

Neopterin Predicts Disease Severity in Hospitalized Patients With COVID-19

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This study evaluates the predictive value of circulating inflammatory markers, especially neopterin, in patients with coronavirus disease 2019 (COVID-19). Within this retrospective analysis of 115 hospitalized COVID-19 patients, elevated neopterin levels upon admission were significantly associated with disease severity, risk for intensive care unit admission, need for mechanical ventilation, and death. Therefore, neopterin is a reliable predictive marker in patients with COVID-19 and may help to improve the clinical management of patients.

Keywords. COVID-19; disease severity; neopterin; outcome; SARS-CoV-2.

The pandemic of novel infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an ongoing challenge for health care systems worldwide [1]. While most subjects experience a mild course of infection, between 15% and 20% need hospitalization, mostly because of shortness of breath and hypoxia on the basis of infection-induced pneumonia. During hospitalization, some patients deteriorate, then need noninvasive ventilation or intensive care unit (ICU) admission and mechanical ventilation. While age, male gender, and preexisting comorbidities have been found to increase the risk of a complicated course or death from the disease, no single biomarker has been found that identifies patients at risk when admitted to the hospital [2, 3]. Therefore, besides clinical presentation, reliable and easily available parameters that can aid in predicting disease course and planning optimal treatment are urgently needed.

Viral infection stimulates the formation of interferon gamma (IFN- γ), which activates monocytes and macrophages to produce the pteridine neopterin, which is an established biomarker

in viral infection, but neopterin is also increased in other diseases involving activation of cellular immune function [4–6]. Neopterin in combination with C-reactive protein (CRP) allows a differentiation between viral and bacterial respiratory infections [7, 8]. Moreover, high neopterin levels have been associated with worse outcome in different viral infections [9–11], although increased interleukin (IL)-6 levels have been shown to be associated with cytokine storm in coronavirus disease 2019 (COVID-19) patients and to be predictive of an increased risk of respiratory failure and death; IL-6 determination does not provide information on its source, as multiple cells and tissues can produce this protein [12]. In contrast, neopterin is exclusively produced by monocytic cells in response to stimulation by the T-helper cell type 1 (Th1)-derived cytokine IFN- γ , thereby providing information on the degree of cell-mediated immune activation in the setting of a specific disease [13]. We thus studied if neopterin, either alone or in combination of other established markers of inflammation such as CRP, procalcitonin (PCT), or IL-6, may be of value in predicting the clinical course of hospitalized patients with SARS-CoV-2 infection.

METHODS

Study Population

We retrospectively analyzed the data and medical reports of 124 consecutive patients who were hospitalized for polymerase chain reaction (PCR)-proven coronavirus disease 2019 (COVID-19) infection at our department at the Innsbruck University Hospital, Tyrol, Austria, between February and May 2020. Proof of infection was brought forward by positive SARS-CoV-2 RNA in naso- or oropharyngeal swab. Finally, 115 patients with available serum neopterin levels upon admission and/or during follow-up were included in further analyses. The data and laboratory parameters of patients were anonymized and extracted from the local clinical information system (KIS). For outcome analysis, we recorded fatal events, ICU admission, and need for mechanical ventilation during hospital stay. The cutoff date for still-hospitalized patients was May 12, 2020 (n = 13).

Patient Consent Statement

This study conformed to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of the Innsbruck Medical University (ID of ethical vote: 1167/2020). All patients gave written informed consent.

Laboratory Measurements

Blood samples were analyzed with fully automated tests in the Central Institute for Medical and Chemical Laboratory

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Diagnosis of the Innsbruck University Hospital, which undergoes regular internal and external quality controls and evaluations. Laboratory parameters were then extracted from the KIS for day 1 ± 1, day 4 ± 1, and day 7 ± 1 since hospitalization if available.

Neopterin was routinely measured with an enzyme-linked immunosorbent assay (ELISA; Magellan BioScience Group, Tampa, FL, USA). As neopterin has been shown to be higher in patients with reduced kidney function [5, 14], estimated glomerular filtration rate (eGFR) with the CKD-EPI formula was used to calculate the ratio of neopterin/eGFR. IL-6 was detected with an electrochemiluminescence immunoassay on a Cobas8000 C602 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). CRP concentrations were measured with an immunoturbidimetric assay on a Cobas8000 C702 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). PCT was detected with an electrochemiluminescence immunoassay on a Cobas8000 C602 analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical Analyses

We used the Shapiro-Wilk test to test for Gaussian distribution. Parameters are depicted as No. (%) or median (25th, 75th percentiles), as they were not normally distributed. The Mann-Whitney *U* test, Kruskal-Wallis test, and Pearson chi-square test were performed to test for significant differences between groups. Logistic regression analysis was performed to analyze the effects of risk factors on probability of ICU admission or need for assisted ventilation. Non-normally distributed parameters were logarithmized with the natural logarithm for the logistic regression analysis. Only parameters with significance in the univariate logistic regression analysis were considered for multivariate logistic regression analysis. All tests were 2-tailed, and *P* values <.05 were regarded as statistically significant. Statistical analysis was performed using SPSS Statistics, version 25.0 for Macintosh (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline Characteristics

We retrospectively analyzed 75 men (65.2%) and 40 women (34.8%) with a median age of 62 years (49–79 years), and 42 patients (36.5%) were over the age of 70; yet, the median age did not significantly differ between men and women (61 vs 63 years; *P* = 0.807). Symptoms had started 7 days (4–11 days) before hospital admission, and the median duration of hospital stay was 9 days (5–15 days), with men requiring significantly longer hospital treatment than women (10 days [7–19 days] vs 7 days [3–10 days]; *P* = 0.006).

Baseline characteristics of patients within the different neopterin levels upon admission are depicted in [Table 1](#). Patients with severe disease according to the World Health

Organization scoring system (score of 5 or higher) had a median neopterin level of 56.6 nmol/L with an interquartile range of 45.4–67.0 nmol/L compared with patients with less severe disease (34.7 nmol/L [15.7–50.7 nmol/L]; *P* < .001). Therefore, we chose a lower quartile value of 45 nmol/L as the cutoff for our subsequent evaluation. When calculating for associations between serum neopterin levels and routinely determined laboratory parameters upon admission, we found a significantly positive correlation with aspartate aminotransferase (AST; *rs* = 0.336; *P* < .001), IL-6 (*rs* = 0.555; *P* < .001), CRP (*rs* = 0.549; *P* < .001), and PCT levels (*rs* = 0.614; *P* < .001) and a significantly negative correlation with hemoglobin levels (*rs* = -0.277; *P* = .003), thrombocyte counts (*rs* = -0.325; *P* < .001), lymphocyte counts (*rs* = -0.503; *P* < .001), and eGFR (*rs* = -0.640; *P* < .001). Neopterin levels further correlated with the oxygen saturation (*rs* = -0.379; *P* < .001) and oxygen requirement (*rs* = 0.298; *P* = .002). When following these parameters over time, we found that mean neopterin and IL-6 levels were highest upon admission and then declined during the clinical course, whereas CRP levels fluctuated ([Supplementary Figure 1A](#)).

Neopterin Is Predictive of the Outcome of COVID-19 Patients

Taking into account the severe stress of ICU treatment with highly invasive ventilation and sedation described in the literature and seen in real life at our clinics, as well as the multiple risk factors and comorbidities of elderly patients associated with a fatal outcome, we aimed at an early stratification. Because of the limited benefit for these patients, elderly multimorbid patients were eventually not referred to the ICU [15]. Therefore, to estimate the predictive potential of the markers under investigation for ICU admission or the need for mechanical ventilation, only patients aged <70 years (*n* = 73) were evaluated, while for death prediction all patients irrespective of age were included (*n* = 115). To evaluate the association of elevated neopterin levels with patients' clinical course, we established different cutoff levels for the course of infection. Herein, patients with neopterin levels > 45 nmol/L upon hospital admission (*n* = 48, 38.7%) had a significantly higher risk of death during hospital stay (19.0% vs 4.5%; *P* = .018) ([Supplementary Figure 1B](#)), ICU admission during hospital stay (68.4% vs 10.4%; *P* < .001) ([Supplementary Figure 1C](#)), and need of mechanical ventilation (63.2% vs 7.5%; *P* < .001) ([Supplementary Figure 1D](#)) compared with patients with neopterin levels ≤45 nmol/L (*n* = 67, 58.3%). These patients were further characterized by longer hospital stays, older age, lower oxygen saturation and higher oxygen requirement, higher temperature, and impaired renal function upon hospital admission ([Table 1](#)).

In logistic regression analysis, patients with neopterin levels > 45 nmol/L had a >4-fold higher risk of death during hospital stay (odds ratio [OR], 4.784; 95% CI, 1.190–19.240; *P* = .027) when compared with patients with neopterin levels ≤45 nmol/L. In patients under the age of 70 years (*n* = 73),

Table 1. Baseline Characteristics of Patients Within Different Neopterin Tertiles

	≤25.0 nmol/L	25.1–45.0 nmol/L	>45.0 nmol/L	
	n = 34	n = 33	n = 48	
	Median (IQR) or No. (%)	Median (IQR) or No. (%)	Median (IQR) or No. (%)	PValue ^a
Neopterin Levels				
Demographic characteristics				
Age, y	50 (36–62)	57 (47–71)	75 (61–80)	<.001
BMI, kg/m ²	25.10 (22.20–26.20)	26.30 (24.45–28.05)	26.85 (24.00–30.20)	.188
Sex, men	17 (50.0)	22 (66.7)	36 (75.0)	.0463
Clinical characteristics				
Temperature, °C	36.7 (36.2–37.4)	37.3 (36.6–37.9)	37.0 (36.2–38.2)	.032
SpO ₂ , %	96 (94–98)	95 (92–96)	92 (89–95)	<.001
O ₂ requirement, L	0 (0–0)	0 (0–1)	1 (0–3)	.003
pO ₂ , mmHg	72.9 (62.1–84.3)	61.4 (57.7–77.3)	70.1 (62.9–73.5)	.290
pCO ₂ , mmHg	35.9 (32.8–39.6)	36.0 (34.6–37.8)	35.9 (32.9–41.8)	.881
Hospitalization, d ^b	6 (4–9)	9 (7–12)	15 (8–27)	<.001
ICU admission ^c	2 (6.7)	5 (20.8)	13 (68.4)	<.001
Mechanic ventilation ^c	1 (3.3)	4 (16.7)	12 (63.2)	<.001
Death during hospital stay ^d	0 (0.0)	3 (9.4)	8 (19.0)	.028
Duration of symptoms until hospitalization, d	8.50 (4.00–13.00)	6.00 (3.00–12.00)	6.50 (4.00–10.00)	.228
Laboratory parameters				
eGFR, mL/min	99.7 (90.2–109.6)	91.4 (80.9–99.2)	61.8 (41.0–82.0)	<.001
AST, U/L	25 (21–36)	34 (24–49)	44 (31–61)	.001
ALT, U/L	20 (16–30)	23 (16–38)	29 (18–48)	.113
Hemoglobin, g/L	140 (133–153)	131 (124–156)	131 (117–145)	.046
Thrombocytes, G/L	263 (188–305)	175 (146–252)	199 (146–257)	<.001
Leukocytes, G/L	6.1 (5.2–7.6)	5.1 (3.7–6.2)	6.1 (4.5–8.8)	.025
Lymphocytes absolute, G/L	1.58 (1.13–1.89)	0.97 (0.76–1.18)	0.89 (0.68–1.01)	<.001
CRP, mg/dL	0.86 (0.17–3.74)	4.48 (1.56–8.68)	7.49 (3.60–14.93)	<.001
IL-6, ng/L	8.5 (2.3–30.6)	26.3 (15.8–62.5)	74.9 (32.6–186.5)	<.001
PCT, ng/mL	0.00 (0.00–0.06)	0.08 (0.06–0.15)	0.20 (0.08–0.57)	<.001

Data depicted in bold indicate significant differences between groups.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IL6, interleukin 6; IQR, interquartile range; O₂, oxygen; pCO₂, partial pressure of carbon dioxide; PCT, procalcitonin; pO₂, oxygen partial pressure; SpO₂, peripheral capillary oxygen saturation.

^aKruskal-Wallis test or Pearson chi-square test.

^bWithout patients who died during hospital stay.

^cOnly patients under the age of 70 with available neopterin levels (n = 73).

^dDischarged patients only.

neopterin levels >45 nmol/L were further associated with a 14-fold higher risk of ICU admission during their hospital stay (OR, 14.548; 95% CI, 4.162–50.852; *P* < .001) and a 16-fold higher risk of need for mechanical ventilation (OR, 16.800; 95% CI, 4.534–62.252; *P* < .001) compared with patients with neopterin levels ≤45 nmol/L. This was independent of sex, age, and oxygen saturation in multivariate logistic regression analysis, and also true when correcting neopterin levels for renal function by calculating a neopterin/eGFR ratio (Table 2).

DISCUSSION

In being produced by cytokine IFN-γ, the macrophage-derived pteridine neopterin has become an established marker in different viral infections including HIV and influenza, where it was linked to disease activity, prediction of clinical course, and

differentiation from bacterial infections [8–11]. In addition, neopterin levels corresponded to severity and outcome of different infectious and/or inflammatory diseases [10, 11].

To our knowledge, this is the first study that has evaluated neopterin in SARS-CoV-2 infection and demonstrated its important clinical and predictive potential in this infection. Neopterin levels >45 nmol/L allow early identification of hospitalized patients at risk of requiring mechanical ventilation and ICU treatment even upon admission, indicating a severe and prolonged course of infection. Neopterin levels decrease over time, however, which may be attributed to diminished viral activity even in patients on mechanical ventilation and those with resolution of inflammation, as evidenced by parallel reduction of IL-6 levels [16]. The associations of high neopterin levels with an increased risk of need for mechanical ventilation, ICU treatment, and adverse outcomes recommend neopterin

Table 2. Logistic Regression Analyses in Terms of Risk for ICU Admission During Hospital Stay and Need for Mechanical Ventilation^a

	Logistic Regression Analysis											
	Risk for ICU Admission						Need for Mechanical Ventilation					
	Univariate Model			Multivariate Model			Univariate Model			Multivariate Model		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Demographic characteristics												
Age, y	1.043	1.001–1.088	.047	0.938	0.858–1.026	.164	1.049	1.000–1.101	.051			
Women vs men	0.224	0.060–0.847	.027	0.118	0.008–1.829	.126	0.216	0.045–1.028	.054			
Clinical characteristics												
SpO ₂ , %	0.847	0.754–0.952	.005	0.969	0.788–1.192	.768	0.829	0.731–0.941	.004	0.977	0.818–1.167	.795
O ₂ requirement, L ^b	1.538	1.185–1.997	.001	1.457	0.854–2.484	.167	1.736	1.257–2.399	.001	1.434	0.874–2.352	.154
Laboratory parameters												
eGFR, mL/min	0.975	0.951–0.999	.043				0.977	0.952–1.003	.081			
Leukocytes, G/L	1.535	1.218–1.936	<.001				1.348	1.114–1.631	.002			
Lymph absolute, G/L ^b	0.234	0.078–0.708	.010				0.249	0.081–0.765	.015			
CRP, mg/dL ^b	3.245	1.816–5.796	<.001				5.360	2.266–12.679	<.001			
IL-6, ng/L ^b	4.621	2.154–9.914	<.001				4.724	2.155–10.356	<.001			
PCT, ng/mL ^b	1.412	0.936–2.129	.100				1.400	0.892–2.199	.144			
Neopterin, nmol/L ^b	9.243	2.553–33.468	.001				16.456	3.215–84.222	.001			
Neopterin/eGFR ratio ^b	4.915	1.893–12.758	.001				7.054	2.220–22.418	.001			
Neopterin at day 7, nmol/L ^b	22.073	2.416–201.652	.006				24.567	2.482–242.174	.006			
Neopterin/eGFR ratio ^b at day 7	8.052	1.683–38.525	.009				11.200	1.746–71.854	.011			
Classifications												
Neopterin >45 nmol/L vs ≤45 nmol/L	14.548	4.162–50.852	<.001				16.800	4.534–62.252	<.001	7.025	1.161–42.511	.034
Neopterin/eGFR ratio >0.650 vs ≤0.650	6.400	1.772–23.110	.005	25.049	1.123–558.583	.042	5.833	1.615–21.075	.007			
IL-6 >80 ng/L vs ≤80 ng/L	68.000	12.472–370.739	<.001	142.956	3.462–5902.918	.009	46.375	10.287–209.059	<.001	7.664	0.500–117.585	.144
CRP >5 mg/dL vs ≤5 mg/dL	9.880	3.125–31.238	<.001	0.319	0.024–4.342	.391	10.789	2.787–41.773	.001	0.581	0.050–6.787	.665

Data depicted in bold indicate significant differences between groups.

Parameters were recorded at day 1 ± 1 if not otherwise depicted. The chi-square test was 37.157 ($P < .001$) for the multivariate model of ICU admission ($n = 67$ —only patients with all included parameters available) and 24.993 ($P < .001$) for the multivariate model of need for mechanical ventilation ($n = 67$ —only patients with all included parameters available).

Abbreviations: CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IL-6, interleukin 6; O₂, oxygen; OR, odds ratio; PCT, procalcitonin; SpO₂, peripheral capillary oxygen saturation.

^aPatients under the age of 70 only ($n = 73$).

^bLogarithmized because not normally distributed.

as a reliable parameter for predicting the prognosis of SARS-CoV-2-infected patients and adapting the treatment algorithm for such patients with an increased risk of adverse outcomes. Specifically, patients with high neopterin levels at initial presentation need intensified monitoring and likewise early referral to noninvasive ventilation to reduce the likelihood for mechanical ventilation and ICU admission, which are associated with potential complications and long-term care. The association of high neopterin with an adverse clinical course is in line with the idea that more advanced, T-cell-triggered immune activation is a major driver of adverse outcomes. The diagnostic benefit of neopterin over IL-6 is due to the fact that neopterin is induced by the Th-1 cytokine IFN- γ , thereby more specifically reflecting T-helper cell type 1–derived immune activation and stimulation of monocytic cell effector functions. This is in line with recent observations demonstrating that T-cell activation plays an important role in triggering severe pulmonary inflammation and impaired ventilation in SARS-CoV-2 infections [17, 18]. However, our results indicate that at initial presentation of COVID-19, patients needing hospitalization present with both,

an activated IFN- γ pathway and a stimulated acute phase response, as reflected by IL-6, which predict the subsequent clinical course [19].

A limitation of our study is that we have not evaluated baseline radiographic features by computed tomography. Therefore we cannot provide information on whether increased neopterin levels are linked with more pronounced pathologic alterations on such images.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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