Increasing the Level of Neopterin in patients infected with SARS-CoV-2 Indicates Fatal Mortality

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Abstract

Background: The severity of Coronavirus Disease-2019 (COVID-19) cases is associated with hyperinflammation. Patients with critical and severe COVID-19 have been observed to have high amounts of circulating cytokines. Neopterin, a crucial cytokine in the antiviral immune response that is released by macrophages upon stimulation with interferon-gamma, can be utilized to forecast the severity of illness in COVID-19 patients. **Methods:** The study included 185 patients with COVID-19. The patients with COVID-19 were divided into three groups according to disease severity as critical disease (n=51), severe disease (n=81), and moderate disease (n=53). All basic demographic and clinical data of the patients were recorded and blood samples were collected. **Results:** Neopterin levels were significantly higher in critical COVID-19 patients compared with severe and moderate COVID-19 patients ($p < 0.0001$). Further, neopterin showed significantly higher levels in the age group ≥50 years of patients with COVID-19 than in the age group <50 years. Neopterin levels were correlated with WBCs, Platelet, CRP, D-Dimer, Ferritin, Fibrinogen, IL-6, and Procalcitonin levels positively (ρ= 0.569, 0.474, 0.338, 0.696, 0.605, 0.77, 0.727, and 0.585; $p < 0.01$ respectively), and correlated with BMI, SpO_2, and lymphocyte negatively (ρ= - 0.165; $p < 0.05$, ρ= - 0.754, - 0. 548; $p < 0.01$ respectively). A cutoff value of 23.62 nmol/L for neopterin predicted COVID-19 with a sensitivity of 95.7% and a specificity of 95.5% (AUC: 0.986; $p < 0.0001$). **Conclusion:** Neopterin may be a useful prognostic biomarker for assessing the severity of COVID-19.

Keywords: Neopterin, IL-6, age, COVID-19, disease severity.

1- Introduction

Since it first surfaced in China in late 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has spread quickly around the world. According to the statistics, about 80% of COVID-19 patients have moderate illness, 20% need hospitalization, and roughly 5% require admission into intensive care (1). In patients who are elderly, male, and have concomitant conditions such diabetes, cardiovascular disease, or chronic obstructive pulmonary disease, the prognosis for COVID-19 is poor (2,3). Hyperinflammation and coagulopathy are linked to illness severity and mortality in SARS-CoV-2 infected individuals (4,5).
The severity of the illness and mortality from COVID-19 are correlated with higher levels of inflammatory markers, including as C-reactive protein, ferritin, D-dimer, inflammatory cytokines, and chemokines (6), as well as elevated neutrophil to lymphocyte ratios. When compared to moderate COVID-19 instances, severe cases have been shown to have higher levels of circulating cytokines, deep lymphopenia, and significant mononuclear cell infiltration in the lungs and other organs (7).
Prior research has demonstrated that the percentage of mononuclear phagocytes in severe instances, macrophage composition altered in favor of macrophages produced from monocytes. As a result, patients with SARS-CoV-2 have been found to have elevated levels of cytokines associated to macrophage activation, such as interferon-γ (8).
The activation of monocytes and macrophages is frequently a component of inflammatory diseases. One of the byproducts of these cells, neopterin, has received much research as a potential biomarker for illnesses including viral infection, cancer, and autoimmune disorders like inflammatory bowel disease. Neopterin has been associated with disease severity in various disorders (9). A plethora of evidence about COVID-19 indicates that inflammatory responses play a crucial role in disease progression. Rapid SARS-CoV-2 multiplication and cellular degeneration trigger an inflammatory response that attracts monocytes and macrophages and leads to the production of cytokines and chemokines, which in turn causes immunological mayhem (8,9).
Neopterin targeting in SARS-CoV-2 infection may thus play a crucial role in the early diagnosis of disease progression and timely treatment of affected people. Few studies have been performed among those infected with SARS-CoV-2, despite the fact that serum neopterin levels have been tested to evaluate immunological activation in a number of disorders. Determining the importance of neopterin as a diagnostic and prognostic marker in COVID-19 patients, whether alone or in association with other inflammatory indicators such C-reactive protein (CRP), IL-6, and procalcitonin, was the goal of this study.

2- Materials and Methods

A case-control study was conducted on COVID-19 patients admitted to COVID-19 Al-Amal specialized hospital for infectious diseases in an Al-Najaf governorate, Iraq during May and August 2022 after

doi.org/10.31838/hiv23.02.67 Received: 03.10.22, Revised: 18.11.22, Accepted: 29.12.22.

obtaining approval of the Ethics Committee of the Iraqi Ministry of Health and Environment and written consent of the participants. A total number of 297 subjects were included: 185 COVID-19 patients (mean age = 50.57 years; standard deviation = 5.28 years; range = 35-65 years; 58.38% males) and 112 controls (mean age = 49.16 years; standard deviation = 6.53 years; range = 36–63 years; 59.82% males). SARS-CoV2 was identified in patient nasopharyngeal swabs using the RealLine SARS-CoV2 test (Bioron Diagnostics GmbH). To confirm the diagnosis, a chest tomography (CT) scan was also completed. Patients who had a positive molecular test, a COVID-19-positive CT scan, and were more than 18 years old were included in the study.

Chronic disease, pregnant women, and obese were excluded. Patients were evaluated in terms of disease severity, and in this context, three categories were adopted; moderate (evident clinical and/or radiological observations of lower respiratory tract infection with ≥94% oxygen saturation), severe (<94% oxygen saturation and ≥30 breaths/minute respiratory rate) and critical (respiratory failure) illness.

Laboratory tests for hemoglobin (Hb), platelet count, white blood cell count (WBC), lymphocyte, C-reactive protein, D-dimer, ferritin, and fibrinogen were also profiled for patients. Blood donors and healthcare workers who were healthy and free of respiratory and chronic illnesses made up the control group. They tested negative for C-reactive protein and anti-COVID19 IgG and IgM antibodies.

Venous blood samples were collected from both the patient and control groups. I took blood samples using two tubes. Allow the sample to clot for 10 to 15 minutes at room temperature before centrifuging 3 ml at 3000 Xg for 10 minutes to extract serum. The serum samples were then divided into tubes and kept in the refrigerator at a temperature of -20°C until they were ready for analysis. The remaining blood (2 ml) was utilized to calculate the complete blood count. Fibrinogen was measured using an immunoturbidimetric approach utilizing an optical method. Fluorescence immunoassay was used to determine serum ferritin, C-reactive protein, and D-dimer levels were measured by (ichroma™). An autohematology analyzer was used to determine the whole blood count (linear, Spain). I used Melsin Medical Co. (Jilin, China) ELISA kits to measure serum neopterin, IL-6, Procalcitonin.

Statistical Analysis

The statistical studies were conducted using IBM SPSS Statistics 26 software. The analyses' findings were presented as mean standard deviation. The cutoff point for statistical significance was $p < 0.05$. The Spearman's correlation coefficient (rho, ρ) analysis was used to assess the nonparametric variables. Analysis of variance (ANOVA) was employed in the study to examine any variations in scale variables between categories. To establish the cutoff value for neopterin, the receiver operating characteristic (ROC) analysis approach was used. The area under curve (AUC) value was calculated using the ROC curve.

3- Results

The 185 patients enrolled in this study were categorized according to severity of COVID-19. Fifty-three patients had moderate disease, while remaining patients experienced either critical or severe illness (51 and 81 patients, respectively). The latter two groups of patients had a significantly higher mean age compared to patients with moderate disease (54.84 ± 5.31 and 49.48 ± 3.77 vs. 48.12 ± 4.91 years, respectively; $p < 0.056$). In fact, more than 60% of moderate cases were classified under the age group < 50 years (68.81%), while 76.47% and 45.68% of critical and severe cases were above the age of 50 years, respectively. These differences were significant ($p < 0.01$). Patients were also defined by the laboratory parameters listed in Table 1. Means of these parameters showed higher significantly differences between the three disease severity groups as well as when compared with control group (Table 1 and Figure 1 A and B).

Serum levels of neopterin showed higher significant differences between COVID-19 patients and controls. Similarly, patients stratified by disease severity and age group show significant differences between neopterin levels in each stratum. Further, patients with critical disease tended to have a higher mean of neopterin than in patients with severe and moderate disease (Table 1 Figure 1).

To examine the concurrent effect of disease severity and patient-related parameters on serum levels of neopterin, each of the three disease severity groups (medium, severe, and critical) were classified into subgroups for each parameter (age: <50 and ≥50 years). Neopterin tended to show higher levels in the age group ≥50 years of patients with severe or critical illness than in the age group <50 years (Figure 1 C and D).

ROC curve analysis demonstrated that neopterin was a poor predictor of COVID-19 as the estimated AUC was 0.986 (Sensitivity 95.7%, specificity 95.5%, cutoff value 23.62 and $p < 0.0001$). A similar predicting good was indicated when the patients stratified by age group (AUC= 0.897, Sensitivity 82.6%, specificity 80.8%, cutoff value 37.38 and $p < 0.0001$). In the case of disease severity a significant AUC was observed in critical versus severe illness (AUC= 0.99, Sensitivity 94.1%, specificity 93.8%, cutoff value 46.24 and $p < 0.0001$), and severe versus moderate (AUC= 0.956, Sensitivity 90.1%, specificity 86.8%, cutoff value 31.56 and $p < 0.0001$) (Figure 2).

Spearman's rank order correlation analysis was performed to calculate correlation coefficients (ρ) between neopterin and laboratory parameters in COVID-19 patients. Neopterin showed negative correlation with BMI ($\rho = -0.165$; $p < 0.05$), SpO_2, and lymphocyte ($\rho = -0.754, -0.548$; $p < 0.01$ respectivily), while it was positively correlated with WBCs, platelet, CRP, D-Dimer, ferritin, fibrinogen, IL-6, and procalcitonin ($\rho = 0.569, 0.474, 0.338, 0.696, 0.605, 0.77, 0.727$, and 0.585; $p < 0.01$ respectivily) (Table 2 and Figure 3).

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

Variables		COVID-19 cases; n = 185			Healthy control (n=112)	p-value
		Critical (n=51)	Severe (n=81)	Moderate (n=53)		
Age (years)		54.84±5.31	49.48±3.77	48.12±4.91	49.16±6.53	< 0.056
Age group, (years)	< 50	12 (23.53) 39 (76.47)	44 (54.32) 37 (45.68)	37 (68.81) 16 (30.19)	52 (46.43) 60 (53.57)	< 0.01
	≥ 50					
Gender	Male	30 (58.82) 21 (41.18)	45 (55.56) 36 (44.44)	33 (62.26) 20 (37.74)	67 (59.82) 45 (40.18)	< 0.097
	Female					
BMI (kg/m^2)		23.99±0.76	24.17±1.08	24.45±1.06	24.85±1.32	< 0.949
SpO_2%		71.72±7.39	86.73±6.43	93.01±3.66	98.86±0.46	< 0.000
Hb (g/dL)		12.51±1.19	12.63±1.41	12.51±1.27	12.7±1.25	< 0.773
WBCs; ×10^9/L		13.13±1.58	11.74±1.27	10.33±1.57	8.59±1.14	< 0.000
Lymphocyte; ×10^9/L		2.37±0.69	2.94±0.83	3.95±0.77	3.99±0.62	< 0.000
Platelets; ×10^9/L		309.24±35.47	264.12±45.74	242.29±39.41	301.45±61.98	< 0.000
CRP (mg/L)		39.44±6.69	31.59±10.02	28.82±7.08	3.91±1.28	< 0.000
D-Dimer (ng/mL)		3487.91±863.62	2512.36±781.21	1078.55±356.01	204.81±95.07	< 0.000
Ferritin (ng/mL)		692.09±111.08	490.83±72.56	437.17±72.84	132.61±5.62	< 0.000
Fibrinogen (mg/dL)		525.79±63.11	385.56±69.05	233.63±65.52	187.48±78.09	< 0.000
IL-6 (pg/mL)		17.4±2.05	14.89±1.72	10.36±1.84	4.55±1.74	< 0.000
Procalcitonin (ng/mL)		0.47±0.18	0.33±0.03	0.27±0.15	0.09±0.051	< 0.000
Neopterin (nmol/L)		57.64±6.38	36.95±4.97	28.01±3.56	15.88±4.45	< 0.000

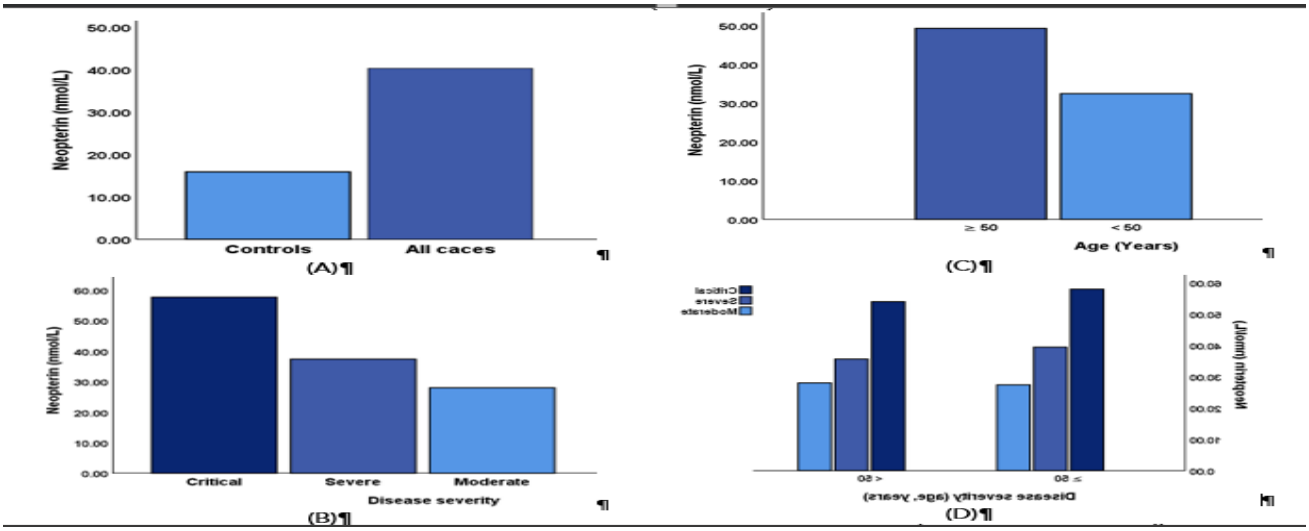


Figure 1. Comparison between groups, (A) All COVID-19 cases and controls, (B) Disease severity, (C) Age, and (D) Disease severity for age of neopterin levels.

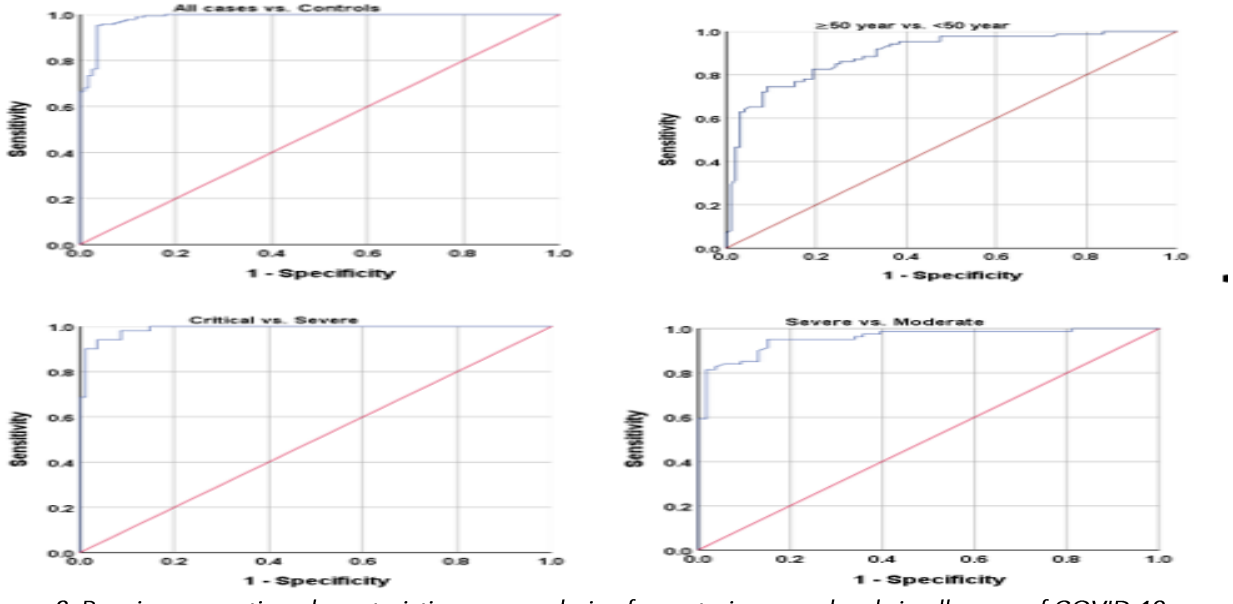
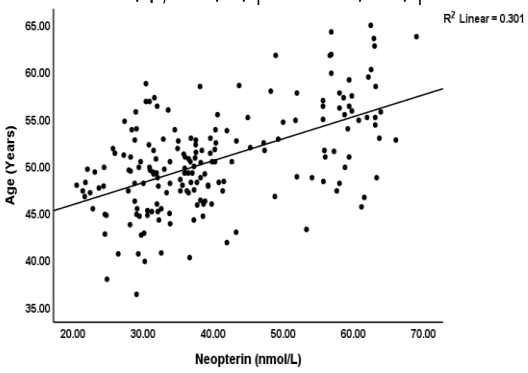


Figure 2. Receiver operating characteristic curve analysis of neopterin serum levels in all cases of COVID-19 versus controls, age group and in COVID-19 cases stratified by disease severity.

Table 2. The correlation between clinical parameters and neopterin serum levels in COVID-19 patients.

Variables	ρ
Age (year)	0.489**
BMI (kg/m^2)	-0.165*
SpO_2%	-0.754**
Hb (g/dl)	-0.056
WBCs ×10^9/L	0.569**
Lymphocyte ×10^9/L	-0.548**
Platelet ×10^9/L	0.474**
CRP (mg/L)	0.338**
D-Dimer (ng/ml)	0.696**
Ferritin (ng/ml)	0.605**
Fibrinogen (mg/dL)	0.770**
IL-6 (pg/mL)	0.727**
Procalcitonin (ng/mL)	0.585**

Abbreviations: BMI, body mass index; SpO_2%, saturation oxygen percentages ; Hb, hemoglobin; WBCs, white blood cells; CRP, C-reactive protein; IL-6, Interleukin-6; ρ, rho; *, $p < 0.05$; ** , $p < 0.01$.



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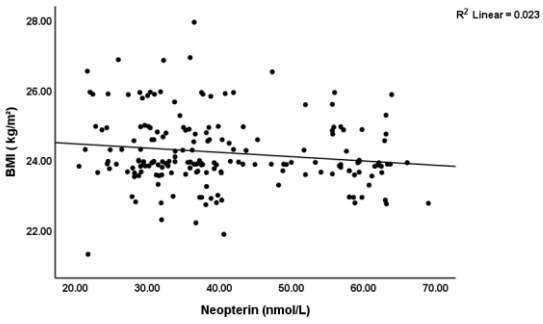

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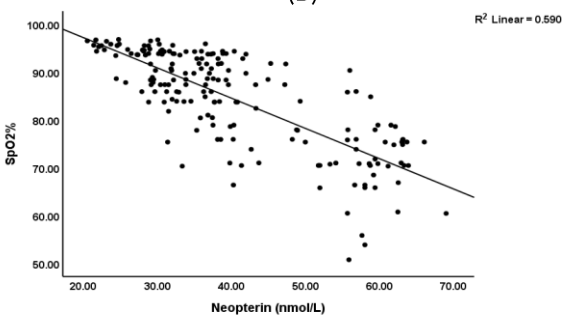

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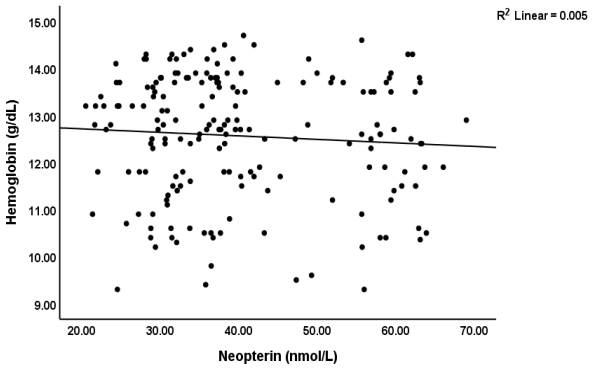

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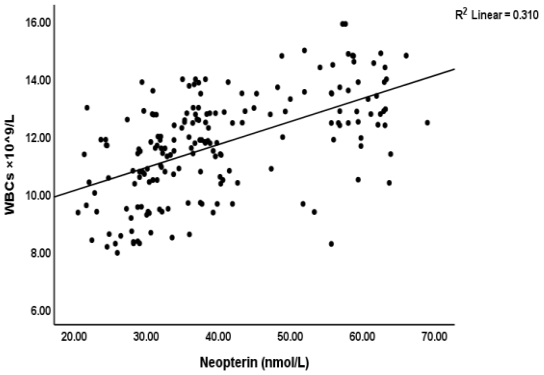

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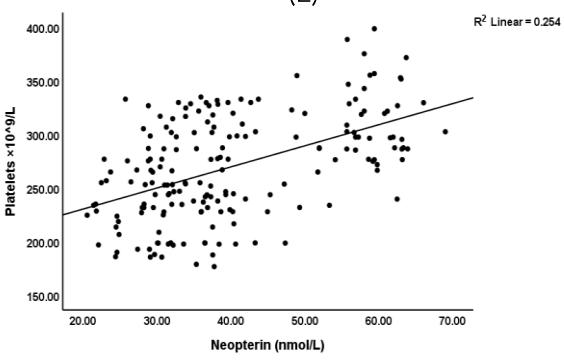

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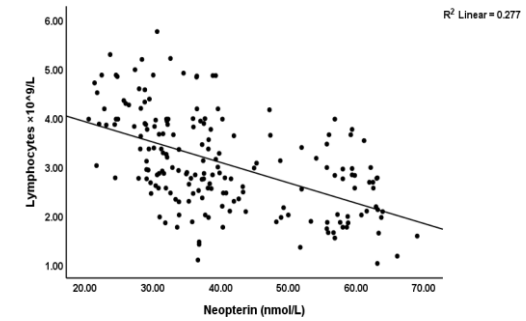

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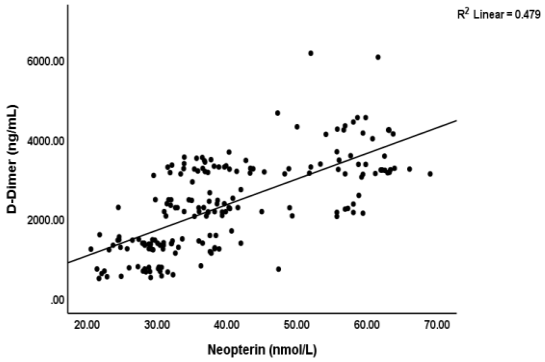

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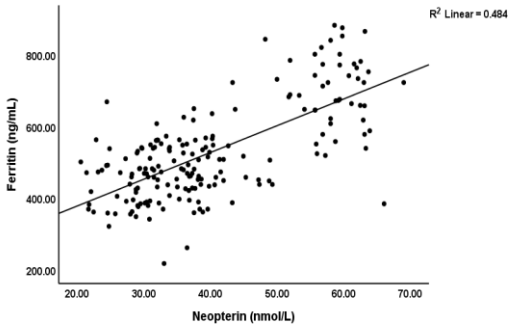

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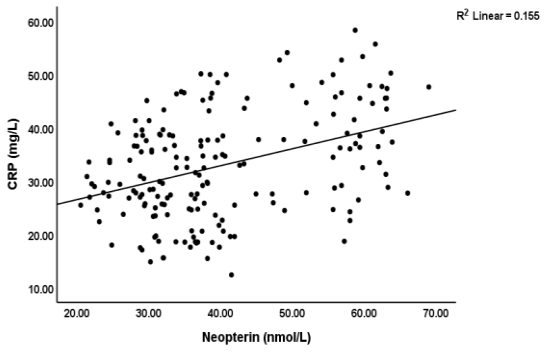

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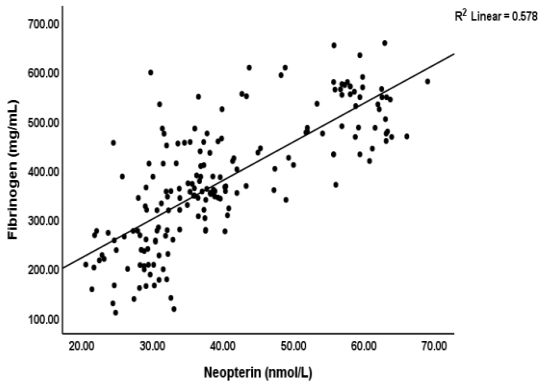

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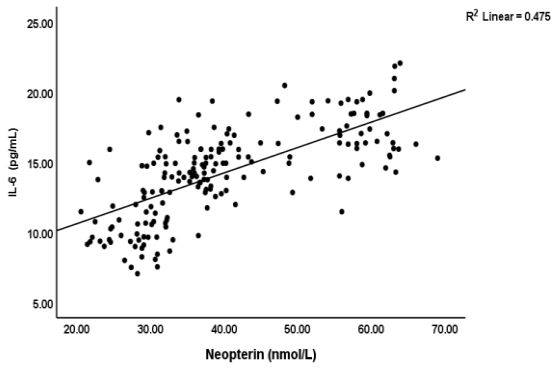

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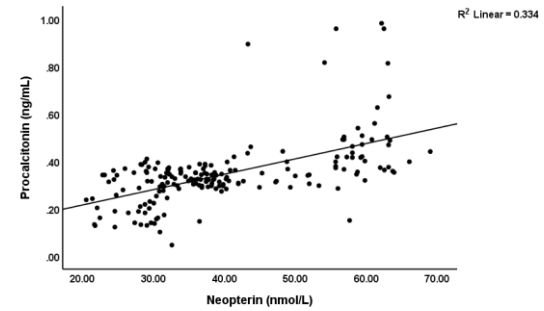

Figure 3. Correlation between neopterin level and (A) Age, (B) BMI, (C) SpO_2%, (D) Hemoglobin, (E) WBCs, (F) Platelet, (G) Lymphocytes, (H) D-Dimer, (I) Ferritin, (J) CRP, (K) Fibrinogen, (L) IL-6, (M) Procalcitonin.

4- Discussion

The macrophage-derived neopterin, which is generated by the cytokine IFN-γ, has established status as a marker in a variety of viral diseases, including HIV and influenza, where it was associated with disease activity, clinical course prediction, and distinction from bacterial infections. Additionally, diverse viral and/or inflammatory disorders' severity and outcomes were correlated with neopterin levels (12). According to research, SARS-CoV-2 infection causes endotheliitis, which in turn causes the production of cytokines that promote inflammation (13). Endothelial inflammation therefore stimulates the production of IL-6 and adhesion molecules such as ICAM-1, MCP-1, and VCAM-1 that promote T cell and monocyte adhesions and infiltrations into vascular neointima with TNF-α release (14,15). Neopterin reduces the activity of macrophage foam cells and is associated with endothelial inflammation through inhibition of adhesion molecules and monocyte migration, as shown by Yan *et al.* (16). Therefore, elevated neopterin levels in COVID-19 patients may have a protective impact to combat endotheliitis and endothelial dysfunctions brought on by SARS-CoV-2. In addition, SARS-CoV-2 infection is linked to macrophage activation and phenotypic acquisition of the pro-inflammatory state.

Neopterin has been suggested as a biomarker for a variety of viral infections and has been linked to disease activity, clinical course prediction, and bacterial infection differentiation (17). Other studies have found that the prevalence of severe clinical

patients is much greater than that of mild clinical patients. According to patients with high neopterin levels, T-cell activation is crucial for starting severe pulmonary inflammation and reducing respiration in SARS-CoV-2 infections (18,19). Neopterin is a useful biomarker of immunological activation of the central nervous system in several viral pathogenic situations, such as HIV-1 infection and influenza (20). Patients with neurological problems and moderate to severe COVID-19 disease had elevated neopterin levels in their blood and cerebrospinal fluid (CSF). Encephalopathy, excessive weariness, memory loss, personality changes, minor neck stiffness, photophobia, sleepiness, dysgeusia, and disorientation were among the neurological symptoms (21).

A strong systemic inflammatory response brought on by SARS-CoV-2 infection may be the cause of high CSF neopterin (22). This finding could clarify the brain damage and CSF inflammation brought on by COVID-19 [21,23]. Regarding the pathophysiological underpinnings of profoundly high CSF neopterin in COVID-19 infection and its utility as a predictive indicator for the emergence of neurological symptoms, there is still a great deal of uncertainty (24,25).

The COVID-19-causing SARS CoV-2 virus has also been linked to increased cytokine levels, organ damage, increased phagocytes, and activated macrophages. Neopterin, a macrophage-produced protein that is involved in viral infections and the immune system, can thus be employed in the early detection of disease severity in COVID-19 patients (26–28).

Neopterin has a diagnostic advantage since it is generated by the Th-1 cytokine IFN-γ, which more accurately reflects immunological activation resulting from T-helper cell type 1 and stimulates the effector actions of monocytic cells. This is consistent with previous findings that T-cell activation contributes significantly to the development of severe pulmonary inflammation and compromised breathing in SARS-CoV-2 infections (29,30). Neopterin is recommended as a reliable parameter for predicting the prognosis of SARSCoV-2-infected patients and adapting the treatment algorithm for such patients with an increased risk of adverse outcomes due to the associations between high neopterin levels and an increased risk of needing mechanical ventilation, intensive care unit (ICU) treatment, and adverse outcomes. To decrease the possibility of mechanical breathing and ICU hospitalization, which are linked to possible problems and long-term care, patients with high neopterin levels at initial presentation require increased surveillance and early referral to noninvasive ventilation. The relationship between high levels of neopterin and a poor clinical outcome is consistent with the theory that more advanced, T-cell-triggered immunological activation is a primary contributor to unfavorable results.

5- Conclusion

Neopterin may be utilized as a biomarker to gauge the severity of the COVID-19 condition. This might lead to an earlier identification of the condition, better monitoring of it, and a reduction in fatalities never before seen.

Acknowledgements

The author thank all patients for their cooperation and the medical staffs in the laboratories of the Al -Amal Hospital AL-Najaf city –Iraq.

Declaration of Interests

The author declare no conflict of interests.

References

1. Long B, Carius BM, Chavez S, Liang SY, Brady WJ, Koyfman A, et al. Clinical update on COVID-19 for the emergency clinician: Presentation and evaluation. Am J Emerg Med. 2022;54:46–57.
2. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. Int J Infect Dis. 2020;94(5):91–5.
3. Bentivegna E, Luciani M, Spuntarelli V, Speranza ML, Guerritore L, Sentimentale A, et al. Extremely Severe Case of COVID-19 Pneumonia Recovered Despite Bad Prognostic Indicators: a Didactic Report. SN Compr Clin Med. 2020;2(8):1204–7.
4. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;81:e16-e25l.
5. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol [Internet]. 2020;20(6):355–62. Available from: http://dx.doi.org/10.1038/s41577-020-0331-4
6. Abd M, Abd A, Ali HA, Ali RA, Serih KH, Mohammed M, et al. Clinical significance of serum Krebs von den Lungen-6 levels as reliable effective marker in COVID-19 patients. Sapporo Med J. 2022;56(08):1-21.
7. Pérez-García N, García-González J, Requena-Mullor M, Rodríguez-Maresca MÁ, Alarcón-Rodríguez R. Comparison of Analytical Values D-Dimer, Glucose, Ferritin and C-Reactive Protein of Symptomatic and Asymptomatic COVID-19 Patients. Int J Environ Res Public Health. 2022;19(9):1–12.
8. Amit Kumar Mandal , Paulami Dam , Octavio L. Franco , Hanen Sellami , Sukhendu Mandal , Gulten Can Sezgin , Kinkar Biswas , Partha Sarathi Nandi IO. Interferon-γ primes macrophages for pathogen ligand-induced killing via a caspase-8 and mitochondrial cell death pathway. Immunity. 2022;55(8):19–21.
9. Forrest CM, Youd P, Kennedy A, Gould SR, Darlington LG, Stone TW. Purine, kynurenine, neopterin and lipid peroxidation levels in inflammatory bowel disease. J Biomed Sci.

2002;9(5):436–42.
10. Carvelli J, Demaria O, Vély F, Batista L, Chouaki N, Miranda LA, et al. Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. Nature. 2021;588(7836):146–50.
11. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol [Internet]. 2020;20(6):363–74. Available from: http://dx.doi.org/10.1038/s41577-020-0311-8
12. Pizzini A, Lunger F, Sahanic A, Nemati N, Fuchs D, Weiss G, et al. Diagnostic and Prognostic Value of Inflammatory Parameters Including Neopterin in the Setting of Pneumonia, COPD, and Acute Exacerbations. COPD J Chronic Obstr Pulm Dis. 2017;14(3):298–303.
13. Thacker V V, Sharma K, Dhar N, Mancini G, Sordet-Dessimoz J, McKinney JD. Rapid endotheliitis and vascular damage characterize SARS-CoV-2 infection in a human lung-on-chip model. EMBO Rep. 2021;22(6):1–19.
14. Chistiakov DA, Melnichenko AA, Myasoedova VA, Grechko A V., Orekhov AN. Mechanisms of foam cell formation in atherosclerosis. J Mol Med. 2017;95(11):1153–65.
15. Abd M, Abd A, Ali HA. Plasma ICAM-1 level is highly associated with disease severity and predict the progression of COVID-19. Sapporo Med J. 2022;56(08).
16. Yan JQ, Tan CZ, Wu JH, Zhang DC, Chen JL, Zeng BY, et al. Neopterin negatively regulates expression of ABCA1 and ABCG1 by the LXRα signaling pathway in THP-1 macrophage-derived foam cells. Mol Cell Biochem. 2013;379(1–2):123–31.
17. Prat C, Domínguez J, Andreo F, Blanco S, Pallarés A, Cuchillo F, et al. Procalcitonin and neopterin correlation with aetiology and severity of pneumonia. J Infect. 2006;52(3):169–77.
18. Abu Shady MM, Fathy HA, Ali A, Youness ER, Fathy GA. Association of neopterin as a marker of immune system activation and juvenile rheumatoid arthritis activity. J Pediatr (Rio J) [Internet]. 2015;91(4):352–7. Available from: http://dx.doi.org/10.1016/j.jped.2014.09.007
19. Ozger HS, Dizbay M, Corbacioglu SK, Aysert P, Demirbas Z, Tunccan OG, et al. The prognostic role of neopterin in COVID-19 patients. J Med Virol. 2021;93(3):1520–5.
20. Robertson J, Gostner JM, Nilsson S, Andersson LM, Fuchs D, Gisslen M. Serum neopterin levels in relation to mild and severe COVID-19. BMC Infect Dis. 2020;20(1):1–6.
21. Zierhut M, De Smet MD, Gupta V, Pavesio C, Nguyen QD, Chee SP, et al. Evolving Consensus Experience of the IUSG-IOIS-FOIS with Uveitis in the Time of COVID-19 Infection. Ocul Immunol Inflamm [Internet]. 2020;28(5):709–13. Available from: https://doi.org/10.1080/09273948.2020.1780273
22. Edén A, Kanberg N, Gostner J, Fuchs D, Hagberg L, Andersson LM, et al. CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series. Neurology. 2021;96(2):e294–300.
23. Zeng F, Huang Y, Guo Y, Yin M, Chen X. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis. 2020;96(January):467–74.
24. Holmes E, Wist J, Masuda R, Lodge S, Nitschke P, Kimhofer T, et al. Incomplete Systemic Recovery and Metabolic Phenoreversion in Post-Acute-Phase Nonhospitalized COVID-19 Patients: Implications for Assessment of Post-Acute COVID-19 Syndrome. J Proteome Res. 2021;20(6):3315–29.
25. Edén A, Grahn A, Bremell D, Aghvanyan A, Bathala P, Fuchs D, et al. Viral Antigen and Inflammatory Biomarkers in Cerebrospinal Fluid in Patients with COVID-19 Infection and Neurologic Symptoms Compared with Control Participants Without Infection or Neurologic Symptoms. JAMA Netw Open. 2022;5(5):1–15.
26. Kandasamy M. NF-κB signalling as a pharmacological target in COVID-19: potential roles for IKKβ inhibitors. Naunyn Schmiedebergs Arch Pharmacol. 2021;394(3):561–7.
27. Rodrigo Garcia Motta, Angélica Link, Viviane Aparecida Bussolaro G de NJ, Palmeira G, Riet-Correa F, Moojen V, Roehe PM, Weiblen R, et al. Defining the Immune Responses for SARS-CoV-2-Human Macrophage Interactions. Pesqui Vet Bras [Internet]. 2021;26(2):173–80. Available from: http://www.ufrgs.br/actavet/31-1/artigo552.pdf
28. Robba C, Battaglini D, Pelosi P, Rocco PRM. Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2. Expert Rev Respir Med [Internet]. 2020;14(9):865–8. Available from: https://doi.org/10.1080/17476348.2020.1778470
29. Yanchun Peng, Alexander J. Mentzer, Guihai Liu, Xuan Yao, Zixi Yin et. al. Europe PMC Funders Group SARS-CoV-2 in UK convalescent individuals following COVID-19. Nat Immunol. 2021;21(11):1336–45.
30. Mcgonagle D, Sharif K, Regan AO, Bridgewood C. The role of cytokines including IL-6 in COVID-19 induced pneumonia and MAS-like disease. Autoimmun Rev [Internet]. 2020;19(102537):8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7195002/pdf/main.pdf