# Evaluation of serum Neuropilin-1 level as a Potential Marker of COVID-19 severity in Iraqi population.

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**Abstract**
Background: The protein neuropilin-1 (NRP1) has multiple functions in the body, both normally and when things go wrong. Axon guidance in peripheral nervous systems and the central, cell survival, angiogenesis, vascular permeability, differentiation, proliferation, and migration are just few of the many biological activities that NRP1 regulates. Since NRP1 was revealed to be the facilitator and cofactor of SARS-CoV-2 entrance during COVID-19 infection, this may indicate a new potential target for intervention against COVID-19. Objective: to determine if serum levels of Neuropilin-1 are associated with the severity of COVID-19 infection for used as a disease predictive marker. Materials and Methods: One hundred twenty patients with COVID-19(80males, 40 females) participated in the study. and 60 controls (40 males, 20 females) who were a apparently healthy adults (ages above 25 years). Subjects were collected from the AL-Amal hospitals and the AL-Shefaa center in AL- Najaf, Iraq, between January 2022 and May 2022. Murray score were used to rank the degree of illness in patients who were gathered at the time of admission. The ill and healthy groups had blood samples obtained, and their demographic and clinical information was recorded. Serum levels of C-reactive protein and neuropilin-1 were measured by enzyme-linked immunosorbent assays (ELISA). Serum ferritin, D-dimer, and CBC were measured in FIA by ichroma. Results: Serum levels of Neuropilin-1 were found to be higher in patients group, especially in cases of mild/moderate (0.911±0.182) (P. 0.001), severe(1.88±0.606) (P. 0.001), and critical(3.68±0.84) (P. 0.001) cases as compared to healthy controls (0.547±0.115) groups respectively. While, show a significant negative correlation was obtained between (SPO2, TC, HDL.C, LDL.C, and Lymphocyte, p.value=0.001 with NRP1 levels in the COVID-19 patients group. At the same time, a significant positive correlation was obtained between (TG, VLDL.C, WBCs, neutrophil, N/L ratio, D-dimer, Ferritin, and CRP, p.value=0.001 with NRP1 levels in the COVID-19 patients group. Conclusion: Serum NRP1 concentration was higher in COVID-19 patients specially in sever and critical cases compared to healthy controls, and mild/moderate patients group. which might be a valuable indicator of the disease's severity. High level NRP1 concentrations in the early stage of COVID-19 should be closely monitored in order to avoid the development of pulmonary fibrosis as soon as possible and other injury organs.
Keywords: COVID-19; Neuropilin-1 (NRP1) , D-Dimer, Ferritin, NLR.

## 1. Introduction

The distinguishing feature of coronaviruses' S protein, which resembles a halo effect observed during a solar eclipse or a crown-like look when seen under an electron microscope, is the origin of the coronaviruses' name. The S protein has a roughly cylindrical shape and is heavily glycosylated.[1][2]
The first human coronavirus was identified in the 1960s, and by 1975, the family Coronaviridae had been created under the order Nidovirales in the Taxonomy of Viruses.[2][3] The 2019 coronavirus epidemic (COVID-19) is an outbreak of a newly discovered coronavirus that causes a severe form of acute respiratory syndrome (SARS-CoV-2).[4] Since then, over 216 additional countries and territories have fallen victim to the pandemic. A pandemic of COVID-19 was proclaimed by the World Health Organization (WHO), to be in full swing by the end of January 2020, and it had been going strong since the beginning of March of that year. It has subsequently been dubbed "the most urgent global health calamity of the century" and "the biggest issue humanity has faced since World War II."[5][6] The NRPs consist of a group of small (130 kDa), single-pass transmembrane proteins. NRP1 and NRP2 are the two members of the NRP family found in mammals and most vertebrates; they have a 44% average sequence identity and have the same overall domain structure.[7] The roles of NRP-1 in cell proliferation, immunology, and both normal and abnormal angiogenesis are wide-ranging. Evidence suggests that NRP-1 may have a role in the pathophysiology of SARS-CoV-2 and its essential involvement in axon and neuronal development.[8]
Curiously, NRP-1 was shown to attach the host cell surface with more affinity than the S1 subunit.

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Consequently, it was hypothesized that NRP-1 causes destabilization of the triggers the release of S2 from the S1 subunit. and S protein complex During the first stage of NRP-1 binding, S2 is dissociated from S1. However, it has been established that the S1 subunit binds to the receptor. In contrast, the S2 domain is the most conserved part of the Spike protein and is in charge of fusion and replication.[9][10]

At first, it was thought that SARS-CoV-2 spread mostly through contact with intermediate host animals or through ingesting wild animals.[11]

NRPs are candidates for possible therapeutic intervention since their expression is increased in illness. First identified in the brain and spinal cord, NRP-1 is also widely expressed in other organs and tissues, such as the cardiovascular system, lungs, pancreas, skeletal muscles, and the liver. Evidence that NRP-1 aids SARS-CoV-2 in entering a host cells has brought this protein into the limelight because of its pervasive expression.[12] [13]

The elevated expression of NRP-1 in the liver under both physiological settings and in patients with liver disorders raises the possibility that NRP-1 has a role in modulating coronavirus disease 2019 (COVID-19) infection. Possible correlation between SARS-CoV-2 infection and NRP-1 expression in the liver, and the involvement of NRP-1 in the development and severity of COVID-19.[14] In additionally to its growing involvement in the immune system, NRP-1 also has a role in pain.[15] Neuronal, endothelial, immunological, smooth muscle, and tumor cells are only some of the many cell types that express NRPs.[16]

## 2. Materials and Methods

In this case-control study, the participants included 120 patients(80males, 40 females), and 60 healthy volunteers(40 males, 20 females) of comparable age to the patients served as a control group. The patients were among those infected with the COVID-19 virus who were admitted to both Al-Amal Hospital; Al-Shifaa Center (Al-Najaf, Iraq). They were diagnosed quantitatively by RT-PCR and chest X-ray or CT scan at 7-12 days from the onset of symptoms. They were all older than 25 years old 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.[17] Sample collection was conducted during the period from January 2022 to May 2022..

Patients who were people with a history of vasculitis connective tissue disease, those currently undergoing long-term oral corticosteroid, anti-IL-6, or anti-TNF treatment, were not included in the study. Chronic diseases such as diabetes mellitus, cardiovascular disease, infection and inflammation were also excluded from the study. Patients suffering from cancer and renal disorders, smokers, and thyroid gland problems are not eligible for this study. Additionally, any patient who has received this vaccination in the past six months or less, as well as any patient less than 25 years old, are also not eligible.

Each patient and member of the control group had five milliliters of venous blood extracted using medical syringes. Two milliliters of this blood were placed in EDTA tubes to do a full blood count (CBC). Other three milliliters of blood were poured into gel tubes, allowed to coagulate for 10–15 minutes at ambient temperature, centrifuged, and then analyzed at a speed of three thousand times per second for ten minutes in order to separate the serum. The sera were separated into three Eppendorf tubes and kept at a temperature of -20 degrees Celsius until the biochemical analysis was completed.

The remaining blood was run through an auto hematology analyzer (linear, Spain) to get a complete blood count (CBC), which stands for a complete blood count (2 ml). Fluorescence immunoassay (FIA) was used to quantify serum ferritin and D-dimer levels. Enzyme-linked immune sorbent assays were used to detect the concentration of Neuropilin-1 kit assays in serum samples by (MyBioSource, USA) kit. Neuropilin-1 kit assays in serum samples by (MyBioSource, USA) kit were used to detect the concentration of CRP kit assays in serum samples (ichromaTM).

Based on the patient's temperature, the patient's respiratory symptoms, and radiological indicators of pneumonia, it was determined that the patient had mild to moderate COVID-19. Patients were categorized as having severe COVID-19 if any one of the following alterations was found in their bodies: [17]

(i) Distractions to the respiratory system (less than 30 per minute)

(ii) Resting oxygen saturation of less than 90 percent.

(iii) arterial oxygen (PaO2) to the fraction of inspired oxygen ratio of less than 300 mmHg.

(iv) A breakdown of the respiratory system that necessitates the use of mechanical ventilation and admission to an intensive care unit.

In addition, a patient who has passed away is 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 ever began. The patients were asked to fill out registration forms, after which a list containing their names was given to them.

## 3. Statistical Analyses

The statistical research was carried out with the assistance of IBM Statistical Package for Social Sciences, Version 26. The analysis outcomes were provided as a mean and a standard deviation. A value of p less than 0.05 was chosen as the threshold for statistical significance. A comparison of two independent samples was carried out using the student's t-test. To evaluate the parametric variables, Pearson's correlation analysis was carried out. In this study, we used analysis of variance, also known as

ANOVA, to investigate whether or not there were any significant differences in scale variables between categories. The receiver operating characteristic (ROC) analysis method was utilized as the means by which the cutoff value for Neuropilin-1 was determined. The area under the curve (AUC) was determined by fitting the data to the ROC curve.

## 4. 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 fifty-five patients had moderate symptoms, thirty-five severe symptoms, and thirty critical symptoms.

**Table (1): Demographic and clinical characteristics of the patient's categories and control groups**

| Parameters | Control Group Mean±S.D | Patient Groups | | | P. value | | |
|---|---|---|---|---|---|---|---|
| | | mild/moderate Mean±S.D | severe Mean±S.D | Critical Mean±S.D | | | |
| No . | 60 | 55 | 35 | 30 | | | |
| No . M/F | 40/20 | 35/20 | 25/10 | 20/10 | | | |
| Age (Years) | 47.35±12.53 | 50.4±10.93 | 44.74±13.24 | 49.92±10.75 | A0.050 | B 0.341 | C0.241 |
| Height (m) | 1.71±0.09 | 1.69±0.101 | 1.66±0.081 | 1.68±0.091 | A0.080 | B0.006 | C0.435 |
| Weight (kg) | 82.25±11.43 | 77.86±12.03 | 76.71±8.17 | 77.38±10.52 | A0.021 | B0.011 | C0.092 |
| BMI (kg/m$^2$) | 27.908±3.42 | 27.03±3.99 | 27.807±3.01 | 27.25±3.58 | A0.317 | B0.885 | C 0.286 |
| SBP(mmHg) | 126.70 ±3.25 | 128.23 ± 4.69 | 134.52 ± 5.66 | 139.15 ± 4.66 | A0.624 | B0.011 | C0.011 |
| DBP(mmHg) | 77.12 ± 2.33 | 78.56 ± 3.32 | 74.77± 3.12 | 82.12 ± 3.45 | A0.523 | B0.685 | C0.012 |
| $SpO_2$% | 97.99 ± 0.52 | 94.44 ± 1.11 | 88.22 ± 6.52 | 68.88 ± 9.49 | A0.532 | B0.011 | C0.013 |
| Hb (g/dL) | 12.66±1.28 | 12.98±1.39 | 12.44±1.43 | 12.75±1.09 | A0.746 | B0.447 | C0.202 |
| T-WBC ×10$^9$/L | 8.49±0.964 | 12.96±1.189 | 10.52±1.48 | 14.28±1.23 | A0.001 | B0.001 | C0.001 |
| Neut. ×10$^9$/L | 5.018±1.019 | 8.45±1.89 | 6.63±1.63 | 10.08±1.52 | A0.001 | B0.001 | C0.001 |
| Lym. ×10$^9$/L | 3.847±0.661 | 3.076±0.85 | 4.038±0.838 | 2.398±0.676 | A0.167 | B0.001 | C0.001 |
| NLR | 1.35±0.38 | 1.729±0.634 | 2.94±0.973 | 4.64±1.86 | A0.001 | B0.001 | C0.001 |
| PLT ×10$^9$/L | 306.43±34.44 | 240.34±50.13 | 265.55±49.37 | 308.72±35.5 | A0.001 | B0.001 | C0.769 |
| D-dimer(ng/mL) | 312.7±114.98 | 1205.28±420.7 | 3116.88±846.78 | 3719.105±918.9 | A0.001 | B0.001 | C0.001 |
| Ferritin(ng/mL) | 136.25±46.2 | 447.65±73.108 | 514.34±71.32 | 751.96±84.51 | A0.001 | B0.001 | C0.001 |
| CRP (ng/mL) | 3.22±1.53 | 31.57±7.93 | 37.17±10.61 | 60.11±8.63 | A0.001 | B0.001 | C0.001 |
| TG(mg/dL) | 133.91±9.14 | 235.52±22.14 | 282.25±9.07 | 281.53±21.63 | A0.001 | B0.001 | C0.001 |
| TC(mg/dL) | 175.05±13.02 | 172.44±14.59 | 167.09±10.02 | 155.52±10.14 | A0.001 | B0.001 | C0.001 |
| HDL.C(mg/dL) | 50.22±5.33 | 36.77±5.85 | 33.35±8.03 | 30.34±3.66 | A0.001 | B0.001 | C0.001 |
| VLDL.C(mg/dL) | 26.78±1.82 | 47.105±4.42 | 56.45±1.81 | 56.308±4.32 | A0.001 | B0.001 | C0.001 |
| LDL.C(mg/dL) | 98.05±12.66 | 88.56±16.77 | 77.29±12.11 | 68.86±10.97 | A0.001 | B0.001 | C0.001 |
| Neuropilin-1(ng/mL) | 0.547±0.115 | 0.911±0.182 | 1.88±0.606 | 3.68±0.84 | A0.001 | B0.001 | C0.001 |

Data represented as Mean ± SD: standard deviation, SBP: Systolic blood, Pressure, DBP diastolic blood pressure $SPO_2$: 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: VeryLow Density Lipoprotein cholesterol., A=p.value(Control + mild/moderate) B= p.value (Control +sever) C=p.value(Control + critical) .

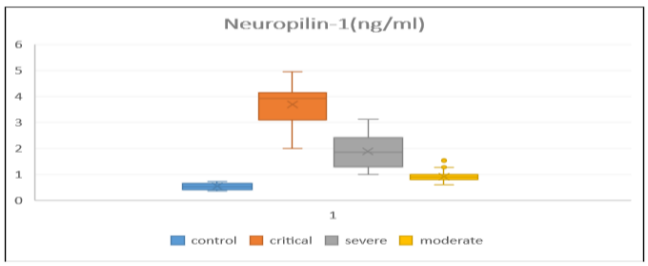
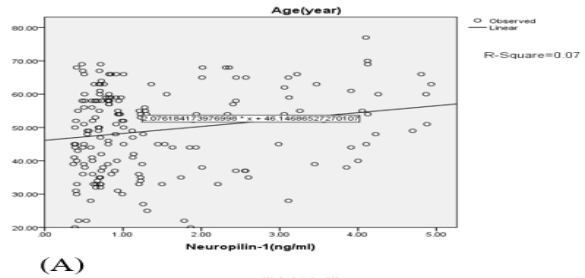



*Figure 1: Comparison of serum Neuropilin-1 level between COVID-19 patient's cases and healthy control group.*

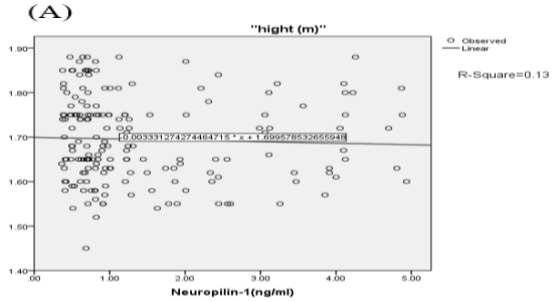
Table (1), the mean age in group of patients (mild/moderate) has a significant difference compared with healthy group (47.35±12.53, 50.4±10.93 years, respectively; p = 0.05). There were no statistically significant variations in the BMI subgroup distributions among the three disease severity categories. 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 COVID-19, were compared with controls in the data of serum Neuropilin-1 levels (0.547±0.115 ,0.911±0.182, 1.88±0.606, 3.68±0.84), ferritin (136.25±46.2, 447.65±73.108, 514.34±71.32, 751.96±84.51), D-dimer (312.7±114.98 ,1205.28±420.7 ,3116.88±846.78, 3719.105±918.9), CRP (3.22±1.53, 31.57±7.93, 37.17±10.61, 60.11±8.63) Control, mild/moderate, severe, and Critical values, ($p<0.001$) respectively.

In (Table 2 and Figure 2) show a significant negative correlation was obtained between (Height, SBP, DBP, $SPO_2$, TC, HDL.C, LDL.C, and Lymphocyte) levels in the COVID-19 patients group. At the same time, a significant positive correlation was obtained between (Age, Weight, BMI, TG, VLDL.C, WBCs, neutrophil, N/L ratio, D-dimer, Ferritin, and CRP) levels with Neuropilin-1 in the COVID-19 patients group.

| Table (2): Correlation between serum Neuropilin-1 Level with clinical Parameters in COVID-19 patients group | | |
|---|---|---|
| Parameters | r | P.value |
| Age(years) | 0.201 | 0.007 |
| Height(m) | -0.042 | 0.576 |
| Weight (kg) | 0.125 | 0.094 |
| BMI(kg/m$^2$) | 0.100 | 0.183 |
| SBP(mmHg) | -0.14 | 0.071 |
| DBP (mmHg) | -0.084 | 0.119 |
| $SPO_2$ % | -0.59 | 0.001 |
| TG(mg/dL) | 0.658 | 0.001 |
| TC(mg/dL) | -0.453 | 0.001 |
| HDL-C(mg/dL) | -0.558 | 0.001 |
| VLDL-C(mg/dL) | 0.658 | 0.001 |
| LDL-C(mg/dL) | -0.549 | 0.001 |
| Hb(g/dL) | 0.031 | 0.684 |
| T-WBCs ×10$^9$/L | 0.700 | 0.001 |
| Neut. ×10$^9$/L | 0.722 | 0.001 |
| Lym. ×10$^9$/L | -0.551 | 0.001 |
| PLT ×10$^9$/L | 0.108 | 0.150 |
| N/L Ratio | 0.765 | 0.001 |
| D-dimer(ng/mL) | 0.783 | 0.001 |
| Ferritin(ng/mL) | 0.786 | 0.001 |
| CRP(ng/mL) | 0.767 | 0.001 |
| Abbreviation: r =Pearson correlation coefficient | | |




(A)

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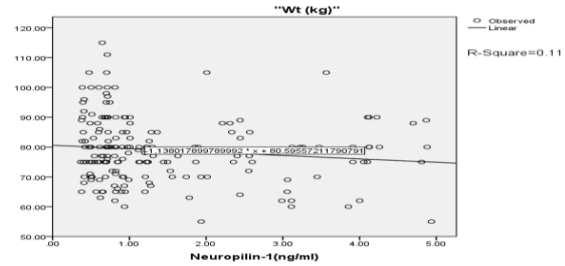


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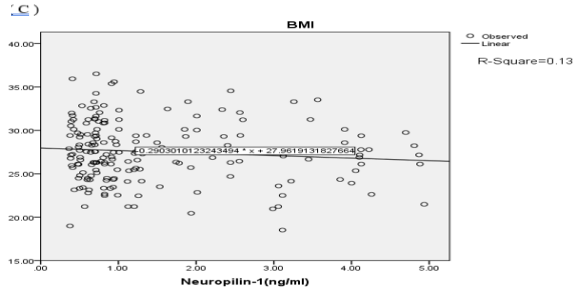


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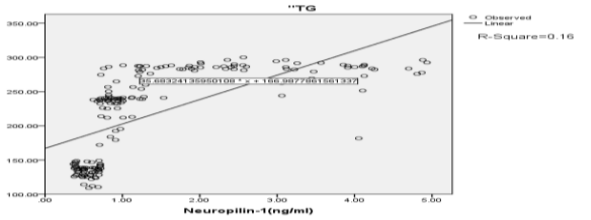


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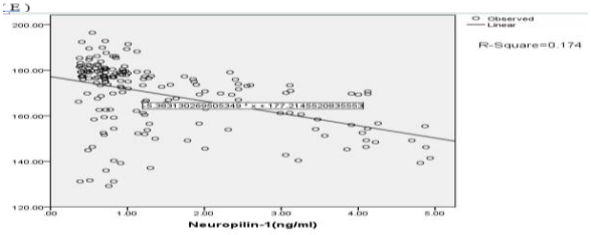


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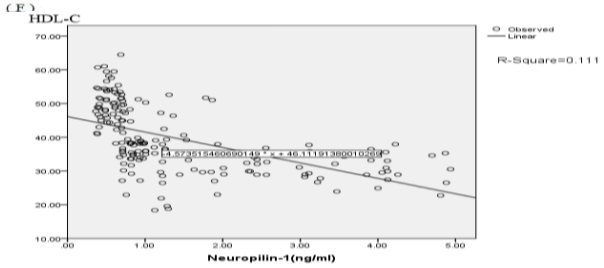


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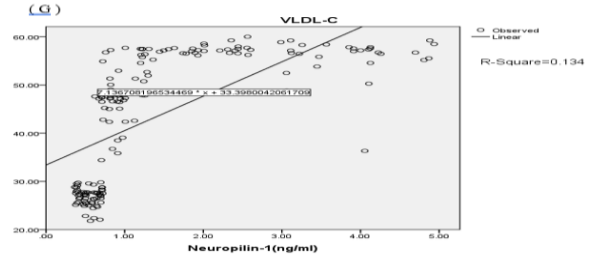


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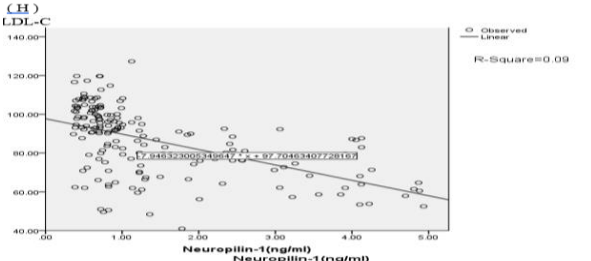
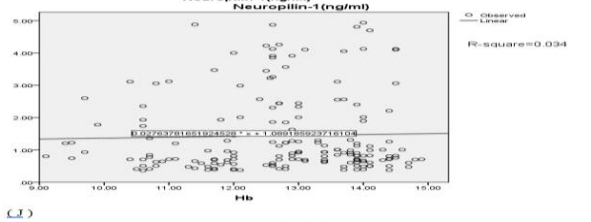



(I)

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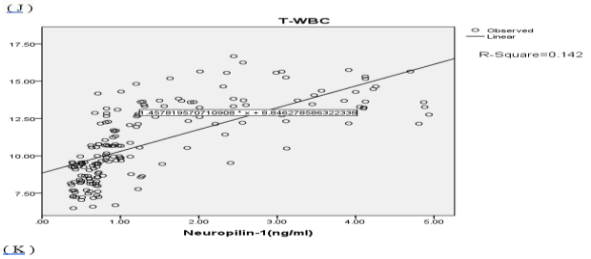


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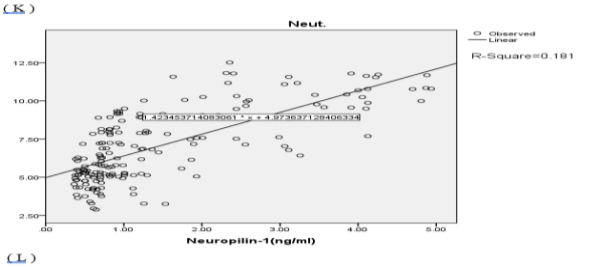


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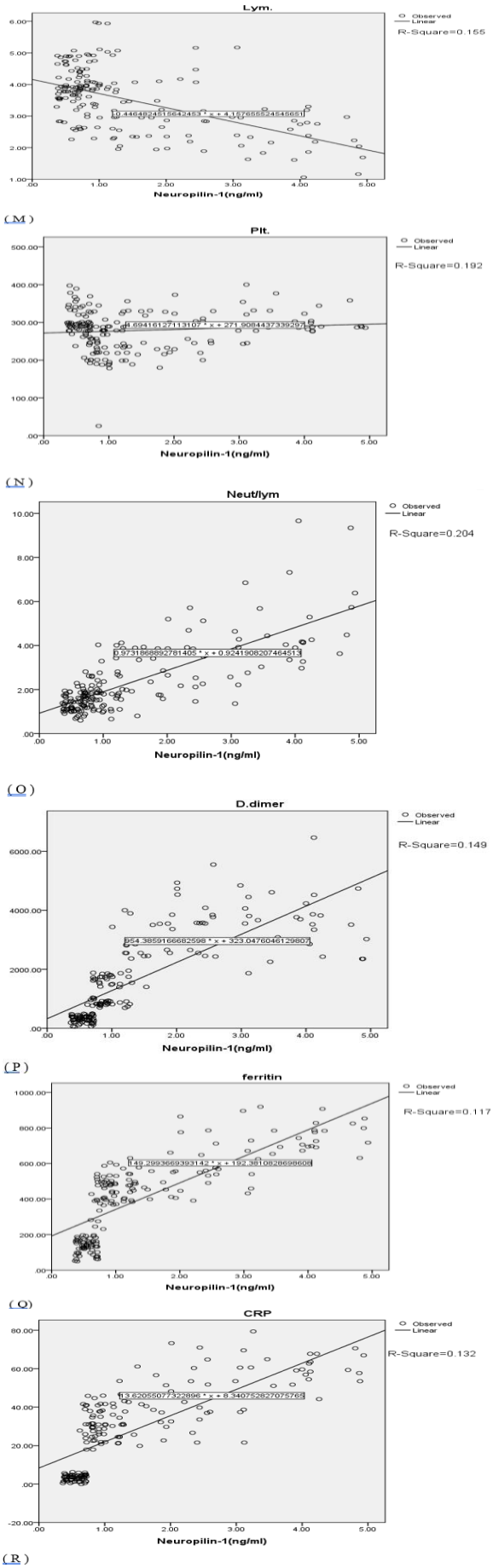


*Figure 2: Correlation between serum level of Neuropilin-1 with following parameters: (A) Age ,(B) Height, (C)Weight, (D) BMI,(E) TG, (F) TC, (G) HDL-C, (H) VLDL-C, (I) LDL-C, (J) ,Hb, (K) T-WBC,(L) Neut.,(M) Lym., (N) PLT, (O) N/L Ratio, (P)D-dimer, (Q) Ferritin, (R) CRP.*

In figure (3) demonstrates Using a ROC analysis, the capacity of Neuropilin-1 to foretell the progression of illness was assessed. The area under the curve (AUC) for Neuropilin-1 was 0.946 (95% CI, 0.911-0.981, p 0.001). The sensitivity of Neuropilin-1 for predicting the severity of illness was calculated to be 92.5% when the cutoff value of 0.7235 was established, while the specificity was calculated to be 86.7%.

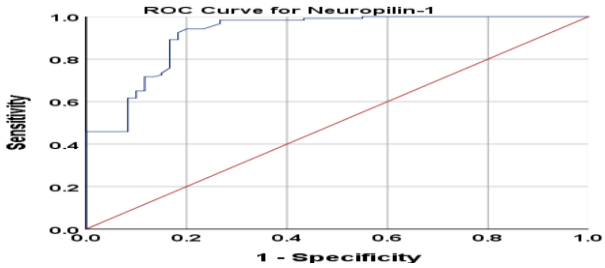


*Figure 3 : Receiver operating characteristic curve of serum Neuropilin-1 for diagnosis of COVID-19 patients groupDiscussion*

Despite the fact that the SARS-CoV-2 coronavirus infects host cells via the angiotensin-converting enzyme 2 (ACE2) receptor, ACE2 expression does not correlate with the SARS-CoV-2 tissue burden. Cofactor neuropilin-1 (NRP1), when expressed alone, displays low viral infectivity, but when co-expressed with acetylcholinesterase 2 (ACE2), significantly improves viral infectivity. [18] Transmembrane glycoprotein NRP1 acts as a receptor for a vascular endothelial growth factor (VEGF) and is expressed in endothelial cells. SARS-CoV-2 employs cell entrance protein (viral spike), cleaving the protein that connects to NRP1 after that [19], and both NRP1 and VEGF expression are elevated in COVID-19 patients. [20]

Therefore, patients expressing greater NRP1 may be at a higher risk, and tissues rich in NRP1 have an elevated risk of infectivity.[21] For this reason, current evidence suggests that a protein/receptor known as neuropilin1 (NRP1) may also play a role in the SARS-CoV2 infection. [22] Inducing several effects such as cell proliferation, angiogenesis, and axon regulation, Unlike most other transmembrane receptors, NRP1 does not include a protein kinase domain in its cytoplasm; instead, it serves primarily as a co-receptor. [15]

This paper provides an in-depth computational investigation of NRP1 expression in the human brain, drawing attention to the possibility that NRP1 plays a role in SARS-CoV-2 infection mediation in the central nervous system (CNS) via NRP1-expressing cells. Our current results provide more evidence that NRP1 may be involved in the neurologic characteristics and CNS involvement of COVID-19. [12] Since NRP-1 has been proven to control Treg cells, it may dampen the overactive immune response that exacerbates COVID-19. [23]. Multiple investigations have shown that NRP-1 acts as a co-receptor for SARS- CoV-2, easing the virus's passage through the olfactory epithelium and into the brain. Neurological symptoms such as headache,

disorientation, hallucinations, and convulsions may result from the transmission of In the nasal cavity, SARS-CoV-2 infects the olfactory epithelium and then travels to the brain via NRP-1. Neurological symptoms were seen in around 45 percent of confirmed COVID-19 patients. As a result, NRP-1 inhibitors may provide hope as a treatment for SARS-CoV-2 infections with neurological consequences.[24][25]

With its varied expression and functional features, NRP-1 is a suitable extracellular target for SARS-CoV-2 and may contribute to the systemic effects of COVID-19. The expression of NRP -1 genes and Proven expression of NRP-1 in the central nervous system, with effects on olfactory-related areas such the olfactory tubercles and paraolfactory gyri; may have a role in neurologic complications of COVID-19 as an alternative entry route for SARS-CoV-2.[27]

Marked neutrophilia and a high neutrophil-lymphocyte ratio (NLR) are seen in patients with severe COVID-19, along with lymphopenia, eosinopenia, basophilia, monocytopenia, a decrease in B and T cell counts, and a decrease in total white blood cell count.[30]Without ACE2, SARS-CoV-2 has extremely limited infectivity, and some scientists have hypothesized that NRP-1 is a cofactor of ACE2 and S protein binding. SARS-CoV-2 is likewise unable to infect cells that express NRP1 but lack ACE2, as has previously been shown. In contrast, NRP1-knockout ACE2-positive cells are susceptible to infection by SARS-CoV-2.[31]

It has been also observed that SARS-CoV-Coagulation rates are higher in those with a type 2 infection. Recognizing that NRP-1 also regulates coagulation suggests that an unbalanced clotting response may contribute to the pathophysiology in the Brain in people with COVID-19. The olfactory epithelium in the nose has been proposed as a portal of entry for SARS-CoV-2 into the central nervous system. Therefore, Davies et al. used single-cell RNA sequencing to analyze NRP-1 RNA expression in selected human brain cells. Endothelial cells, macrophages, neurons, fetal astrocytes, and oligodendrocytes were all shown to express NRP-1, with the greatest levels seen in mature astrocytes.[32]

An intriguing new function for NRP1 in COVID-19 infection has been uncovered by these investigations; NRP1 was revealed to be a cofactor and facilitator of SARS-CoV-2 entrance, which opens the door to a new potential target of intervention for COVID-19.[33] The NRP1 receptor has recently been revealed as a novel target for pain inhibitors in the treatment of chronic pain.[34]

## 5. Conclusions

Among COVID-19 patients, we found that elevated blood levels of Neuropilin-1 were associated with more severe disease and may be revealed as anoval target and facilitator of SARS-COV2entrance. Individuals with elevated levels of serum Neuropilin-1 have serious conditions that need aggressive proteins was greatest in the hippocampus formation.[26][27]

In addition, even in moderate cases of COVID-19, brainstem injury may compromise circulatory, gastrointestinal, respiratory, and neurological functioning, potentially leading to long-term catastrophic effects.[28] Infections and certain drugs are only two of the many causes of systemic inflammation that can precipitate a cytokine storm, which is defined as the uncontrolled release of inflammatory cytokines. [29]

Davies et al. conducted a research to determine this.

treatments and close monitoring.

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### Declaration of Interests

The authors declare no conflict of interests .

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