Neopterin predicts disease severity in hospitalized patients with COVID-19

Rosa Bellmann-Weiler[1], Lukas Lanser[1], Francesco Burkert[1], Stefanie Seiwald[1], Gernot Fritsche[1], Sophie Wildner[1], Andrea Schroll[1], Sabine Koppelstätter[1], Katharina Kurz[1], Andrea Griesmacher[2], Günter Weiss[1]*

[1] Department of Internal Medicine II, Innsbruck Medical University, Innsbruck, Austria;

[2] Central Institute for Medical and Chemical Laboratory Diagnosis, Innsbruck University Hospital, Innsbruck, Austria

Medical University of Innsbruck, Department of Internal Medicine II

***Corresponding author:** Günter Weiss

Department of Internal Medicine II, Medical University of Innsbruck

Anichstraße 35, 6020 Innsbruck, Austria

E-mail guenter.weiss@i-med.ac.at

Telephone: +43 512 504 23251

Fax: +43 512 504 23317

Footnote page

Conflict of interest: The authors declare no conflict of interest.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Presentation: The information within this manuscript has not been presented before.

Corresponding author: Günter Weiss

Department of Internal Medicine II, Medical University of Innsbruck

Anichstraße 35, 6020 Innsbruck, Austria

E-mail guenter.weiss@i-med.ac.at

Telephone: +43 512 504 23251

Fax: +43 512 504 23317

Abstract

This study evaluates the predictive value of circulating inflammatory markers, especially neopterin, in patients with 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 ICU 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: Neopterin, COVID-19, SARS-CoV-2, outcome, disease severity

Background

The novel pandemic 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 the infection, between 15 to 20% need hospitalization mostly because of shortness of breath, and hypoxia on the basis of infection induced pneumonia. During hospitalization some patients deteriorate, then needing non-invasive ventilation or intensive care unit (ICU) admission with the need for mechanical ventilation. While age, male gender and pre-existing co-morbidities along have been found to increase the risk for a complicated course or death from the disease, no single biomarker has been found which identifies patients at risk when admitted to the hospital (2, 3). Therefore, besides the clinical presentation, reliable and easily available parameters allowing to predict the course and to plan 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 were associated with a worse outcome in different viral infections (9-11). Although, increased IL-6 levels were shown to be associated with a cytokine storm in COVID-19 patients and being predictive for an increased risk of respiratory failure and death, IL-6 determination does not provide information on its source since 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

interleukin-6 (IL-6) may be of value to predict the clinical course of hospitalized patients with SARS-CoV-2 infection.

Methods

Study population

We retrospectively analyzed 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 proof in naso- or oropharyngeal swab respectively. 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. Cut-off 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 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, USA). As neopterin was shown to be higher in patients with reduced kidney function (5, 14), the routinely estimated glomerular filtration rate (eGFR) with the CKD-EPI formula was taken 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 electrochemiluminescense 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 n (%) or medians (25^{th}, 75^{th} percentile), since they were not normally distributed. Mann-Whitney-U test, Kruskal-Wallis test or Pearson chi-square tests 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. Not 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 two tailed and p-values < 0.05 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 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 WHO scoring system (score of five or higher) had median neopterin levels of 56.6 nmol/L with an IQR of 45.4 – 67.0 nmol/L compared to patients with less severe disease (34.7 nmol/L [15.7 – 50.7 nmol/L], p < 0.001). Therefore, we chose the lower quartile value of 45 nmol/L as cut-off 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 < 0.001), IL-6 (rs = 0.555, p < 0.001), CRP (rs = 0.549, p < 0.001) and PCT levels (rs = 0.614, p < 0.001), and a significantly negative correlation with hemoglobin levels (rs = - 0.277, p = 0.003), thrombocyte counts (rs = - 0.325, p < 0.001), lymphocyte counts (rs = - 0.503, p < 0.001) and eGFR (rs = - 0.640, p < 0.001). Neopterin levels further correlated with the oxygen saturation (rs = - 0.379, p < 0.001) and the oxygen requirement (rs = 0.298, p = 0.002). 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 were fluctuating (*Supplementary Figure 1A*).

Neopterin is predictive for the outcome of COVID-19 patients

Taking into account the severe stress of ICU treatment with highly invasive ventilation and sedation described in literature and seen in real life at our clinics, and 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 them, such elderly multi-morbid patients were eventually not referred to ICU (15). Therefore, to estimate the predictive potential of the markers under investigation for ICU admission or the need of mechanical ventilation only patients below the age of 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 cut-off levels allowing to presume the course of the infection. Herein, patients with neopterin levels > 45 nmol/L upon hospital admission (n = 48, 38.7 %) had a significantly higher risk for death during hospital stay (19.0% *vs.* 4.5%, p = 0.018, *Supplementary Figure 1B*), ICU admission during hospital stay (68.4% *vs.* 10.4%, p < 0.001, *Supplementary Figure 1C*) and need of mechanical ventilation (63.2% *vs.* 7.5%, p < 0.001, *Supplementary Figure 1D*) compared to 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 as well as impaired renal function upon hospital admission (*Table 1*).

In logistic regression analysis, patients with neopterin levels > 45 nmol/L had a more than fourfold higher risk to die during hospital stay (OR 4.784 [95% CI 1.190 – 19.240], p = 0.027) when compared to patients with neopterin levels ≤ 45 nmol/L. In patients under the age of 70 years (n = 73), neopterin levels > 45 nmol/L were further associated with a 14-fold higher risk for ICU admission during their hospital stay (OR 14.548 [95% CI 4.162 – 50.852], p < 0.001) and a 16-fold higher risk of need of mechanical ventilation (OR 16.800 [95% CI 4.534 – 62.252], p < 0.001) compared to 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 their clinical course and for 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 which evaluated neopterin in SARS-CoV-2 infection and demonstrates its important clinical and predictive potential in this infection. Neopterin levels above 45 nmol/L allow early identification of hospitalized patients at risk of requirement for mechanical ventilation and ICU treatment even upon admission, indicating a severe and prolonged course of infection. Though neopterin levels decrease over time, which may be attributed to diminished viral activity even in patients under mechanical ventilation and resolution of inflammation as evidenced by parallel reduction of IL-6 levels (16). The association of high neopterin levels with an increased risk of need of mechanical ventilation, ICU treatment and adverse outcome recommends neopterin as reliable parameter for predicting the prognosis of SARS-CoV-2 infected patients and to adapt the treatment algorithm for such patients with an increased risk of adverse outcome. Specifically, patients with high neopterin levels at initial presentation need intensified monitoring and likewise early referral to non-invasive ventilation to reduce the likelihood for mechanical ventilation and ICU admission which is 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 for an adverse outcome. 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 a T-helper cell type 1 derived immune activation and stimulation of monocytic cell effector functions. This is in a line with recent observations demonstrating that T-cell activation plays an important role for triggering severe pulmonary inflammation and impaired ventilation in SARS-CoV-2 infections (17, 18). However, our results indicate that already at initial presentation of COVID-19 patients needing hospitalization, both the IFN-γ pathway and the acute phase response of the immune system as reflected by IL-6 are already activated and predict the response of 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 whether or not increased neopterin levels are linked more pronounced pathologic alterations on such images.

Funding

This research received no external funding.

Conflict of Interests

The authors declare no conflict of interest.

References

1. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, et al. COVID-19: towards controlling of a pandemic. Lancet. 2020;395(10229):1015-8.

2. Chen ATC, Coura-Filho GB, Rehder MHH. Clinical Characteristics of Covid-19 in China. N Engl J Med. 2020;382.

3. Wang X, Fang J, Zhu Y, Chen L, Ding F, Zhou R, et al. Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang Hospital. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2020.

4. Fuchs D, Weiss G, Wachter H. Neopterin, Biochemistry and Clinical Use as a Marker for Cellular Immune-Reactions. Int Arch Allergy Imm. 1993;101(1):1-6.

5. Lanser L, Pölzl G, Fuchs D, Weiss G, Kurz K. Neopterin is Associated with Disease Severity and Outcome in Patients with Non-Ischaemic Heart Failure. J Clin Med. 2019;8(12).

6. Reibnegger G, Fuchs D, Fuith LC, Hausen A, Werner ER, Werner-Felmayer G, et al. Neopterin as a marker for activated cell-mediated immunity: application in malignant disease. Cancer Detect Prev. 1991;15(6):483-90.

7. Bellmann-Weiler R, Ausserwinkler M, Kurz K, Theurl I, Weiss G. Clinical potential of C-reactive protein and procalcitonin serum concentrations to guide differential diagnosis and clinical management of pneumococcal and Legionella pneumonia. J Clin Microbiol. 2010;48(5):1915-7.

8. 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. 2017;14(3):298-303.

9. Geisler S, Lytton SD, Toan NL, Nghia TH, Nam NM, Hung HV, et al. Neopterin levels and Kyn/Trp ratios were significantly increased in dengue virus patients and subsequently decreased after recovery. Int J Infect Dis. 2020;91:162-8.

10. De Scheerder MA, Van Hecke C, Zetterberg H, Fuchs D, De Langhe N, Rutsaert S, et al. Evaluating predictive markers for viral rebound and safety assessment in blood and lumbar fluid during HIV-1 treatment interruption. J Antimicrob Chemother. 2020;75(5):1311-20.

11. Bellmann-Weiler R, Schroecksnadel K, Holzer C, Larcher C, Fuchs D, Weiss G. IFN-gamma mediated pathways in patients with fatigue and chronic active Epstein Barr virus-infection. J Affect Disord. 2008;108(1-2):171-6.

12. Chen LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: Interleukin-6 and the COVID-19 cytokine storm syndrome. European Respiratory Journal. 2020:2003006.

13. Fuchs D, Weiss G, Wachter H. Neopterin, biochemistry and clinical use as a marker for cellular immune reactions. Int Arch Allergy Immunol. 1993;101(1):1-6.

14. Estelberger W, Weiss G, Petek W, Paletta B, Wachter H, Reibnegger G. Determination of renal clearance of neopterin by a pharmacokinetic approach. FEBS Lett. 1993;329(1-2):13-6.

15. Lee J, Abrukin L, Flores S, Gavin N, Romney ML, Blinderman CD, et al. Early Intervention of Palliative Care in the Emergency Department During the COVID-19 Pandemic. JAMA internal medicine. 2020.

16. Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. J Clin Invest. 2020;130(5):2202-5.

17. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmunity reviews. 2020;19(6):102537.

18. Peng Y, Mentzer AJ, Liu G, Yao X, Yin Z, Dong D, et al. Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. Nature Immunology. 2020.

19. Tanaka T, Narazaki M, Masuda K, Kishimoto T. Regulation of IL-6 in Immunity and Diseases. Adv Exp Med Biol. 2016;941:79-88.

Tables

Table 1 Baseline characteristics of patients within different neopterin tertiles

Neopterin levels	≤ 25.0 nmol/L	25.1 - 45.0 nmol/L	> 45.0 nmol/L	
	n = 34	n = 33	n = 48	
	Median (IQR) or n (%)	Median (IQR) or n (%)	Median (IQR) or n (%)	p-Value *
Demographic characteristics				
Age, years	**50 (36 - 62)**	**57 (47 - 71)**	**75 (61 - 80)**	**< 0.001**
BMI, kg/m^2	25.10 (22.20 - 26.20)	26.30 (24.45 - 28.05)	26.85 (24.00 - 30.20)	0.188
Sex, men	17 (50.0 %)	22 (66.7 %)	36 (75.0 %)	0.0463
Clinical characteristics				
Temperature, °C	**36.7 (36.2 - 37.4)**	**37.3 (36.6 - 37.9)**	**37.0 (36.2 - 38.2)**	**0.032**
SpO2, %	**96 (94 - 98)**	**95 (92 - 96)**	**92 (89 - 95)**	**< 0.001**
O2 requirement, L	**0 (0 - 0)**	**0 (0 - 1)**	**1 (0 - 3)**	**0.003**
pO2, mmHg	72.9 (62.1 - 84.3)	61.4 (57.7 - 77.3)	70.1 (62.9 - 73.5)	0.290
pCO2, mmHg	35.9 (32.8 - 39.6)	36.0 (34.6 - 37.8)	35.9 (32.9 - 41.8)	0.881
Hospitalization, days †	**6 (4 - 9)**	**9 (7 - 12)**	**15 (8 - 27)**	**< 0.001**
ICU admission ‡	**2 (6.7 %)**	**5 (20.8 %)**	**13 (68.4 %)**	**< 0.001**
Mechanic ventilation ‡	**1 (3.3 %)**	**4 (16.7 %)**	**12 (63.2 %)**	**< 0.001**
Death during hospital stay §	**0 (0.0 %)**	**3 (9.4 %)**	**8 (19.0 %)**	**0.028**
Duration symptoms till hospitalization, days	8.50 (4.00 - 13.00)	6.00 (3.00 - 12.00)	6.50 (4.00 - 10.00)	0.228
Laboratory parameters				
eGFR, mL/min	**99.7 (90.2 - 109.6)**	**91.4 (80.9 - 99.2)**	**61.8 (41.0 - 82.0)**	**< 0.001**
AST, U/L	**25 (21 - 36)**	**34 (24 - 49)**	**44 (31 - 61)**	**0.001**
ALT, U/L	20 (16 - 30)	23 (16 - 38)	29 (18 - 48)	0.113
Hemoglobin, g/L	**140 (133 - 153)**	**131 (124 - 156)**	**131 (117 - 145)**	**0.046**
Thrombocytes, G/L	**263 (188 - 305)**	**175 (146 - 252)**	**199 (146 - 257)**	**< 0.001**
Leukocytes, G/L	**6.1 (5.2 - 7.6)**	**5.1 (3.7 - 6.2)**	**6.1 (4.5 - 8.8)**	**0.025**
Lymphocytes absolute, G/L	**1.58 (1.13 - 1.89)**	**0.97 (0.76 - 1.18)**	**0.89 (0.68 - 1.01)**	**< 0.001**
CRP, mg/dL	**0.86 (0.17 - 3.74)**	**4.48 (1.56 - 8.68)**	**7.49 (3.60 -**	**< 0.001**

Neopterin levels	≤ 25.0 nmol/L	25.1 - 45.0 nmol/L	> 45.0 nmol/L	
	n = 34	n = 33	n = 48	
	Median (IQR) or n (%)	Median (IQR) or n (%)	Median (IQR) or n (%)	p-Value *
			14.93)	
IL-6, ng/L			**74.9 (32.6 -**	**< 0.001**
	8.5 (2.3 - 30.6)	**26.3 (15.8 - 62.5)**	**186.5)**	
PCT, ng/mL	**0.00 (0.00 - 0.06)**	**0.08 (0.06 - 0.15)**	**0.20 (0.08 - 0.57)**	**< 0.001**

* Kruskal-Wallis test or Pearson Chi-Square test, † without patients who died during hospital stay, ‡ only patients under the age of 70 with available neopterin levels (n = 73), § discharged patients only

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

Table 2 Logistic Regression Analyses in terms of risk for ICU admission during hospital stay and need for mechanical ventilation *

	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, years	**1.043**	**1.001 - 1.088**	**0.047**	0.938	0.858 - 1.026	0.164	1.049	1.000 - 1.101	0.051			
Women *vs.* men	**0.224**	**0.060 - 0.847**	**0.027**	0.118	0.008 - 1.829	0.126	0.216	0.045 - 1.028	0.054			
Clinical characteristics												
SpO2, %	**0.847**	**0.754 - 0.952**	**0.005**	0.969	0.788 - 1.192	0.768	**0.829**	**0.731 - 0.941**	**0.004**	0.977	0.818 - 1.167	0.795
O2 requirement, L †	**1.538**	**1.185 - 1.997**	**0.001**	1.457	0.854 - 2.484	0.167	**1.736**	**1.257 - 2.399**	**0.001**	1.434	0.874 - 2.352	0.154
Laboratory parameters												
eGFR, mL/min	**0.975**	**0.951 - 0.999**	**0.043**				0.977	0.952 - 1.003	0.081			
Leukocytes, G/L	**1.535**	**1.218 - 1.936**	**< 0.001**				**1.348**	**1.114 - 1.631**	**0.002**			
Lymph. absolute, G/L †	**0.234**	**0.078 - 0.708**	**0.010**				**0.249**	**0.081 - 0.765**	**0.015**			
CRP, mg/dL †	**3.245**	**1.816 - 5.796**	**< 0.001**				**5.360**	**2.266 - 12.679**	**< 0.001**			
IL-6, ng/L †	**4.621**	**2.154 - 9.914**	**< 0.001**				**4.724**	**2.155 - 10.356**	**< 0.001**			
PCT, ng/mL †	1.412	0.936 - 2.129	0.100				1.400	0.892 - 2.199	0.144			
Neopterin, nmol/L †	**9.243**	**2.553 - 33.468**	**0.001**				**16.456**	**3.215 - 84.222**	**0.001**			
Neopterin/eGFR ratio †	**4.915**	**1.893 - 12.758**	**0.001**				**7.054**	**2.220 - 22.418**	**0.001**			
Neopterin at Day 7, nmol/L †	**22.073**	**2.416 - 201.652**	**0.006**				**24.567**	**2.482 - 242.174**	**0.006**			
Neopterin/eGFR ratio † at Day 7	**8.052**	**1.683 - 38.525**	**0.009**				**11.200**	**1.746 - 71.854**	**0.011**			
Classifications												
Neopterin > 45	**14.548**	**4.162 -**	**<**				**16.800**	**4.534 -**	**<**	**7.025**	**1.161 -**	**0.034**

	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*
nmol/L *vs.* ≤ 45 nmol/L		**50.852**	**0.001**					**62.252**	**0.001**		**42.511**	
Neopterin/eGFR ratio > 0.650 *vs.* ≤ 0.650	**6.400**	**1.772 - 23.110**	**0.005**	**25.049**	**1.123 - 558.583**	**0.042**	**5.833**	**1.615 - 21.075**	**0.007**			
IL-6 > 80 ng/L *vs.* ≤ 80 ng/L	**68.000**	**12.472 - 370.739**	**< 0.001**	**142.956**	**3.462 - 5902.918**	**0.009**	**46.375**	**10.287 - 209.059**	**< 0.001**	7.664	0.500 - 117.585	0.144
CRP > 5 mg/dL *vs.* ≤ 5 mg/dL	**9.880**	**3.125 - 31.238**	**< 0.001**	0.319	0.024 - 4.342	0.391	**10.789**	**2.787 - 41.773**	**0.001**	0.581	0.050 - 6.787	0.665

Parameters were recorded at day 1 ± 1 if not other depicted. The chi-square test was 37.157 ($p < 0.001$) for multivariate model of ICU admission (n = 67 – only patients with all included parameters available) and 24.993 ($p < 0.001$) for multivariate model of need for mechanical ventilation (n = 67 – only patients with all included parameters available).

OR = odds ratio; CI = confidence interval; ICU = intensive care unit; SpO2 = peripheral capillary oxygen saturation; O2 = oxygen; eGFR = estimated glomerular filtration rate; CRP = C-reactive protein; IL-6 = interleukin 6; PCT = procalcitonin

* Patients under the age of 70 only (n = 73), † logarithmized because not normally distributed