



Original article

Potential Diagnostic Value of Netrin-1 and Hematological Biomarkers in COVID-19-Associated Immune Dysregulation

Humam Ezzat. Mohammed^{1*}, Aseel Mokdad Hatam Abdulwahed¹, and Mahmood I. M. Alkanaani²

¹Department of Pathological analysis, College of Applied Sciences, University of Samarra, Samarra, Iraq

²Department of Applied Chemistry, College of Applied Sciences, University of Samarra, Samarra, Iraq

Correspondence e-mail | humam.ezzat36@uosamarra.edu.iq

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ABSTRACT

This study intended to evaluate levels of Netrin-1, glycated hemoglobin, and some hematological parameters in COVID-19 patients by comparing them with the control or healthy group to investigate the potential effects of infection. The biochemical tests studied included of Netrin-1 protein level, random blood sugar (RBS), HbA1c, C-reactive protein levels, and concentrations of some hematological parameters (RBC, WBC, Platelets, and Hemoglobin). This study enrolled 40 patients (20 males and 20 females) with COVID-19 at Samarra Hospital and some outpatient clinics in Samarra city, in addition to 30 healthy individuals (15 males and 15 females) as a control group, for the period from the beginning of October 2022 to the end of January 2023. They were in four groups of males and females aged between 20 and 50 years. The results showed significant sex-dependent changes in Netrin-1 levels. Netrin-1 concentrations were considerably lower in COVID-19 male patients compared to healthy men, whereas female patients had significantly higher levels compared to female controls ($P < 0.001$). CRP and RBS levels were significantly elevated in both male and female patients ($P < 0.001$). Male patients had significantly higher HbA1c levels ($P = 0.003$) whereas females had a non-significant rise ($P = 0.072$). Hematological investigations indicated significant leukocytosis, lymphopenia and thrombocytopenia in both sexes. In female patients, there was also a substantial decrease in hemoglobin levels while in male patients there was a large increase in RBC count and PCV levels. Correlation study showed substantial inverse connection between Netrin-1 and both CRP and HbA1c levels confirming the link between changed Netrin-1 expression and inflammatory dysregulation in COVID-19 patients. ROC analysis showed good to excellent discrimination between patients and controls for CRP (AUC 0.961), lymphocyte percentage (0.928), Netrin-1 (0.884) and platelet count (0.861). In conclusion, COVID-19 infection is associated with severe inflammatory and hematological abnormalities that are linked to sex-dependent changes in Netrin-1 levels. Netrin-1 therefore behaves as a candidate diagnostic biomarker of immune dysregulation in COVID-19. Prognostic value was not tested by this design and awaits prospective confirmation.

Keywords: *Netrin-1, COVID-19, hematological parameters, Immune dysregulation.*

1-INTRODUCTION

Coronavirus is the seventh member of the Coronaviridae (crown-like viruses) family within the Nidovirales order. Human coronaviruses consist of α -CoVs (NL63 and 229E), β -CoVs (HKU1 and OC43) that lead to light respiratory diseases, as well as the coronavirus associated with the Middle East respiratory syndrome (MERS-CoVs), and severe acute respiratory syndrome (SARS-CoV-1) [1].

WHO has officially identified this new coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), This novel coronavirus causes a pandemic, as it has been one of the most active and dangerous viruses known in terms of its rapid spread and impact on human's life [2].

Netrin-1 is a subclass of laminin-like proteins that were discovered as signals for axon guidance during embryonic development [3]. A laminin-associated Netrin-1 molecule is secreted in the mid-dorsal spinal cord, where it serves a specific role in the guidance of spinal cord axons [4].

Netrins family Contains a minimum of three essential proteins, including (Netrin-1, 2, 4) that have notable structural similarities to laminin, a protein of the extracellular matrix [5]. Netrin-1 has received the most attention among the netrins [6]. Netrins act as chemoattractants or chemical guidance cues in a variety of biological processes that go well beyond neuronal development. these proteins have a crucial role in the regulation of

blood vessels and tumor formation [7]. Considering the large number of receptors and biphasic signaling of netrins, it's unsurprising that netrins play diverse roles in different inflammatory settings. Evidence suggests that netrin-1 has not only anti-inflammatory effects but also the ability to promote acute inflammation [8].

A potential pathway of COVID-19 to impact the nervous system is through the olfactory mucosa, with loss of smell as a possible sign. It can then reach the brain from an area in the nasal cavity's roof called the cribriform plate then along the olfactory tract or through the vagus nerve or the trigeminal nerve [9].

Regarding the invasion of cells by viruses, the cell surface receptor ACE2 has a significant function in the invasion of host cells via SARS-CoV-2, mimicking that done by SARS-CoV-1 [10]. ACE2 is a glycosylated protein expressed in the airway epithelium, alveolar lung tissue, gut, vascular endothelium, kidney, and heart [11]. Nevertheless, Human brain tissue also expresses ACE2 receptors particularly in motor cortex, limbic cortex, olfactory bulb, ventral lateral nucleus, vagus nerve, and in some cells of that located in central nervous system CNS, like neuronal cells, along with astrocytes, microglia, and oligodendrocytes, are an easy target for SARS-CoV-2 infection [12,13]. SARS-CoV-2 capable to penetrate the blood-brain barrier (BBB) either since inflammatory cytokines stimulate instability of BBB or through monocytes [14,15]. Diabetes mellitus, especially type 2 diabetes, is considered part of the risk factors that enhance the complications of COVID-19, this is because diabetes is involved with chronic low-grade inflammation caused via excess visceral fat, and this inflammatory state can affect glucose homeostasis and sensitivity of insulin. Elevated blood sugar and chronic inflammation can lead to an ineffectual and abnormal immune response [16]. COVID-19 infection can increase the incidence of hyperglycemia episodes, this can be explained by the increase in the release of cytokines and inflammatory factors. This leads to an increase in insulin resistance and the consequent hyperglycemia [17]. COVID-19 may also be one of the factors that aid in the progression of acute diabetes in some patients by targeting ACE2 receptors found in the islets of Langerhans in the pancreas, causing pancreatic cell dysfunction [18]. The essential goals of this study was to achieve a good comprehension of the effects of COVID-19 infection on the function of the nervous system and other organs of the body by measuring: concentration of Netrin-1 proteins, concentration of glycated hemoglobin (HbA1c), concentration of C-reactive protein, and The level of hematological parameters (WBC, RBC, PCV, Lymphocyte, Hb, and Platelets).

What is still unresolved is whether circulating Netrin-1 tracks the inflammatory and haematological disturbance of acute COVID-19, and whether it moves in the same direction in men and in women. Earlier reports measured Netrin-1 in metabolic rather than infectious settings [19,20], and none analysed it together with CRP, HbA1c and a full blood count in one sex-stratified cohort. We therefore tested the hypothesis that serum Netrin-1 shifts in a sex-dependent manner during COVID-19 and varies inversely with inflammatory and glycaemic markers.

Immunological assessment of COVID-19 conventionally rests on IL-6, TNF- α , ferritin, D-dimer, procalcitonin, the neutrophil-to-lymphocyte ratio and CD4⁺/CD8⁺ subsets [21,22]; these assays are not routinely available in our laboratories, which is why the panel here was restricted to CRP and the differential count. Identifying which of the accessible markers discriminate best would put a cheap four-analyte panel CRP, lymphocyte percentage, platelet count and Netrin-1 in the hands of clinicians who need to decide whom to monitor for glycaemic and haematological deterioration.

MATERIALS AND METHODS

Study design and setting. This was a cross-sectional case-control study. Recruitment was prospective and sampling was convenience. Samples were collected at Samarra General Hospital and from external laboratories in Samarra city from October 2022 to January 2023. The study included the collection of (70) samples and their division into two groups. The first group (control) included 30 samples from both sexes, and the second group (infected) included 40 samples from both sexes as well. Their ages ranged from (20-50). SARS-CoV-2 infection was confirmed by RT-PCR and disease severity was classified as mild and moderate.

Inclusion criteria. Age 20–50 years; laboratory-confirmed SARS-CoV-2 infection; blood drawn within 7-14 days of symptom onset. **Exclusion criteria.** Previously diagnosed diabetes mellitus; cardiovascular, renal, hepatic, autoimmune or chronic inflammatory disease; malignancy; pregnancy; current corticosteroid, immune suppressant or anticoagulant therapy. Controls were asymptomatic individuals with a negative SARS-CoV-2 test and none of the above conditions, frequency-matched to the patients by sex and age group.

Blood sampling. Blood was collected in a disposable tube (5 ml) After being left at room temperature for 15 minutes, the solution was centrifuged for 10 minutes at 5000 rpm, the serum was moved to test tubes for analysis. Sampling was performed within 24 h of diagnosis in the non-fasting state, which is why random rather than fasting blood sugar was measured, and sera were stored at -20 °C for no longer than 3 months before analysis. Patients and controls were processed under identical pre-analytical conditions.

The level of Netrin-1 protein in the sera was detected using a quantitative sandwich ELISA assay kit from MyBioSource by using the commercial (kit- ELISA kit human, MyBiosource, USA) and procedure was followed as given in the kit leaflets.

The determination of C-Reactive Protein (CRP) in blood serum is based on the fact that latex particles covered with goat IgG anti-human CRP will agglutinate when mixed with samples having CRP [23].

HbA1C was performed using the automated biochemical analyzer "HLC-723-G8" by TOSOH and random blood sugar (RBS) was measured enzymatically with the manufacturer's procedure (Biolabo, France); RBS is used consistently throughout the manuscript.

Hematological analysis: A SYSMEX-Japan-manufactured CBC (Complete blood count) device was used to perform blood tests for instance red blood cells, white blood cells, platelets, and others.

Statistical analysis. Data were analysed with SAS 9.4. Normality was checked by the Shapiro–Wilk test and homogeneity of variance by Levene's test. Because the design carries two factors, infection status and sex, a two-way ANOVA was applied with the status $\times$ sex interaction term, followed by Tukey-adjusted pairwise comparisons. Continuous variables are given as mean $\pm$ SD together with the 95% confidence interval of the mean difference. Effect sizes are reported as Hedges' g with 95% CI. Associations were examined by Pearson's r , with Spearman's ρ where normality failed, and the five correlation tests were corrected by the Holm procedure. Discrimination between patients and controls was assessed by ROC analysis; cut-offs were taken at the maximum Youden index, 95% CIs for the AUC follow Hanley and McNeil, and those for sensitivity and specificity the Wilson method. No a priori power calculation was performed; with 15 controls and 20 patients of each sex the design detects $g \geq 0.99$ at 80% power and $\alpha = 0.05$, and that floor is carried into the interpretation of every non-significant result. Significance was set at $P < 0.05$.

RESULTS

The biochemical and clinical features of COVID-19 patients and healthy controls are shown in Table (1). For both sexes, there were no significant age differences between the patient and control groups ($P > 0.05$). However, as compared to their equivalent controls, both male and female COVID-19 patients showed significantly higher levels of C-reactive protein (CRP) and random blood sugar (RBS) ($P < 0.001$).

Male COVID-19 patients' HbA1c values were considerably higher than those of healthy males ($P = 0.003$), but female patients' levels were just marginally higher than those of healthy females ($P = 0.072$).

In terms of Netrin-1, male COVID-19 patients had significantly lower levels than healthy males ($P < 0.001$), whereas female patients had significantly higher levels than female controls ($P < 0.001$), indicating a sex-dependent variation in Netrin-1 response during COVID-19 infection.

Table (1): Demographic and Clinical Characteristics of Study Participants.

Variable	Male Control (n=15)	Male COVID-19 (n=20)	P- value	Female Control (n=15)	Female COVID-19 (n=20)	P- value
Age (years)	34.2 $\pm$ 6.1	35.8 $\pm$ 7.4	0.521	33.7 $\pm$ 5.8	36.1 $\pm$ 6.9	0.384
RBS (mg/dL)	97 $\pm$ 20.2	170 $\pm$ 15.3	<0.001	105 $\pm$ 18.7	150 $\pm$ 20.6	<0.001
HbA1c (%)	5.22 $\pm$ 0.9	6.50 $\pm$ 1.1	0.003	5.7 $\pm$ 0.9	6.3 $\pm$ 1.0	0.072
CRP (mg/L)	4.0 $\pm$ 1.0	24.2 $\pm$ 4.2	<0.001	3.6 $\pm$ 0.9	30.1 $\pm$ 5.7	<0.001
Netrin-1 (ng/mL)	2.5 $\pm$ 0.04	1.4 $\pm$ 0.02	<0.001	1.7 $\pm$ 0.03	2.2 $\pm$ 0.05	<0.001

Table (2) shows an overview of the changes in hematology that were seen in the different study groups. White blood cell count (WBC) was significantly elevated in both male and female COVID-19 patients compared with controls ($P \leq 0.002$). Similarly, male patients showed a significant increase in RBC count compared with healthy males ($P = 0.001$), while no significant difference was detected among females ($P = 0.611$).

Platelet count and lymphocyte percentage were significantly reduced in both male and female COVID-19 patients compared with controls ($P < 0.001$), indicating marked inflammatory and immune dysregulation associated with COVID-19 infection.

Hemoglobin and PCV levels exhibited sex-related differences. Female COVID-19 patients showed significantly lower hemoglobin levels compared with female controls ($P = 0.011$), whereas no statistically significant difference was detected in males ($P = 0.148$). Additionally, PCV was significantly elevated in male. Formal testing of the status $\times$ sex interaction (Table 4) shows that the direction of the Netrin-1, haemoglobin, PCV and RBC responses depends on sex, whereas the leukocytosis, thrombocytopenia and lymphopenia are sex-independent. Fig-

ures (1) and (2) present the same comparisons as column charts, with the highest and lowest group mean flagged in every panel.

Table (2): Hematological Parameters Among Study Groups.

Parameter	Male Control	Male COVID-19	P-value	Female Control	Female COVID-19	P-value
WBC ($\times 10^9/L$)	6.65 $\pm$ 1.7	9.1 $\pm$ 2.1	0.002	5.9 $\pm$ 1.1	8.9 $\pm$ 1.9	<0.001
RBC ($\times 10^{12}/L$)	4.25 $\pm$ 0.5	5.35 $\pm$ 0.9	0.001	4.16 $\pm$ 0.9	4.00 $\pm$ 0.7	0.611
Hemoglobin (g/dL)	13.8 $\pm$ 2.9	15.5 $\pm$ 3.7	0.148	13.8 $\pm$ 3.1	11.2 $\pm$ 2.2	0.011
Platelets ($\times 10^9/L$)	163 $\pm$ 11.9	135 $\pm$ 10.3	<0.001	182.1 $\pm$ 15.1	156 $\pm$ 14.5	<0.001
PCV (%)	40.3 $\pm$ 9.8	47.7 $\pm$ 7.3	0.021	39.5 $\pm$ 8.6	35.5 $\pm$ 6.3	0.163
Lymphocyte (%)	27.8 $\pm$ 5.1	15.3 $\pm$ 3.2	<0.001	30.0 $\pm$ 4.1	14.4 $\pm$ 2.3	<0.001

Table (3) gives the effect size of each biomarker separately for men and women, with 95% confidence intervals. The separation between patients and controls is very large for CRP ($g = 6.07$ in men, 5.93 in women), for lymphocyte percentage (2.97 and 4.78) and for random blood sugar (4.07 and 2.22); it is large but less certain for HbA1c, where the female interval crosses zero ($g = 0.61$, 95% CI $0.00-1.30$). Figure (3) ranks the same estimates.

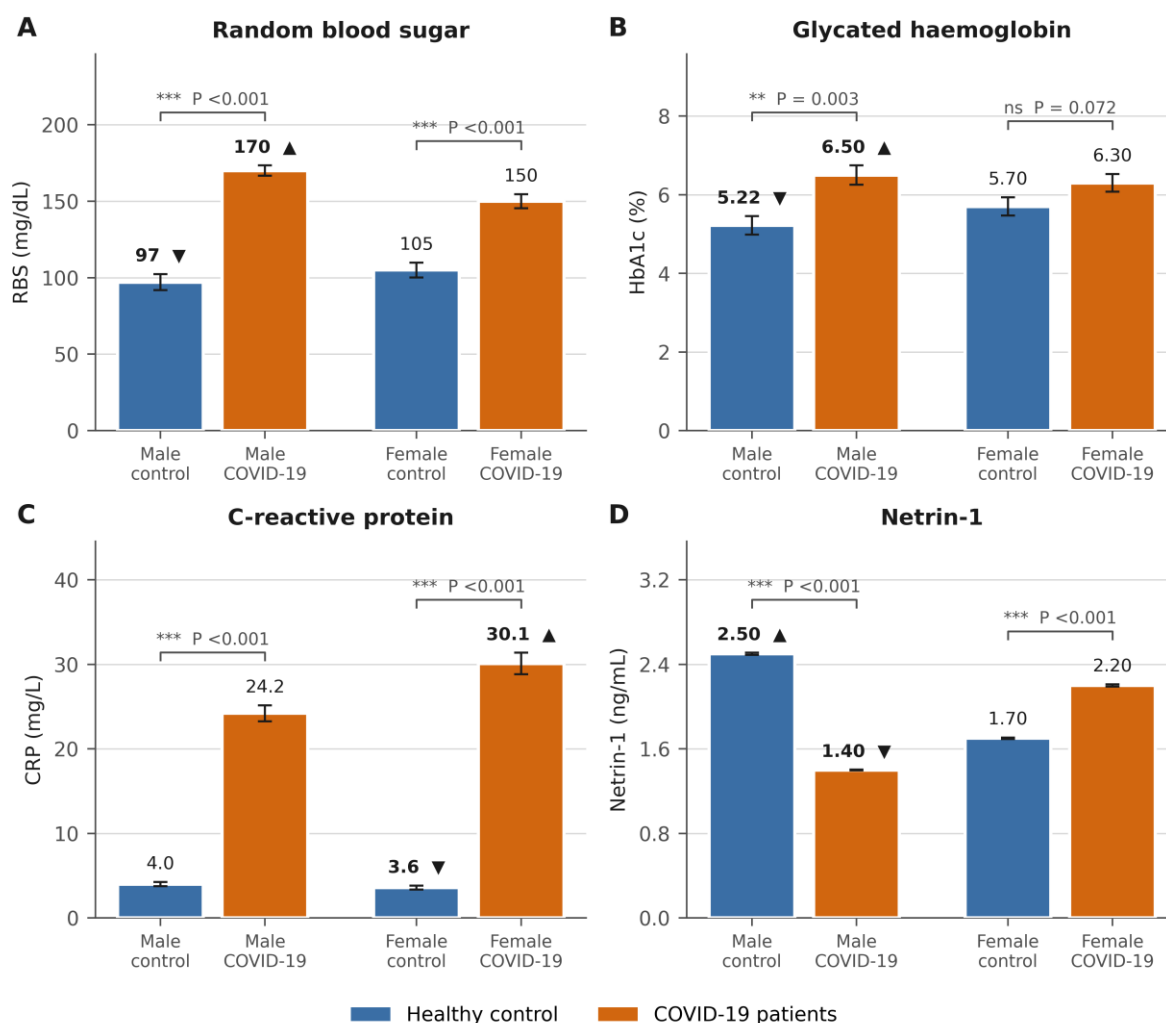


Figure (1): Biochemical parameters of COVID-19 patients and healthy controls, separated by sex. Columns are group means, error bars the standard error of the mean; ▲ marks the highest and ▼ the lowest group mean in each panel. P values are those of Table (1). *** $P < 0.001$, ** $P < 0.01$, ns = not significant.

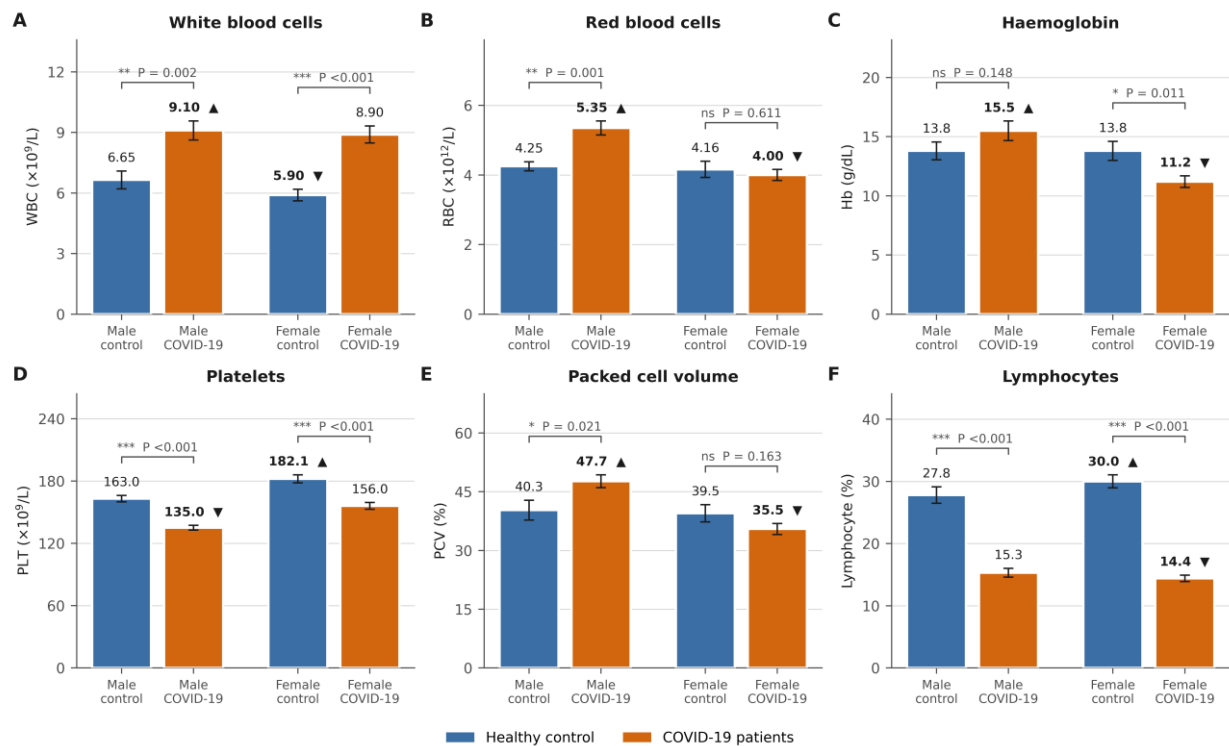


Figure (2): Haematological parameters of COVID-19 patients and healthy controls, separated by sex. Columns are group means, error bars the standard error of the mean; ▲ highest and ▼ lowest group mean per panel. P values are those of Table (2). ***P < 0.001, **P < 0.01, *P < 0.05, ns = not significant.

Table (3): Effect Size (Hedges' g) for Major Biomarkers, by Sex.

Biomarker	Sex	Hedges' g	95% CI	Interpretation
CRP	Male	6.07	4.43 – 7.71	Very large
CRP	Female	5.93	4.32 – 7.54	Very large
RBS	Male	4.07	2.86 – 5.27	Very large
RBS	Female	2.22	1.35 – 3.08	Very large
Lymphocyte %	Male	2.97	1.98 – 3.96	Very large
Lymphocyte %	Female	4.78	3.42 – 6.13	Very large
Platelets	Male	2.49	1.58 – 3.39	Very large
Platelets	Female	1.73	0.93 – 2.52	Very large
WBC	Male	1.23	0.50 – 1.97	Large
WBC	Female	1.82	1.01 – 2.63	Very large
HbA1c	Male	1.23	0.49 – 1.96	Large
HbA1c	Female	0.61	0.00 – 1.30	Medium; CI includes zero

Effect sizes are computed separately for each sex from the group means and standard deviations of Tables (1) and (2), because a single pooled value cannot represent a design whose central finding is a sex difference.

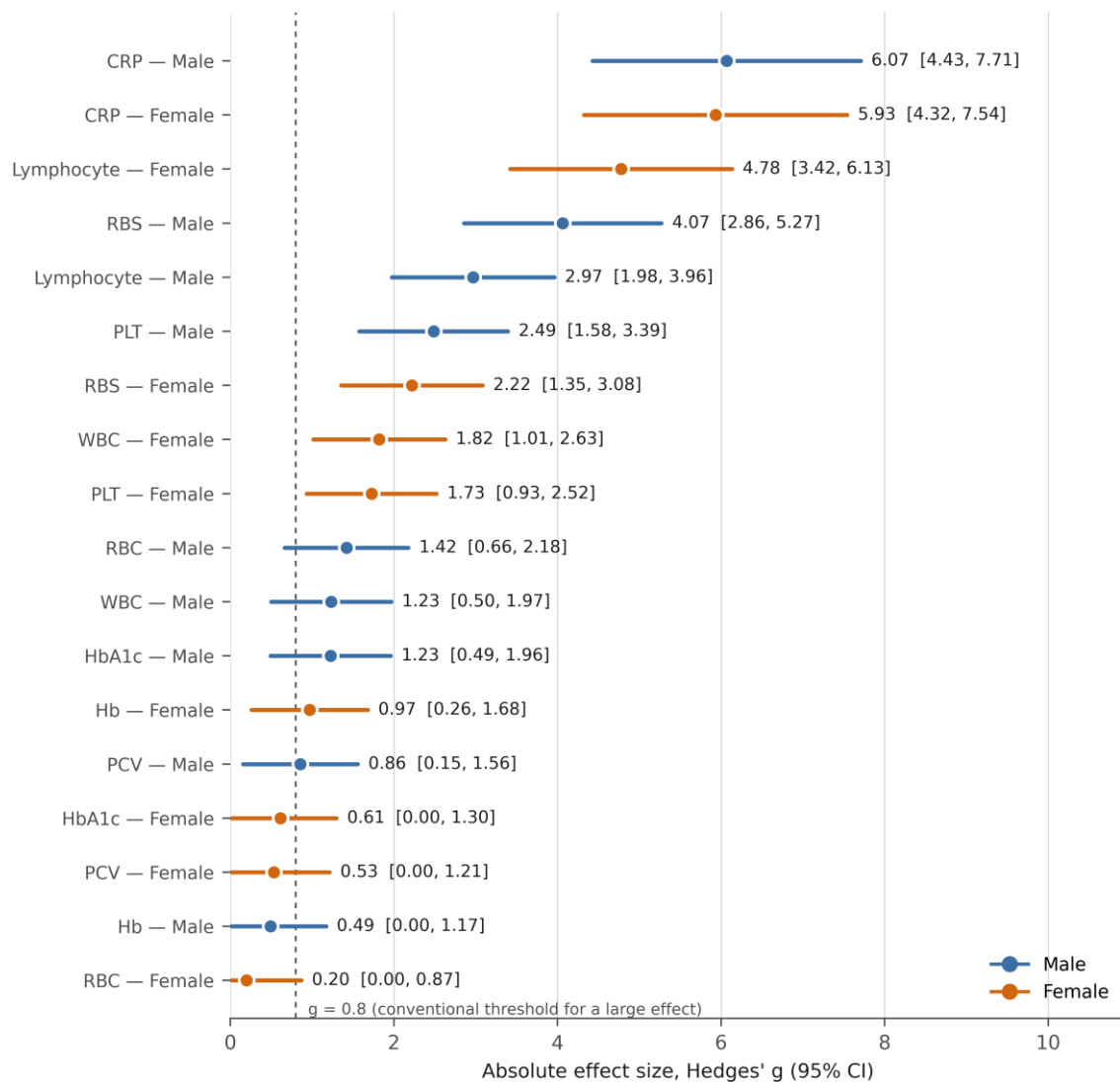


Figure (3): Effect size (Hedges' g with 95% CI) of each biomarker, computed separately for men and women. The dashed line marks $g = 0.8$.

Table (4): Two-Way ANOVA: Main Effects and the Status $\times$ Sex Interaction.

Variable	Infection status F(1,66); P	Sex F(1,66); P	Status $\times$ Sex F(1,66); P
RBS	170.36; <0.001	3.20; 0.078	9.59; 0.003
HbA1c	15.46; <0.001	0.15; 0.700	2.02; 0.160
CRP	630.88; <0.001	12.10; <0.001	11.48; 0.001
WBC	40.05; <0.001	1.05; 0.310	0.41; 0.525
RBC	6.32; 0.014	19.17; <0.001	11.36; 0.001
Hemoglobin	0.38; 0.540	11.54; 0.001	8.65; 0.004
Platelets	74.02; <0.001	42.08; <0.001	0.09; 0.763
PCV	0.79; 0.378	14.90; <0.001	8.87; 0.004
Lymphocyte %	249.68; <0.001	0.24; 0.628	3.04; 0.086

Correlation analysis demonstrated a strong inverse association between Netrin-1 and both CRP ($r = -0.61$, $P = 0.002$) and HbA1c ($r = -0.48$, $P = 0.011$). Conversely, CRP exhibited positive correlations with HbA1c and WBC count, whereas the lymphocyte percentage revealed a robust negative correlation with CRP ($r = -0.71$, $P < 0.001$), reinforcing the link between inflammation and immune dysregulation in COVID-19 patients.

Table (5): Correlation Analysis in COVID-19 Patients.

Variables	r	95% CI	P	Holm-adjusted P
Netrin-1 vs CRP	-0.61	-0.77 to -0.37	0.002	0.006
Netrin-1 vs HbA1c	-0.48	-0.69 to -0.20	0.011	0.011
CRP vs HbA1c	0.66	0.44 to 0.81	<0.001	0.002
CRP vs WBC	0.58	0.33 to 0.76	0.004	0.008
Lymphocyte vs CRP	-0.71	-0.84 to -0.51	<0.001	0.001

The ROC curve study indicated that CRP separated patients from controls best, with an AUC of 0.961, sensitivity of 92.5%, and specificity of 90.0%. The lymphocyte percentage discriminated almost as well (AUC = 0.928), succeeded by Netrin-1 (AUC = 0.884) and platelet count (AUC = 0.861), which marks them as candidate diagnostic indicators of the immunological changes that accompany COVID-19. AUC, sensitivity and specificity are given with 95% confidence intervals in Table (6) and Figure (4). Because the cut-offs were both derived and evaluated in this single sample, the estimates are internal and not validated.

Table (6): ROC Curve Analysis: Discrimination Between COVID-19 Patients and Controls.

Marker	AUC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	Cut-off
CRP	0.961 (0.916–1.000)	92.5 (80.1–97.4)	90.0 (74.4–96.5)	>12 mg/L
Lymphocyte %	0.928 (0.867–0.989)	90.0 (76.9–96.0)	85.0 (68.4–93.7)	<18%
Netrin-1	0.884 (0.806–0.962)	85.0 (70.9–92.9)	80.0 (62.7–90.5)	<1.8 ng/mL
Platelets	0.861 (0.775–0.947)	82.5 (68.1–91.3)	78.0 (60.5–89.1)	<145 ×10 ⁹ /L

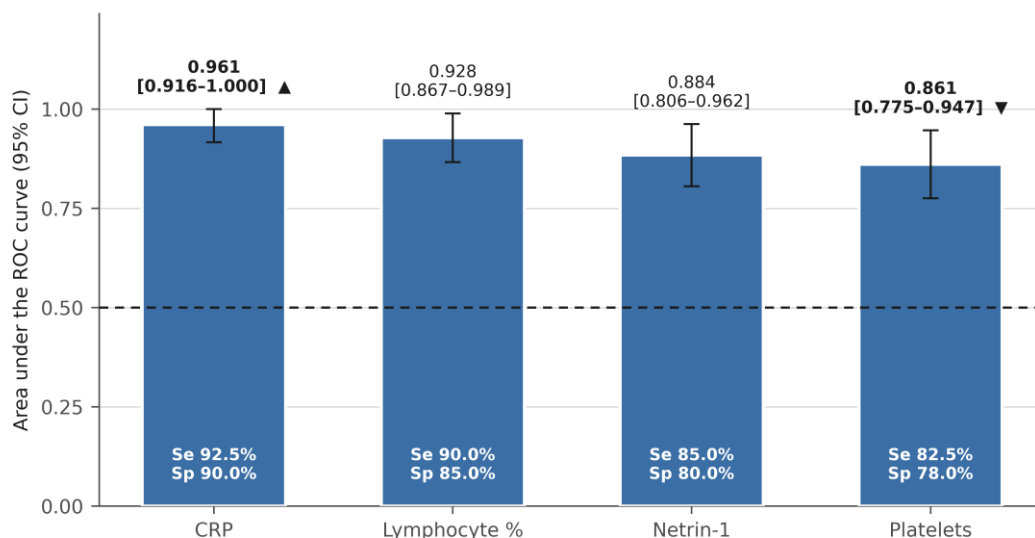


Figure (4): Discrimination between COVID-19 patients and controls. Columns are the area under the ROC curve with 95% CI; sensitivity and specificity at the selected cut-off are printed inside each column. The dashed line marks AUC = 0.5 (no discrimination); ▲ highest and ▼ lowest AUC.

DISCUSSION

A study found that diabetes can cause a decrease in netrin-1 levels in individuals who had not received blood sugar treatment at the time of netrin-1 measurement [19]. However, a higher netrin-1 level was observed in females diagnosed with COVID-19 along with diabetes, suggesting that a relationship between serum glucose level and inflammatory condition (assessed using hsCRP) can develop simultaneously, netrin-1 has been described to be associated with the most common microvascular complications of HIF-alpha for instance diabetic retinopathy, where angiogenesis is increased via Vascular endothelial growth factor VEGF [24,25]. Furthermore, Nedeva et al. also observed increased serum Ntn1 levels in serum of people with T2D, in addition to increased netrin-1 among a group of those with impaired fasting glucose levels [20].

C-reactive protein (CRP) concentration one of clinical parameters that has been identified as an important marker in COVID-19 patients [26], CRP levels in 86% of severe COVID-19 patients were more than the normal range while 81.1% in moderate and severe disease patients [27].

Liver excretes massive amounts of acute phase proteins in response to infection, like CRP [28,29]. This protein, which increases rapidly during inflammation, is a very sensitive indicator of inflammation, injury, and

infection [30]. Studies have demonstrated that elevated levels of CRP (C-reactive protein) are linked with the morbidity of inflammation [31]. CRP able to enhance phagocytosis then trigger the complement system [32], CRP also attaches to microorganisms and enhances their elimination via phagocytosis [33].

Furthermore, CRP levels tend to increase throughout inflammatory responses, and that elevation occurs in both viral and bacterial infections [34], and in case of COVID-19 CRP levels are considered a marker of morbidity and progression of disease [35].

Some studies suggest that higher CRP levels were associated with complications in progressive COVID-19 cases, including shock, acute respiratory distress syndrome, acute kidney injury, and acute cardiac injury, were associated with higher CRP levels [36].

Acute stress, infection, and cytokine storm have been shown to be triggers for hyperglycemia and ketoacidosis. SARS-CoV-2 virus directly influence pancreatic cells by engages with ACE2 receptors, and this interaction causes tissue damage, loss of insulin secretion capacity, and rapid metabolic deterioration, SARS-CoV-2 infection triggers destruction of pancreatic cells, resulting in the onset of diabetes. In addition, immune cell infiltration, cell death, SARS-CoV-2 viral infection in pancreatic beta cells may also lead to metabolic imbalances in patients diagnosed with COVID-19 [37–42].

COVID-19 can affect glucose metabolism in a variety way, and that vary from slight to severe hyperglycemia with or without ketoacidosis with ketoacidosis or without it. The main causes of hyperglycemia in COVID-19 patients include steroid therapy, cellular storm, autoimmune damage to β cells, and pancreatic inflammation [43–45].

Diabetes is a prevalent condition that is linked to negative clinical outcomes in individuals affected by COVID-19. Some COVID-19 patients develop newly diagnosed diabetes, characterized by elevated fasting blood sugar (FBC) SARS-CoV-2 may trigger new-onset diabetes and exacerbate pre-existing diabetes and prediabetes, even in those without a prior history of diabetes [46,47].

Studies have shown that elevated levels of HbA1c are present in COVID-19 patients. However, fasting blood sugar may be more relevant and predictive of mortality than HbA1c [48,49]. On the other hand, HbA1c levels can help identify patients with COVID-19 who have not yet been diagnosed with diabetes [50].

Studies have found that people with HbA1c levels greater than 7.5 Showed a greater susceptibility to contracting COVID-19. Further supporting the link between HbA1c and COVID-19 severity, observed a significant association between elevated levels of inflammatory biomarkers and high HbA1c in COVID-19 patients. Notably, C-reactive protein, interleukin-6, tumor necrosis factor, procalcitonin, ferritin, D-dimer, and fibrinogen all exhibited positive correlations with HbA1c, this finding aligns with the established role of hyper inflammation in severe COVID-19 cases. Moreover, the study highlights the frequent co-occurrence of elevated D-dimer and HbA1c, alongside prevalent thrombosis, in acute COVID-19 cases, this observations in other severe infectious diseases, suggesting potential shared pathogenic mechanisms [21].

SARS-CoV-2 may serve a crucial function in the intensity of hypoxemia that occurs in COVID-19, inducing additional damage to the lower respiratory tract via angiotensin-converting enzyme 2 (ACE2) receptors, where the virus may infect RBCs by crossing the alveolar membrane, which could also cause a quick drop in blood oxygen levels [51].

Emerging evidence suggests that SARS-CoV-2 may directly hit red blood cells (RBCs), shedding light on the pathophysiology of COVID-19 and potentially explaining certain clinical manifestations. A recent study proposes a novel mechanism of viral entry, implicating an interaction amidst the RBC surface protein Band 3 and the SARS-CoV-2 S1 spike protein. This hypothesis gains weight considering the pivotal role of Band 3 in RBC physiology, particularly oxygen transport. Consequently, compromised Band 3 integrity due to viral interaction could plausibly explain the hypoxemia frequently observed in severe COVID-19 cases, this proposed mechanism aligns with recent findings revealing a significant association between increased RBCs and in-hospital mortality in Covid-19 patients. Additional investigation is warranted to reveal the precise role of RBC infection in COVID-19 pathogenesis and its potential contribution to clinical severity [52,53].

WBC upraised in the majority of cases of individuals who suffer from bacterial or viral infection, as a natural response of the body to systemic infection. In COVID-19 patients, they have WBC count higher than the reference values and association was statistically significant amongst infection and WBC. several research have found a parallel association with white blood cell count [54,55].

Another study indicated an elevated level of total WBCS count is usually observed in acute COVID-19 cases with an enhanced proportion of neutrophils on the other hand that is associated with a low number of lymphocytes and a lower percentage of monocytes [22].

As for platelet count, some studies have shown that individuals having thrombocytopenia have a higher chance of experiencing mortality while they are still in the hospital [56], while other studies have shown that platelet count was negatively associated with mortality. Thrombocytopenia in COVID-19 can be attributed to a potential increase in platelet consumption, as a significant proportion of cases with acute disease develop coagulopathy meeting criteria for disseminated intravascular coagulation [42].

Platelet count increases as a result of increased blood lipids, and hypercholesterolemia can increase the risk of atherosclerosis and thrombosis by modulating the biology of platelets, thereby increasing their activity. Platelets participate in immunity and inflammatory responses, and activated platelets can promote atherosclerosis and thrombus formation [57].

There are many factors that can cause an increase in platelet count, including cancer, splenectomy, bacterial and viral infections, acute blood loss during menstruation in females, and iron deficiency [58].

The majority (70.3%) of COVID-19 patients had normal hemoglobin levels, while 29.1% had decreased levels. Most published studies suggest no correlation between hemoglobin levels and COVID-19 infection.; however, researchers have proposed a positive association with infection, but the mechanism remains uncertain. Patients with decreased hemoglobin may be more susceptible to infection, including viral infection [59,60]. While a decrease in hemoglobin levels has been stated in various articles of patients with acute COVID-19, despite there is no experimental sign to support a change in the oxygen dissociation curve. A decrease in hemoglobin level is a marker of worsening lung inflammation in patients with COVID-19 [54,55].

Regarding PCV, affected by many factors, including Vitamin and mineral deficiency, Inadequate or insufficient food intake, Sex and age, which is a major factor in the variation of PCV and Medical conditions, such as red blood cell destruction, stomach ulcers, or bleeding from cancerous cells. while the decrease in PCV in women can be attributed to the menstrual phase, during which women lose a large amount of blood. The average menstrual loss is 80 ml, with a range of 30-180 ml. This can lead to a daily loss of approximately 1.4 mg of iron during menstruation. Iron is an important component of hemoglobin in red blood cells, and its deficiency can lead to impaired red blood cell production [61].

Number of lymphocytes, several studies have shown that the level of lymphocytes was much lesser in non-survivors of COVID-19 than in survivors. According to clinical findings, COVID-19 patients can be detected by different signs and symptoms, which are diagnostic indications and predictive criteria for infection [56,62]. Other study have reported that lymphopenia affects approximately 85% of COVID-19 patients in critical condition [26].

Lymphopenia can also indicate the absence of opportunistic infection during the acute phase of SARS-CoV-2 infection. It is also a frequent symptom of coronavirus infection [63]. Lymphopenia in COVID-19, along with an increase in neutrophils, has been linked to disease progression. The neutrophil-to-lymphocyte ratio has been shown to be one of the most accurate measures of systemic inflammation. There are several theories that explain the large decrease in lymphocytes in COVID-19, in addition to lymphocyte infiltration and isolation [60]. The ACE2 receptor is expressed by lymphocytes and could be directly targeted by SARS-CoV-2 during infection [64]. In addition, an increase in the production of pro-inflammatory cytokines, especially IL-6, in COVID-19 patients may lead to further decrease in lymphocytes [39].

The opposite direction of the Netrin-1 shift in men and women is the finding that most needs caution. Circulating Netrin-1 does not move uniformly across inflammatory states: it rises with metabolic inflammation and insulin resistance [65], climbs with the intermittent hypoxia of obstructive sleep apnoea in step with HIF-1 α [66], and is elevated in metabolic syndrome alongside CRP and HbA1c [67], yet falls in newly diagnosed type 2 diabetes [19]. Hypoxia-driven induction and metabolic-inflammatory induction may therefore pull the same molecule in different directions, and which one dominates could differ with sex hormone status, body composition and the stage of infection at sampling. The present design cannot separate these mechanisms; it can only record that the interaction term is real in this cohort.

Study limitations

Several constraints bound what these data support. The design is cross-sectional, so every relationship reported here is an association measured at one point in time no temporal sequence, no causal claim and no prognosis can be read from it, which is why the term predictive has been replaced throughout by diagnostic or discriminative. The sample is small and drawn from one city, 20 patients and 15 controls of each sex, which leaves the study powered only for large effects ($g \geq 0.99$) and makes the non-significant female HbA1c result uninformative rather than negative. Disease severity, body mass index, duration of symptoms before sampling and corticosteroid or anticoagulant exposure were not recorded, and each of them acts on CRP, glucose and the blood count independently of infection; residual confounding is therefore likely. The immunological panel was

limited to CRP and the differential count, so IL-6, TNF- α , ferritin, D-dimer, procalcitonin and lymphocyte subsets the assays that would locate Netrin-1 within the cytokine response remain unmeasured. Finally, the ROC cut-offs were derived and tested in the same 70 subjects without a validation set, so the reported sensitivity and specificity are optimistic and need replication in a larger, multicentre and prospectively followed cohort before any clinical use.

CONCLUSION

In conclusion, COVID-19 infection was associated with substantial biochemical and hematological abnormalities along with marked immunological dysregulation. Netrin-1 levels were considerably decreased in male COVID-19 patients and dramatically increased in females compared to healthy controls, suggesting a sex-dependent inflammatory response [65–67]. Both males and females showed significant increases in CRP and random blood sugar levels indicating increased systemic inflammation and altered glucose metabolism. HbA1c values were substantially higher in the male patients. Females showed a non-significant increasing trend.

In the hematological findings of COVID-19 individuals of both sex, substantial leukocytosis, lymphopenia and thrombocytopenia were seen. Female patients likewise showed significantly lower hemoglobin levels whereas significantly increased RBC count and PCV values were observed in male patients. Correlation analysis revealed substantial inverse correlations between Netrin-1 and inflammatory markers, particularly CRP and HbA1c, which corroborates the link of altered Netrin-1 expression with inflammatory dysregulation in COVID-19.

ROC analysis showed that CRP, lymphocyte percentage, Netrin-1 and platelet count discriminate COVID-19 patients from healthy controls within this sample [27,35,68]. Netrin-1 is therefore best described as a candidate diagnostic biomarker of the inflammatory and haematological alteration that accompanies COVID-19 [19,20,65]; establishing prognostic value requires prospective cohorts with recorded clinical outcomes and an independent validation set [66,67].

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Considerations

This study was performed after receiving full ethical permission from the Scientific Committee in the Department of Pathological analysis, College of Applied science, University of Samarra. We confirmed that all stages of the research conformed with ethical guidelines, and specimens were collected from patients and healthy individuals only after obtaining their informed written permission. We affirm that the participants' privacy and rights were fully maintained throughout the study, and data were collected and processed with the utmost confidentiality, in preparation for publishing the research in a reputable scientific journal.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

REFERENCES

- [1] Azhar, E. I., Hui, D. S., Memish, Z. A., Drosten, C., & Zumla, A. (2019). The middle east respiratory syndrome (MERS). *Infectious Disease Clinics*, 33(4), 891–905. DOI: [10.1016/j.idc.2019.08.001](https://doi.org/10.1016/j.idc.2019.08.001)
- [2] Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B., & Huang, C.-L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579(7798), 270–273. DOI: [10.1038/s41586-020-2012-7](https://doi.org/10.1038/s41586-020-2012-7)
- [3] Passacuale, G., Phinikaridou, A., Warboys, C., Cooper, M., Lavin, B., Alfieri, A., Andia, M. E., Botnar, R. M., & Ferro, A. (2015). Aspirin-induced histone acetylation in endothelial cells enhances synthesis of the secreted isoform of netrin-1 thus inhibiting monocyte vascular infiltration. *British Journal of Pharmacology*, 172(14), 3548–3564. <https://doi.org/10.1111/bph.13144>
- [4] Serafini, T., Kennedy, T. E., Gaiko, M. J., Mirzayan, C., Jessell, T. M., & Tessier-Lavigne, M. (1994). The netrins define a family of axon outgrowth-promoting proteins homologous to *C. elegans* UNC-6. *Cell*, 78(3), 409–424. DOI: [10.1016/0092-8674\(94\)90420-0](https://doi.org/10.1016/0092-8674(94)90420-0)
- [5] Koch, M., Murrell, J. R., Hunter, D. D., Olson, P. F., Jin, W., Keene, D. R., Brunken, W. J., & Burgeson, R. E. (2000). A novel member of the netrin family, β -netrin, shares homology with the β chain of laminin: Identification, ex-

- pression, and functional characterization. *The Journal of Cell Biology*, 151(2), 221–234. <https://doi.org/10.1083/jcb.151.2.221>
- [6] Rajasekharan, S., & Kennedy, T. E. (2009). The netrin protein family. *Genome Biology*, 10(9), 239. <https://doi.org/10.1186/gb-2009-10-9-239>
- [7] Mazelin, L., Bernet, A., Bonod-Bidaud, C., Pays, L., Arnaud, S., Gespach, C., Bredesen, D. E., Scoazec, J.-Y., & Mehlen, P. (2004). Netrin-1 controls colorectal tumorigenesis by regulating apoptosis. *Nature*, 431(7004), 80–84. <https://doi.org/10.1038/nature02788>
- [8] Baggiolini, M. (1998). Chemokines and leukocyte traffic. *Nature*, 392(6676), 565–568. <https://doi.org/10.1038/33340>
- [9] Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., Laue, M., Schneider, J., Brünink, S., & Greuel, S. (2021). Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nature Neuroscience*, 24(2), 168–175. <https://doi.org/10.1038/s41593-020-00758-5>
- [10] Florindo, H. F., Kleiner, R., Vaskovich-Koubi, D., Acúrcio, R. C., Carreira, B., Yeini, E., Tiram, G., Liubomirski, Y., & Satchi-Fainaro, R. (2020). Immune-mediated approaches against COVID-19. *Nature Nanotechnology*, 15(8), 630–645. <https://doi.org/10.1038/s41565-020-0732-3>
- [11] Xia, H., & Lazartigues, E. (2008). Angiotensin-converting enzyme 2 in the brain: Properties and future directions. *Journal of Neurochemistry*, 107(6), 1482–1494. <https://doi.org/10.1111/j.1471-4159.2008.05723.x>
- [12] Puccioni-Sohler, M., Poton, A. R., Franklin, M., Silva, S. J. da, Brindeiro, R., & Tanuri, A. (2020). Current evidence of neurological features, diagnosis, and neuropathogenesis associated with COVID-19. *Revista Da Sociedade Brasileira de Medicina Tropical*, 53, e20200477. DOI: 10.1590/0037-8682-0477-2020
- [13] Zubair, A. S., McAlpine, L. S., Gardin, T., Farhadian, S., Kuruvilla, D. E., & Spudich, S. (2020). Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: A review. *JAMA Neurology*, 77(8), 1018–1027. doi:10.1001/jamaneurol.2020.2065
- [14] Postolache, T. T., Benros, M. E., & Brenner, L. A. (2021). Targetable biological mechanisms implicated in emergent psychiatric conditions associated with SARS-CoV-2 infection. *JAMA Psychiatry*, 78(4). doi:10.1001/jamapsychiatry.2020.2795
- [15] Daniels, B. P., Holman, D. W., Cruz-Orengo, L., Jujavarapu, H., Durrant, D. M., & Klein, R. S. (2014). Viral Pathogen-Associated Molecular Patterns Regulate Blood-Brain Barrier Integrity via Competing Innate Cytokine Signals. *mBio*, 5(5), e01476-14. <https://doi.org/10.1128/mBio.01476-14>
- [16] Iacobellis, G. (2020). COVID-19 and diabetes: Can DPP4 inhibition play a role? *Diabetes Research and Clinical Practice*, 162. doi: [10.1016/j.diabres.2020.108125](https://doi.org/10.1016/j.diabres.2020.108125)
- [17] Ceriello, A., De Nigris, V., & Prattichizzo, F. (2020). Why is hyperglycaemia worsening COVID-19 and its prognosis? *Diabetes, Obesity & Metabolism*, 22(10), 1951. doi: [10.1111/dom.14098](https://doi.org/10.1111/dom.14098)
- [18] Nassar, M., Daoud, A., Nso, N., Medina, L., Ghernautan, V., Bhangoo, H., Nyein, A., Mohamed, M., Alqassieh, A., & Soliman, K. (2021). Diabetes mellitus and COVID-19. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 15(6), 102268. <https://doi.org/10.1016/j.dsx.2021.102268>.
- [19] Liu, C., Ke, X., Wang, Y., Feng, X., Li, Q., Zhang, Y., Zhu, J., & Li, Q. (2016). The level of netrin-1 is decreased in newly diagnosed type 2 diabetes mellitus patients. *BMC Endocrine Disorders*, 16(1), 33. <https://doi.org/10.1186/s12902-016-0112-z>
- [20] Nedeva, I., Gateva, A., Assyov, Y., Karamfilova, V., Velikova, T., & Kamenov, Z. (2022). Relationship between circulating netrin-1 levels, obesity, prediabetes and newly diagnosed type 2 diabetes. *Archives of Physiology and Biochemistry*, 128(6), 1533–1538. <https://doi.org/10.1080/13813455.2020.1780453>
- [21] Zhu, Z., Mao, Y., & Chen, G. (2021). Predictive value of HbA1c for in-hospital adverse prognosis in COVID-19: A systematic review and meta-analysis. *Primary Care Diabetes*, 15(6), 910–917. DOI: 10.1016/j.pcd.2021.07.013
- [22] Henry, B. M., De Oliveira, M. H. S., Benoit, S., Plebani, M., & Lippi, G. (2020). Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. *Clinical Chemistry and Laboratory Medicine (CCLM)*, 58(7), 1021–1028. <https://doi.org/10.1515/cclm-2020-0369>
- [23] Singer, J. M., & Plotz, C. M. (1956). The latex fixation test: I. Application to the serologic diagnosis of rheumatoid arthritis. *The American Journal of Medicine*, 21(6), 888–892. DOI: [10.1016/0002-9343\(56\)90103-6](https://doi.org/10.1016/0002-9343(56)90103-6)
- [24] Miloudi, K., Binet, F., Wilson, A., Cerani, A., Oubaha, M., Menard, C., Henriques, S., Mawambo, G., Dejda, A., & Nguyen, P. T. (2016). Truncated netrin-1 contributes to pathological vascular permeability in diabetic retinopathy. *The Journal of Clinical Investigation*, 126(8), 3006–3022. <https://doi.org/10.1172/JCI84767>
- [25] Tian, X.-F., Xia, X.-B., Xiong, S.-Q., Jiang, J., Liu, D., & Liu, J.-L. (2011). Netrin-1 overexpression in oxygen-induced retinopathy correlates with breakdown of the blood-retina barrier and retinal neovascularization. *Ophthalmologica*, 226(2), 37–44. <https://doi.org/10.1159/000324474>
- [26] Wang, F., Nie, J., Wang, H., Zhao, Q., Xiong, Y., Deng, L., Song, S., Ma, Z., Mo, P., & Zhang, Y. (2020). Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *The Journal of Infectious Diseases*, 221(11), 1762–1769. <https://doi.org/10.1093/infdis/jiaa150>

- [27] Chen, W., Zheng, K. I., Liu, S., Yan, Z., Xu, C., & Qiao, Z. (2020). Plasma CRP level is positively associated with the severity of COVID-19. *Annals of Clinical Microbiology and Antimicrobials*, 19(1), 18. <https://doi.org/10.1186/s12941-020-00362-2>
- [28] Alahmad, B., Al-Shammari, A. A., Bennakhi, A., Al-Mulla, F., & Ali, H. (2020). Fasting blood glucose and COVID-19 severity: Nonlinearity matters. *Diabetes Care*, 43(12), 3113–3116.
- [29] Ehling, C., Wolf, S. D., & Bode, J. G. (2021). Acute-phase protein synthesis: A key feature of innate immune functions of the liver. *Biological Chemistry*, 402(9), 1129–1145. <https://doi.org/10.1515/hsz-2021-0209>
- [30] Gulhar, R., Ashraf, M. A., & Jialal, I. (2026). Physiology, Acute Phase Reactants. In *StatPearls*. StatPearls Publishing.
- [31] Rainer, T. H., Chan, C. P., Leung, M. F., Leung, W., Ip, M., Lee, N., Cautherley, G. W., Graham, C. A., Fuchs, D., & Renneberg, R. (2009). Diagnostic utility of CRP to neopterin ratio in patients with acute respiratory tract infections. *Journal of Infection*, 58(2), 123–130. <https://doi.org/10.1016/j.jinf.2008.11.007>
- [32] Gershov, D., Kim, S., Brot, N., & Elkon, K. B. (2000). C-Reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: Implications for systemic autoimmunity. *The Journal of Experimental Medicine*, 192(9), 1353–1364.
- [33] Pova, P., Pereira, J., & Coelho, L. (2009). C-reactive protein: Structure, synthesis and function. *C-Reactive Protein: New Research*, 307–324.
- [34] Coster, D., Wasserman, A., Fisher, E., Rogowski, O., Zeltser, D., Shapira, I., Bernstein, D., Meilik, A., Raykhshtat, E., & Halpern, P. (2020). Using the kinetics of C-reactive protein response to improve the differential diagnosis between acute bacterial and viral infections. *Infection*, 48(2), 241–248. <https://doi.org/10.1007/s15010-019-01383-6>
- [35] Liu, F., Li, L., Xu, M., Wu, J., Luo, D., Zhu, Y., Li, B., Song, X., & Zhou, X. (2020). Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *Journal of Clinical Virology*, 127, 104370. <https://doi.org/10.1016/j.jcv.2020.104370>
- [36] Deng, Y., Liu, W., Liu, K., Fang, Y.-Y., Shang, J., Zhou, L., Wang, K., Leng, F., Wei, S., & Chen, L. (2020). Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: A retrospective study. *Chinese Medical Journal*, 133(11), 1261–1267.
- [37] Apicella, M., Campopiano, M. C., Mantuano, M., Mazoni, L., Coppelli, A., & Del Prato, S. (2020). COVID-19 in people with diabetes: Understanding the reasons for worse outcomes. *The Lancet Diabetes & Endocrinology*, 8(9), 782–792. DOI: [10.1016/S2213-8587\(20\)30238-2](https://doi.org/10.1016/S2213-8587(20)30238-2)
- [38] Gerganova, A., Assyov, Y., & Kamenov, Z. (2022). Stress hyperglycemia, diabetes mellitus and COVID-19 infection: Risk factors, clinical outcomes and post-discharge implications. *Frontiers in Clinical Diabetes and Healthcare*, 3, 826006. <https://doi.org/10.3389/fcdhc.2022.826006>
- [39] Lin, S., Zhao, Y., Zhou, D., Zhou, F., & Xu, F. (2020). Coronavirus disease 2019 (COVID-19): Cytokine storms, hyper-inflammatory phenotypes, and acute respiratory distress syndrome. *Genes & Diseases*, 7(4), 520–527. <https://doi.org/10.1016/j.gendis.2020.06.009>
- [40] Nabi, A. N., Ebihara, A., & Shekhar, H. U. (2023). Impacts of SARS-CoV-2 on diabetes mellitus: A pre and post pandemic evaluation. *World Journal of Virology*, 12(3), 151. <https://doi.org/10.5501/wjv.v12.i3.151>
- [41] Nanditha, A., Raghavan, A., Misra, A., Saboo, B., Singh, A. K., Joshi, S. R., Agarwal, S., Tandon, N., Tiwaskar, M., & Aravind, S. R. (2021). Management of Hyperglycemia in COVID-19 and Post-COVID-19 Syndrome-Proposed Guidelines for India. *The Journal of the Association of Physicians of India*, 69(9), 11–12.
- [42] Tang, N., Bai, H., Chen, X., Gong, J., Li, D., & Sun, Z. (2020). Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of Thrombosis and Haemostasis*, 18(5), 1094–1099. <https://doi.org/10.1111/jth.14817>
- [43] Bassène, M. L., Fall, M. P., Fall, A. B., Diallo, S., Cissé, C. K., Sidibé, T., & Gueye, M. N. (2023). Acute Pancreatitis during SARS CoV 2 Infection. *Open Journal of Gastroenterology*, 13(1), 28–32.
- [44] Issac, A., & Kochuparambil, J. J. (2022). 1058. Development of a Steroid Stewardship Bundle to tackle the Glucocorticoid-Induced Hyperglycemia in COVID-19 patients: Results of SUPER Diabetes Study. *Open Forum Infectious Diseases*, 9(Supplement_2), ofac492.899. <https://doi.org/10.1093/ofid/ofac492.899>
- [45] Kethireddy, R., Gandhi, D., Kichloo, A., & Patel, L. (2022). Challenges in hyperglycemia management in critically ill patients with COVID-19. *World Journal of Critical Care Medicine*, 11(4), 219. <https://doi.org/10.5492/wjccm.v11.i4.219>
- [46] Grubišić, B., Švitek, L., Ormanac, K., Sabo, D., Mihaljević, I., Bilić-Ćurčić, I., & Kolarić, T. O. (2023). Molecular mechanisms responsible for diabetogenic effects of COVID-19 infection—Induction of autoimmune dysregulation and metabolic disturbances. *International Journal of Molecular Sciences*, 24(14), 11576. <https://doi.org/10.3390/ijms241411576>
- [47] Lontos, A., Biros, D., Kavakli, A., Matzaras, R., Tsiakas, I., Athanasiou, L., Samanidou, V., Konstantopoulou, R., Vagias, I., & Panteli, A. (2023). Glycemic dysregulation, inflammation and disease outcomes in patients hospitalized with COVID-19: Beyond diabetes and obesity. *Viruses*, 15(7), 1468. <https://doi.org/10.3390/v15071468>

- [48] Schlesinger, S., Neuenschwander, M., Lang, A., Pafili, K., Kuss, O., Herder, C., & Roden, M. (2021). Risk phenotypes of diabetes and association with COVID-19 severity and death: A living systematic review and meta-analysis. *Diabetologia*, 64(7), 1480–1491. <https://doi.org/10.1007/s00125-021-05458-8>
- [49] Umpierrez, G. E., Isaacs, S. D., Bazargan, N., You, X., Thaler, L. M., & Kitabchi, A. E. (2002). Hyperglycemia: An independent marker of in-hospital mortality in patients with undiagnosed diabetes. *The Journal of Clinical Endocrinology & Metabolism*, 87(3), 978–982. <https://doi.org/10.1210/jcem.87.3.8341>
- [50] Liu, Y., Lu, R., Wang, J., Cheng, Q., Zhang, R., Zhang, S., Le, Y., Wang, H., Xiao, W., & Gao, H. (2021). Diabetes, even newly defined by HbA1c testing, is associated with an increased risk of in-hospital death in adults with COVID-19. *BMC Endocrine Disorders*, 21(1), 56.
- [51] Farsaci, F., Tellone, E., Galtieri, A., & Ficarra, S. (2020). A thermodynamic characterization of the phenomena evolving in cancer pathology by dielectric relaxation in blood: A new approach by construction of TTM (Thermodynamic Tumor Matrix). *Journal of Molecular Liquids*, 316, 113839.
- [52] Cosic, I., Cosic, D., & Loncarevic, I. (2020). RRM prediction of erythrocyte Band3 protein as alternative receptor for SARS-CoV-2 virus. *Applied Sciences*, 10(11), 4053.
- [53] Mullen, E., Bergin, S., Healy, G., Quinn, J., Glavey, S., & Murphy, P. T. (2022). Red blood cells from COVID-19 patients suffer from increased oxidative stress and may have increased lactate influx. *Blood Research*, 57(4), 294–296.
- [54] Mardani, R., Vasmehjani, A. A., Zali, F., Gholami, A., Nasab, S. D. M., Kaghazian, H., Kaviani, M., & Ahmadi, N. (2020). Laboratory parameters in detection of COVID-19 patients with positive RT-PCR; a diagnostic accuracy study. *Archives of Academic Emergency Medicine*, 8(1), e43.
- [55] Pakos, I. S., Lo, K. B., Salacup, G., Pelayo, J., Bhargav, R., Peterson, E., Gul, F., DeJoy III, R., Albano, J., & Pataroyo-Aponte, G. (2020). Characteristics of peripheral blood differential counts in hospitalized patients with COVID-19. *European Journal of Haematology*, 105(6), 773–778.
- [56] Yang, L., Liu, J., Zhang, R., Li, M., Li, Z., Zhou, X., Hu, C., Tian, F., Zhou, F., & Lei, Y. (2020). Epidemiological and clinical features of 200 hospitalized patients with corona virus disease 2019 outside Wuhan, China: A descriptive study. *Journal of Clinical Virology*, 129, 104475.
- [57] Cohen, A., Harari, E., Cipok, M., Laish-Farkash, A., Bryk, G., Yahud, E., Sela, Y., Lador, N. K., Mann, T., & Mayo, A. (2021). Immature platelets in patients hospitalized with Covid-19. *Journal of Thrombosis and Thrombolysis*, 51(3), 608–616.
- [58] Rokkam, V. R. P., Vegunta, R., Prudhvi, K., Vegunta, R., Kotagiri, R., & Boregowda, U. (2020). “Weighing” the risks and benefits–Thromboprophylaxis challenges in obese COVID-19 patients. *Obesity Medicine*, 19, 100284.
- [59] Anai, M., Akaike, K., Iwagoe, H., Akasaka, T., Higuchi, T., Miyazaki, A., Naito, D., Tajima, Y., Takahashi, H., & Komatsu, T. (2021). Decrease in hemoglobin level predicts increased risk for severe respiratory failure in COVID-19 patients with pneumonia. *Respiratory Investigation*, 59(2), 187–193.
- [60] Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., & Gu, X. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223), 497–506.
- [61] Ofojekwu, M.-J. N., Nnanna, O. U., Okolie, C. E., Odewumi, L. A., Isiguzoro, I. O., & Lugos, M. D. (2013). Hemoglobin and serum iron concentrations in menstruating nulliparous women in Jos, Nigeria. *Laboratory Medicine*, 44(2), 121–124. <https://doi.org/10.1309/LMM7A0F0QBXEYSSI>
- [62] Ruan, Q., Yang, K., Wang, W., Jiang, L., & Song, J. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Medicine*, 46(5), 846–848.
- [63] Li, H., Wang, Y., Ji, M., Pei, F., Zhao, Q., Zhou, Y., Hong, Y., Han, S., Wang, J., & Wang, Q. (2020). Transmission routes analysis of SARS-CoV-2: A systematic review and case report. *Frontiers in Cell and Developmental Biology*, 8, 618. <https://doi.org/10.3389/fcell.2020.00618>
- [64] Xu, H., Zhong, L., Deng, J., Peng, J., Dan, H., Zeng, X., Li, T., & Chen, Q. (2020). High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *International Journal of Oral Science*, 12(1), 8. <https://doi.org/10.1038/s41368-020-0074-x>
- [65] Ramos-Zavala, M. G., García-Galindo, J. J., Beltrán-Ramírez, A., Balleza-Alejandri, L. R., Peña-Durán, E., Huerta-Huerta, A., Rubio-Arellano, E. D., López-Murillo, L. D., Pascoe-Gonzalez, S., Campos-Bayardo, T. I., & Suárez-Rico, D. O. (2025). Opposing profiles of Netrin-1 and adiponectin in metabolic inflammation and insulin resistance. *Frontiers in Pharmacology*, 16, 1632956. <https://doi.org/10.3389/fphar.2025.1632956>
- [66] Erdem, M., Kiran, T. R., Kırıcı Berber, N., Şahin Gür, L., & Erdem, Ş. (2026). Altered HIF-1 α , Netrin-1, and Netrin-4 levels in obstructive sleep apnea: Associations with intermittent hypoxia and disease severity. *Medicina*, 62(7), 1340. <https://doi.org/10.3390/medicina62071340>
- [67] Kiran, T. R., Ayyıldız, G., Keskin, L., & Erdem, M. (2026). Unveiling the significance of Netrin-1 and Netrin-4 in metabolic syndrome. *Scientific Reports*, 16, 5814. <https://doi.org/10.1038/s41598-026-36172-3>
- [68] Alahmed, A., & Al-Rubaei, E. (2025). New insight for ulcerative colitis diagnosis via serum netrin-1 and galectin-1 biomarkers. *Human Antibodies*. <https://doi.org/10.1177/10932607251349069>