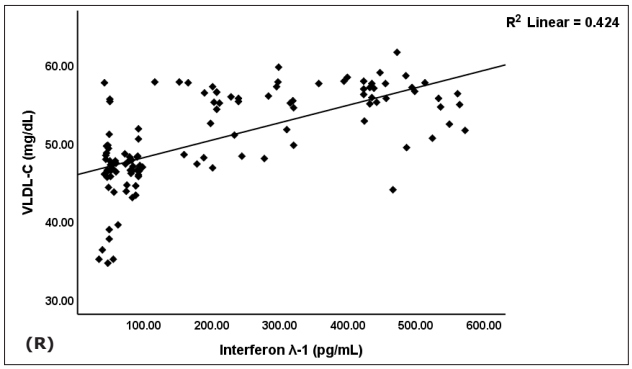


Figure 2. Correlation between serum Interferon (IFN)-λ1 levels and A – Age, B – Height, C – Weight, D – BMI, E – Hemoglobin, F – T-WBCs, G – Neutrophil, H – Lymphocytes, I – NLR, J – Platelet, K – D-Dimer, L – Ferritin, M – CRP, N – TG, O – TC, P – HDL-C, Q – LDL-C, and R – VLDL-C

Table 3. Receiver operating characteristic-area under curve analysis of the measured Interferon-λ1 for the diagnosis of COVID-19

Variable	Cut-off concentration	Sensitivity %	Specificity %	AUC	95% CI of AUC	p-value
Interferon λ-1 (pg/mL)	50.50	82.5	80.9	0.910	0.870-0.950	<0.0001

Also we show in Figure 3 demonstrates that in using a ROC analysis, the capacity of Interferon-λ1 to foretell the progression of illness is assessible. The area under the curve (AUC) for Interferon-λ1 was 0.910 (95% CI, 0.870-0.950, p<0.0001). The sensitivity of Interferon-λ1 for predicting the severity of illness was calculated to be the specificity was calculated to be 80.9%.

82.5% when the cutoff value of 50.50 was established, while

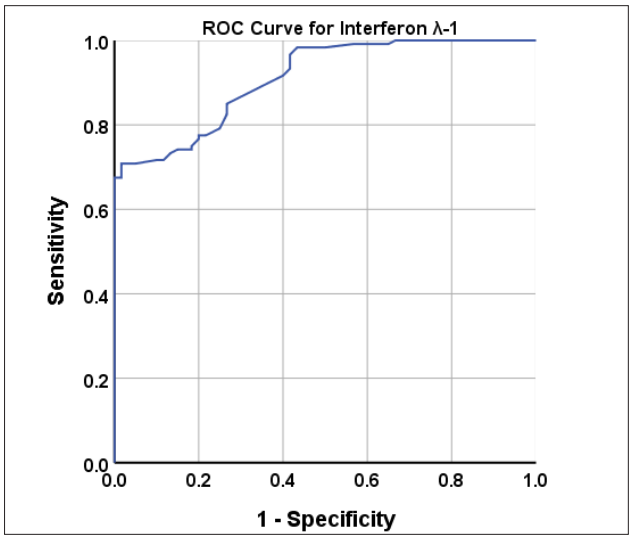


Figure 3. Sensitivity and specificity calculations in the ROC analysis

DISCUSSION

There is considerable interest in the correlation between gender and illness severity with regard to COVID-19. Despite the fact that there were an equal number of male and female cases in the Chinese series, according to the data, men died from severe illnesses at a higher rate than women [26,27].

Comparable outcomes were shown by the data from other nations [27]. Comorbidities such as hypertension, heart disease and lung disease were linked to negative COVID-19 results. These problems are more common in men and are associated with smoking and alcohol consumption [28]. Another factor suggested was sex-based variations in immunology [29]. In addition, a study that looked at factors influencing protective behavior adoption, specifically in the setting of pandemics, discovered that non-pharmaceutical actions, such as hand washing, wearing a face mask and avoiding crowds, were practiced by women almost 50% more frequently than by men [30], which may be in part responsible for the morbidity differences.

A virus's life cycle in a host goes through five stages: attachment, penetration, biosynthesis, maturation and release [31], therefore, interferons (IFNs) and inflammatory cytokines are necessary for the treatment of viral lung infections, but their relative contributions to host defense and the restoration of homeostasis are yet unknown. Type III IFNs (IFN-), in particular, have received a lot of interest since they function largely at mucosal surfaces [32]. Recent research has demonstrated that, in contrast to other IFNs, IFN-signaling stimulates antiviral actions while concomitantly restricting neutrophil capacity to repair damage tissue [34,35].

One study published in the Journal of Interferon & Cytokine Research found that IFN-λ1(IL-29) levels were significantly elevated in COVID-19 patients, as compared to healthy controls, suggesting that IFN-λ1(IL-29) may be involved in the immune response to COVID-19 [35]. Another study published in the Journal of Medical Virology found that IFN-λ 1 (IL-29) had the potential to reduce inflammation and viral replication in COVID-19 patients, making it a potential therapeutic target for COVID-19 treatment [36].

Overall, while more research is needed to fully understand the correlation between IFN-λ1(IL-29) and COVID-19, these studies suggest that IFN-λ1 may play a role in the immune response to COVID-19 and could be a target for future COVID-19 therapies.

Research studies have suggested that interferon lambda 1 (IFN-λ1) could play a role in countering the SARS-CoV-2 virus that causes COVID-19. A review of studies on the subject, published in the Journal of Medical Virology, found that "Type III IFNs (IFN-λ) could play an important role in this and other emerging viral infections", including COVID-19 [37]. Inded, research has shown that interferons, such as IFN-alpha2, can block the coronavirus from infecting human cells [38]. Another study found that lambda interferon can reduce viral load and hyperinflammation in COVID-19 patients [39]. A large-scale trial enrolling the majority of outpatients who received the COVID-19 vaccine and had symptoms of the disease also revealed that a single dose of pegylated interferon lambda decreased the incidence of COVID-19 [40].

Therefore, these studies suggest a possible correlation between interferon lambda 1 and the coronavirus, showing that it could play a role in marking and even countering the virus.

CONCLUSION

IFN-1 plays a unique role in modulating antiviral immunity in the respiratory tract to achieve optimal protection against COVID-19. Overall, while more research is needed to fully understand the relationship between IL-29 and COVID-19, these studies suggest that IL-29 may play a role in the immune response to COVID-19 and could be a target of COVID-19 treatment in future therapy.

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DECLARATION OF INTERESTS

There are no conflicts of interest listed by the authors.

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