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The novel biomarker, neopterin, can predict the severity of COVID-19

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Abstract. – OBJECTIVE: SARS-CoV-2 infection primarily affects T-lymphocytes, particularly CD4+ and CD8+ T cells. However, there is a need for simpler and less expensive laboratory tests with predictive values comparable to CD4+ cell counts. Thus, the goal of this study was to investigate the role of neopterin levels in predicting intensive care and mortality in coronavirus disease patients in 2019.

PATIENTS AND METHODS: This retrospective study included 87 hospitalized patients who were diagnosed with COVID-19. Patients were divided into two groups: those receiving intensive care (Severe COVID-19; S-COVID-19) and those receiving non-intensive care (Moderate COVID-19; M-COVID-19). Patients' clinical characteristics, serum neopterin levels, and other laboratory data were compared across groups.

RESULTS: The average age was 63.9±155.2 years, and 44 (%) of the participants were male. WBC (p = 0.008), neutrophil (p = 0.002), HDL (p = 0.009), ferritin, calcium, albumin, LDH, APTT, lymphocyte, INR, D-dimer, troponin, prothrombin time sedimentation, and PaO_2 (p = 0.001) were all associated with death. The neopterin level in the M-COVID-19 group was 3 (min-max; 3.1–5.9) and 3.2 (2.3–7) in the S-COVID-19 group, with no statistically significant difference (p = 0.456). Gender differences between groups were not significant (p = 0.183). According to the ROC analysis, if parameters such as age, D-Dimer, troponin, ferritin, albumin, LDH, CRP, procalcitonin, and PaO_2 exceed the cut-off values and lymphocyte levels are below, it can predict the need for intensive care and mortality in COVID-19 patients.

CONCLUSIONS: Although we did not find statistically significant results with neopterin in terms of mortality in COVID-19 individuals in our study, more thorough, prospective, randomized controlled studies with expanded patient populations at various phases of the disease are needed.

Key Words:
COVID-19, Cytokine storm, Neopterin, Mortality rate.

Introduction

COVID-19 causes severe interstitial pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure in a large number of people, especially the elderly and those at high risks, such as those with morbidities. As a result of all of this, it is clear that patient mortality rates are high[1-3].

Hyperinflammatory states are clearly connected to death and the severity of illness in COVID-19 patients. This syndrome is caused by excessive production of cytokines such as IFN- γ and IL-6[4-6]. The relationship between IFN- γ and neopterin synthesis suggests that IFN- γ will be a marker for cell-mediated immune activation[7,8]. The level of neopterin steadily drops during the course of COVID-19 in moderate cases, but it is more dramatic in severe ones. The biomarker neopterin can be used to predict the severity of COVID-19 disease[9]. Measurements of neopterin not only provide insight into the condition of the cell-mediated immune response, but also aid in the monitoring of disease severity and prognosis[10-13]. We aimed to examine the role of neopterin alone or in combination with other inflammatory markers such as C-reactive protein (CRP), IL-6 and procalcitonin (PCT) in predicting the clinical course and mortality of SARS-CoV-2 infection in hospitalized patients.

Patients and Methods

In this retrospective, cross-sectional, single-center investigation, 87 patients in critical care and

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non-intensive care units with mild severity of COVID-19 were included. The clinical presentation and positive results from real-time reverse transcription-polymerase chain reaction nucleic acid testing of the throat or nasal swab specimens led to a conclusive diagnosis of COVID-19 in all of the patients. The patients were divided into two groups: those admitted to the critical care unit, known as S-COVID-19 patients, and those admitted to the internal medicine clinic, known as M-COVID-19.

The immunoturbidimetric approach was used to measure biochemical parameters and CRP levels using an Olympus AU5800 auto analyzer (Beckman Coulter, Inc. Brea, CA, USA). The ferritin level was determined by the chemiluminescence method using Abbott Architect I 2000 SR (Abbott Laboratories, Lake Bluff, IL, USA). The CELL-DYN 3700 CD-3700SL (Abbott Laboratories Lake Bluff, IL, USA) was used to identify CBC parameters using laser measurements and the LED flow cell technique. The prothrombin time, activated partial thromboplastin time, and fibrinogen were measured using an immunoturbidimetric approach utilizing an optical method and the latex agglutination method was also used to detect D-dimer using the instrument Diagon Coag XL (Baross, Budapest, Hungary). The immunoassay method was used to measure procalcitonin, and Roche Cobas e 411(Hitachi, Tokyo Japan). The serum was stored at -80°C until the day of the neopterin test. All samples were brought to room temperature (15–18°C) before being combined and homogenized.

Serum neopterin (nmol/L) assay: The serum neopterin levels were determined using a double antibody enzyme-linked immunosorbent assay (ELISA) kit by Elabscience, Bioassay Technology Laboratory (Shanghai, China) and ELISA reader by ELx800 (Winooski, VT, USA). A standard curve is drawn, and the concentration of neopterin in the sample is calculated using interpolation from the standard curve. The reference level for neopterin is 0,1-38 nmol/l. The CV percent of the kits inter and between studies was indicated as 10% in the precision study conducted by the manufacturer. The study was approved by Sakarya University Medicine Faculty Ethics Committee and performed in accordance with the Helsinki Declaration (22.09.2020-8407-71522473/050.01.04/520).

Statistical Analysis

The data was transferred to IBM SPSS Statistics 23 (IBM, Armonk, NY, USA) and processed. Frequency distribution (number, percentage) for categorical variables and descriptive statistics (mean, standard deviation, median, IQR 25%-75%) for numerical variables were provided while assessing the study data. The Kolmogorov-Smirnov test was used to determine if numerical variables followed a normal distribution. For normal distribution variables, the Student's *t*-test was employed to see if there was a difference between the two groups. For variables that did not fit a normal distribution, the Mann-Whitney U test was utilized. To assess the association between two category variables, the Chi-square test was performed. In addition, the cut-offs for the variables were determined using ROC analysis. The statistically significant two tailed *p*-value was considered as <0.05.

Results

The study included 87 COVID-19 patients, with 47 (54%) having M-COVID-19 [(mean age 58.4 years, (SD 14.3)] with mild symptoms and 40 (45.9%) having S-COVID-19 (mean age 70.4 years, (SD 13.7)) with severe symptoms (p =0.001). Gender differences across the groups were not significant (p = 0.183). The most prevalent symptoms in the M-COVID-19 group were fever, cough, and sore throat, whereas the most common symptoms in the S-COVID-19 group were sputum, dyspnea, and headache (Table I). Only chronic arterial disease (CAD) was shown to be statistically significant when comorbidities were evaluated in terms of mortality (p =0.043) (Table I). To examine if neopterin levels were associated with the severity of COVID-19 disease, we analyzed serum neopterin concentrations between patients in the M-COVID-19 group and the S-COVID-19 group. Patients in the S-COVID-19 group (mean value 3.2 nmol/L (2.3-3.7)) had no significant difference in neopterin (0.1-38 nmol/l) value compared to those in the M-COVID-19 group (3 nmol/L (2.2-4.9) (p =0.456) (Table I). WBC (p =0.008), neutrophil (p =0.002), high-density lipoprotein cholesterol (HDL) (p =0.009), ferritin, calcium, albumin, lactate dehydrogenase (LDH), activated partial thromboplastin time (APTT), lymphocyte, INR, D-dimer, troponin, prothrombin time sedimentation, PaO_2 (p =0.001), were significantly associated with mortality. The M-COVID-19 group had a neopterin level of 3 (min-max; 3.1-5.9), while the S-COVID-19 group had a neopterin level of

Table I. Sociodemographic, comorbidities and distribution of laboratory data of the patients.

	M-COVID-19 (n=48)	S-COVID-19 (n=40)	Total (n=88)	p
Age, Mean±SD	58.4±14.3	70.4±13.7	63.9±15.2	**0.000***
Gender, n (%)				
Male	23 (47.9)	21 (52.5)	44 (50)	0.183***
Chronic diseases, n (%)				
Chronic diseases	34 (70.8)	32 (80)	66 (75)	0.323***
Diabetes Mellitus	19 (39.6)	10 (25)	29 (33)	0.147***
Hypertension	27 (56.3)	22 (55)	49 (55.7)	0.906***
Chronic Arterial Disease	**5 (10.6)**	**11 (27.5)**	**16 (18.4)**	**0.043*****
Chronic Heart Failure	1 (2.1)	4 (10)	5 (5.7)	0.172***
COPD	5 (10.4)	4 (10)	9 (10.2)	1.000***
Asthma	2 (4.2)	0 (0)	2 (2.3)	0.498***
Chronic Renal Failure	2 (4.2)	5 (12.5)	7 (8)	0.238***
Malignancy	0 (0)	2 (5)	2 (2.3)	0.209***
Cerebrovascular Disease	2 (4.2)	6 (15)	8 (9.1)	0.134***
Atrial Fibrillation	0 (0)	2 (5)	2 (2.3)	0.204***
Symptoms, n (%)				
Fever	25 (52.1)	10 (25)	35 (39.8)	**0.010*****
Cough	25 (52.1)	19 (47.5)	44 (50)	0.669***
Sputum	0 (0)	6 (15)	6 (6.8)	**0.007*****
Sore throat	4 (8.3)	3 (7.5)	7 (8)	1.000***
Dyspnea	15 (31.3)	28 (70)	43 (48.9)	**0.001*****
Headache	3 (6.3)	3 (7.5)	6 (6.8)	1.000***
Laboratory results, median (IQR 25%-75%) or mean±sd				
White Blood Cell, (K/µL)	6 (5-8.1)	7.7 (5.5-11.4)	6.7 (5.1-9)	**0.008****
Hemoglobin, (g/dL)	12.7±1.2	12.2±1.8	12.5±1.5	0.093*
Hematocrit, (%)	40.8±3.8	38.1±5.6	39.6±4.9	**0.015***
Lymphocyte, (K/µL)	1.3 (1-2.1)	0.8 (0.5-1.2)	1.1 (0.8-1.6)	**0.001****
Neutrophil, (K/µL)	3.8 (2.9-5.2)	5 (4-9.2)	4.7 (3.3-6.5)	**0.002****
Platelet, (K/µL)	195.7±87.9	224.4±128.2	208.7±108.4	0.218*
Prothrombin time, (sn)	12 (11-13.5)	13.3 (12.4-14.4)	13 (11.7-14)	**0.001****
APTT, (sn)	25.4 (24-27.3)	26.2 (24.1-29.2)	26 (24-28)	0.174**
INR	1.1 (1-1.3)	1.2 (1.2-1.3)	1.2 (1.1-1.3)	**0.001****
D-Dimer, (Ug/FEu)	512.5 (260.5-807)	1055 (712-2010)	712 (399-1465)	**0.001****
Troponin, (ng/L)	4 (2.2-8)	13.4 (7-40.9)	6.6 (3.1-15.4)	**0.001****
HDL, (mg/dL)	36.3±9.9	30.1±10.0	33.4±10.4	**0.009***
Ferritin, (mg/dL)	168.5 (71.5-353)	560 (292.5-1097)	313.5 (113.5-679)	**0.001****
Urea, (mg/dL)	31 (28-37)	57 (39-78)	42 (31-66)	**0.001****
Creatinine	0.8 (0.7-1)	1 (0.7-1.2)	0.8 (0.7-1.1)	0.180**
Uric acid, (mg/dL)	4.2 (3.5-6)	6.1 (4.3-7.7)	4.8 (3.9-6.9)	**0.002****
Calcium, (mg/dL)	9 (8.5-9.2)	8.4 (8-8.8)	8.7 (8.2-9)	**0.001****
AST, (U/L)	28.5 (24.5-38)	43 (29.5-64.5)	32 (26-47)	**0.002****
Albumin, (U/L)	3.5 (3.3-3.7)	30.3 (27-33.2)	4 (3.5-30.2)	**0.001****
Globulin, (U/L)	2.9 (2.7-3)	31.9 (27.5-35.7)	3.4 (2.9-30.5)	**0.000****
LDH, (U/L)	293.8±94.9	456.9±174.0	368.0±158.4	**0.001***
CRP, (mg/L)	24.2 (7.8-72.3)	110 (62.5-172.5)	64 (19-141)	**0.001****
Procalcitonin, (ng/mL)	0.1 (0.1-0.2)	0.2 (0.1-0.4)	0.1 (0.1-0.3)	**0.003****
Sedimentation, (mm/s)	30 (20.5-49.5)	66 (53-73)	49 (24-71)	**0.001****
Fibrinogen, (mg/dL)	318 (298-387)	409 (337-472)	348.5 (302-434)	**0.003****
CK, (U/L)	74 (51-121)	108 (74-394)	85 (57-182)	**0.017****
PH	7.4 (7.4-7.4)	7.4 (7.3-7.5)	7.4 (7.4-7.4)	0.129**
PO_2, (mmHg)	30.9 (23.4-42)	41.8 (34.8-72.2)	35.5 (26-52)	**0.001****
PCO_2, (mmHg)	43.2±7.5	41.5±11.0	42.4±9.2	0.408*
SpO_2 Saturation	58.9±23.7	71.1±24.7	64.5±24.8	**0.023***
HCO_3, (mmol/L)	23.7±3.3	24.6±4.4	24.1±3.8	0.299*
Lactat, (mmol/L)	1.8±0.6	1.9±0.7	1.8±0.7	0.403*
Neopterin (0.1-38 nmol/l)	3 (2.2-4.9)	3.2 (2.3-7)	3.1 (2.2-5.9)	0.456**

Data depicted in bold indicate significant differences between groups.
Abbreviations: APTT: Activated Partial thromboplastin time, HDL: High Density Lipoproteins, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-Reactive Protein, CK: Creatine Kinase, pO_2: Oxygen partial pressure, SpO_2: peripheral capillary oxygen saturation.
: Student t-test, **: Mann-Whitney U test, *: Chi-square test.*

Table II. Cut-off values of the parameters predicting the need for Intensive Care in COVID-19 patients.

	Area	Std. Error	p	Area 95% CI		Sensitivity	Specificity	Cut-off point
				Lower	Upper			
Age	0.737	0.055	<0.001	0.630	0.844	0.700	0.729	66.5
Lymphocyte	0.728	0.056	<0.001	0.618	0.837	0.744	0.708	1.085
D-dimer	0.768	0.052	<0.001	0.666	0.870	0.775	0.708	682
Troponin	0.816	0.046	<0.001	0.726	0.906	0.816	0.708	6.05
Ferritin	0.772	0.051	<0.001	0.672	0.872	0.725	0.708	334.5
Albumin	0.966	0.024	<0.001	0.919	1.000	0.975	0.978	12.45
LDH	0.810	0.048	<0.001	0.716	0.904	0.775	0.729	365.5
CRP	0.795	0.049	<0.001	0.700	0.891	0.725	0.723	67.7
Procalcitonin	0.693	0.060	0.003	0.576	0.810	0.703	0.714	0.11
PaO_2	0.712	0.057	<0.001	0.600	0.824	0.744	0.696	35.35
Neopterin	0.546	0.062	0.456	0.424	0.669	-	-	-

LDH: Lactate dehydrogenase, CRP: C-Reactive Protein.

3.2 (2.3-7) (no statistically significant difference) (Table I). The S-COVID-19 group also had considerably higher rates of coronary artery disease (CAD) and troponin increase. CAD and troponin elevation were also observed to be significantly greater in the S-COVID-19 group. The INR and D-Dimer readings in the S-COVID-19 group were found to be considerably higher. The serum ferritin level in the S-COVID-19 group was found to be statistically substantially greater than that in the M-COVID-19 group. In our study, serum CRP, PCT, D-dimer, and ferritin levels were significantly higher in the S-COVID-19 group than in the M-COVID-19 group (Table I). The effect of neopterin on mortality in COVID-19 hospitalized patients was investigated using the ROC curve. While age, D-Dimer, troponin, ferritin, albumin, LDH, CRP, procalcitonin, and PaO_2 all exceed the prescribed cut-off values, if lymphocyte is below the cut-off value, it can be predicted as an independent risk factor for intensive care and mortality, according to the ROC analysis in Table II. The neopterin parameter, however, was found to be unreliable in predicting this requirement. The sensitivity and specificity of the neopterin mortality predicted cut-off value in COVID-19 disease could not be determined using the ROC curve analysis.

Discussion

In the present study, we investigated whether there was a significant difference in serum neopterin levels between the two groups (M-COVID-19 and S-COVID-19 groups). We found that serum neopterin blood levels measured from patients with moderate pneumonia and severe pneumonia at their hospitalization were not closely associated with the mortality of the disease (p >0.05). Moreover, no correlation was found between neopterin levels and CRP, procalcitonin and ferritin. There is currently no viable predictive biomarker for COVID-19 patients that can predict disease severity and prognosis[14].

Several infectious and non-communicable diseases are caused by cytokine storms (CS). The term "cytokine storm" was initially used in 1993 in a paper on graft-versus-host disease, and then later in viral infectious disorders such as cytomegalovirus, EBV-associated hemophagocytic lymphohistiocytosis, and SARS-CoV[15]. The cytokine storm is a COVID-19 patient profile characterized by low interferon levels and strong IL-6 expression in the presence of high chemokines[16]. Acute respiratory distress syndrome causes damage to lung parenchyma tissue, and a cytokine storm develops after monocyte-macrophage activation, resulting in morbidity and mortality in COVID-19 infection. In seriously affected SARS-CoV-2 patients, prolonged monocyte-macrophage activation could lead to respiratory failure[17]. Neopterin is a cytokine produced by macrophages in response to interferon-gamma activation, and it can be used to predict the severity of disease in COVID-19 cases. The level of serum neopterin indicates where the cellular immune system is in its activation process. Neopterin could be a useful biomarker for COVID-19's MAS immunopathology as a macrophage activation marker[18].

Neopterin has been related to disease activity, clinical course prediction, and bacterial infection differentiation, and it has been recommended

as a biomarker for a range of viral infections[19]. According to other studies, severe clinical patients have a substantially higher prevalence than mild clinical patients[20]. T-cell activation has a vital role in commencing severe pulmonary inflammation and decreasing breathing in SARS-CoV-2 infections, as evidenced by patients with high neopterin levels[21]. Because the patients were at the peak of COVID-19 disease, hospitalizations were delayed, and the neopterin level fell due to its typical characteristic, no significant difference in serum neopterin was identified between the groups in our study. The amount of neopterin declined progressively in both mild and severe patients, according to one study, while high levels lingered longer in severe cases[9]. A reduction in neopterin levels may have happened after a length of time following the onset of symptoms in our investigation. COVID-19 infection is linked to systemic inflammation, a pro-inflammatory cytokine storm, and sepsis, which can lead to multiorgan failure and death. Furthermore, various comorbidities have been linked to poorer clinical outcomes in COVID-19 patients[22-25].

Limitations

The data were obtained from a single clinical research center, not from more than one clinical research center. Fewer patients were included in the study. This study may differ from the results of other scientists at home and abroad and should be further developed in clinical cases. Due to the limitations highlighted above, more comprehensive, prospective, randomized controlled studies with bigger patient populations are needed to replicate these investigations at various phases of the disease.

Conclusions

The COVID-19 pandemic has the potential to spread quickly. The clinical symptoms of this disease can differ even among people who have the same viral infection. Furthermore, the severity of the disease is a predictor of prognosis on its own. Despite the fact that neopterin did not play a role in predicting the severity of COVID-19 infection and the outcome of the illness in our investigation, it is evident that more research is required.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Authors' Contributions

Conceptualization, C.K.; Data curation, S.Y., and K.I.; Formal analysis, T.D. and H.S.; Methodology, E.C., C.K; Supervision, C.V; Writing–original draft, C.K.; Writing–review and editing, A.N., K.O.S, and T.K. All authors have read and agreed to the published version of the manuscript.

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