JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A COMPREHENSIVE ANALYSIS OF NEOPTERIN AS A PROGNOSTIC MARKER FOR SARS-COV-2 PATIENTS

Roma Sharma[1], Dr. Surabhi Singh[2]

Research scholar, School of Basic and Applied Science, Career Point University, Kota India

Head of the Department, School of Basic and Applied Science, Career Point University, Kota India

ABSTRACT

The SARS-CoV-2 pandemic was a grave concern worldwide. It was posing a serious threat to mankind and was acting as a global threat with no effective treatment. There was no definite therapy available and globally it was a challenge to decide on ways to prevent it from spreading. The scientific community was working on all fronts to decide on a single solution to curb the situation at the earliest. The viral infection bourgeons and affects the life score in one form or the other. The biomarkers were limitedly studied as it was not established that they help in identifying poor prognosis in COVID-19 cases. The study of Novel Biomarkers was prioritized in those challenging times. During that time when the viral journey was exponentially increased studies were released on Neopterin (NPT) and it was established that neopterin is one biomarker that signals an active immune system and is a promising tool to detect the severity and prognosis of COVID-19. The objective of this review is to find Neopterin's utility for the diagnosis and prognosis of SARS-CoV-2 infection. The research was comprehensively performed by using databases like Cochrane, PubMed, Scopus, and EMBASE. A total of six out of seven research literature were included for the initial screening of this review. Captivatingly, all studies reported that serum NPT levels were high in all severe cases and the NPT levels were positively correlated with the COVID-19 infection. This study provides the existing evidence through a meta-analysis of relevant studies where it provides a detailed analysis of Neopterin as a potential biomarker. For the best results, PRISMA guidelines were followed. This implies that makeshift can be done using serum NPT levels before hospital admission to determine the severity and prognosis of the disease which helps in close monitoring of such cases with risk stratification for better management in a highly populated country.

Keywords: Neopterin, SARS-COV-2, ACE 2, Prognosis, Biomarker

Abbreviations

NPT	Neopterin
INF-γ	Gamma Interferons
MAS	Macrophage Activation system
RAS	Renin Angiotensin system

ACE 2	Angiotensin-converting enzyme 2
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus-2
ROC	Receiver Operating Curve
AUC	Area under the ROC curve
GTP	Guanosine Triphosphate

I. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2- 2) disease (COVID-19) has spread from China and slowly worldwide we have seen its effect. As a result, the pandemic has challenged the scientific community and the existing healthcare system and asked for unprecedented political, medical, and scientific actions. Slowly and steadily the consequences of this pandemic emerged globally.

This RNA virus belongs to the Coronaviridae family, closely related to SARS (SARS-CoV) and the Middle East respiratory syndrome-related coronavirus (MERS-CoV). These airborne viruses infect epithelium (primarily lung epithelium) as there is a high affinity contact between spike protein and ACE 2 enzyme. There is a proteolytic cleavage of ACE2 with the host transmembrane protein responsible for viral entry. The transmembrane protein is host type II transmembrane serine metalloprotease TMPRSS2 [14] and is responsible for cleaving the SARS-CoV-2 spike protein [15].

When SARS-CoV-2 binds with ACE2 receptors there is dysfunction of RAS which is the Renin Angiotensin system in the human body. ACE2 receptors are expressed in the lungs and present in type II alveolar cells. Therefore, when the RAS system loses its momentum there is serious lung damage due to inflammatory changes. When SARS-CoV-2 initiates a local immune response, monocytes and macrophages are released to the site of infection which activates the cellular immune response. Increases in viral infection and abnormal immune response result in cellular death as IL-1β is released [17].

This virus is responsible for causing serious illnesses like the common cold and SARS. The mechanism responsible for viral spread is through respiratory droplets which are transferred while talking, sneezing, or coughing. It also gets transmitted through contact or contaminated objects and surfaces.

During this pandemic, a wide range of symptoms have been observed, varying from asymptomatic to mild and severe. The most common symptoms are fever, fatigue, cold, loss of taste/smell, and difficulty in breathing. Severe cases have been reported of pneumonia and acute respiratory distress syndrome which can be fatal. Elderly people with a medical history are more susceptible to severe symptoms and have fatal outcomes.

The incubation period differs in non-symptomatic and symptomatic individuals. It was on average 6.4 days for nonsymptomatic [16]. The incubation period gives a replication window to the virus and the individual will become infectious from non-infectious.

It was observed that people affected will suffer from mild disease form and is accompanied by viremia for 8-10 days in the respiratory tract. The patients in this duration either recovered fully or went into a more severe disease form with associated viremia [16] and a pronounced pro-inflammatory signature [6]. The main cause of fatality is the inability to control cytokine reactions when they are severe.

In this course when ongoing efforts were been made to develop therapeutic approaches world faced a challenging time in developing a therapeutic or prophylactic medical intrusion, at the beginning of the pandemic. The healthcare system primarily involves providing a life support system to all the patients. Various strategies were adopted globally at different levels where the political and hospital-level strategies were of the utmost importance.

COVID-19 patients were stratified based on the cellular biomarkers and at this point it is an unmet need in patient care. The primary objective of this study is to characterize the relationship between neopterin

and the severity of SARS-COV-2 infection. Many studies suggested that neopterin is a reliable biomarker that can help in the prediction of severity and prognosis of SARS-CoV-2 infection.

T lymphocytes and macrophages are activated which initiate the immune response for SARS COV-2 and it plays a crucial role in fighting the virus. As a result, the immune cells produce neopterin which is a Biomarker for immune system activation, and it releases gamma interferons. There are lot many studies that highlight the importance of neopterin as a biomarker because it helps in predicting the severity and prognosis of SARS-COV-2 infection. Reliable biomarker identification helps in the accurate assessment of the severity and prognosis of any disease. Recent studies suggest that there is an uncontrolled activation of macrophages and monocytes mediated by gamma interferons in response to SARS-Cov-2.

During 2002-2003 when the SARS outbreak was there it was studied that neopterin helps in predicting the course of disease. The severity of the disease can be revealed in a more impactful way due to the presence of these biomarkers which could help in the interpretation of clinical symptoms linked to mild, severe, and critical forms of any disease [30].

Previous studies highlighted that serum NPT(Neopterin) levels are important in SARS-CoV-2 prognosis and this review is intended to understand the potential of Neopterin as a reliable and informative biomarker for COVID-19 severity and prognosis where further research is required for establishing clinical utility.

Neopterin is pteridine and it is synthesized under the effect of human monocytes and macrophages due to stimulation produced by gamma interferons (INF-γ). It is a product of [GTP] Guanosine triphosphate. It is considered an indicator for stimulation of macrophages, cellular immune response activation, and type1 t-helper cells immune response.

A study reported that if the neopterin levels of 45 nmol/L are identified in hospitalized patients then such individuals are at risk, and they require mechanical ventilation and ICU services at the earliest. Therefore, elevated levels of neopterin are linked with the enhanced immune response which possibly points towards negative consequences.

It is released into body fluids like serum, cerebrospinal fluid, pancreatic juice, synovial fluid, urine, saliva, and other fluids. There are studies suggesting that NPT concentration is linked to the release of hydrogen peroxide in cells and as a result, it reflects the level of oxidative stress.

During infections, autoimmune disorders, allograft rejections, varied types of malignancies, and renal and cardiac failures the level of neopterin shoots us and the measurements give us an insight into CMI (Cell-mediated immune response) and help in understanding the disease progression prognosis. NPT, or neopterin acts as an oxidized form of dihydro neopterin during oxidative reaction [3]. It was highlighted that high levels of NPT are present in serum and other fluids in the human body resulting in the elevated release of reactive oxygen species. This can induce oxidative stress because of cellular immunity [8].

NPT, or neopterin, acts as an oxidized form of dihydro neopterin during oxidative reactions. When there are high levels of NPT present in the serum and other fluids in the human body, it results in the elevated release of reactive oxygen species. This can induce oxidative stress because of cellular immunity [10].

The discovery of neopterin was first listed in pigments of bee larvae and it was later put forth as a biomarker of macrophage activation which is released by human macrophages and monocytes. It is principally used in the early detection of numerous diseases [7,9].

An indicative of SARS-CoV-2 severe infection is the Macrophage activation system (MAS). Hence, assessing NPT levels might prove beneficial in the early prediction of disease progression and assist in the timely management of infected patients. This review will explain the significance of NPT levels in the human body as a prognostic and diagnostic marker in COVID-19 patients [20, 28].

2. Materials and Methods

2.1 Strategy for Literature Search

Published studies on neopterin and its association with SARS-Cov-2 were searched from March 2020 to November 2023. Databases like PubMed, EMBASE, Cochrane, Frontier, and SCOPUS were thoroughly used to write this review.

2.2 Extraction of Data

Out of all the three authors first two authors worked on the articles independently and searched varied keywords from plenty of studies to work on this topic. The final article was decided on mutual consent of both authors. We have chosen research literature that has evaluated the importance of Neopterin as a biomarker in correlation with SARS-COV-2. Following this, the data were extracted from selected articles using the Author's Name, Place of study, NPT features, Serum NPT level, and its utility as an independent prognostic factor for COVID-19 severity. Data was extracted by one author and rechecked by the other two for accuracy. Data concerning neopterin and its related factors should be accessed in available databases like PubMed, Cochrane, Scopus, and Google Scholar as well.

2.3 Results and Discussion

We primarily retrieved a total of seven research literature from different databases. Finally, we have selected six research works of literature for this review to conclude. All the available literature provides insights differently.

Figure 1 depicts the flow of the process for the selection of research literature according to the PRISMA guideline.

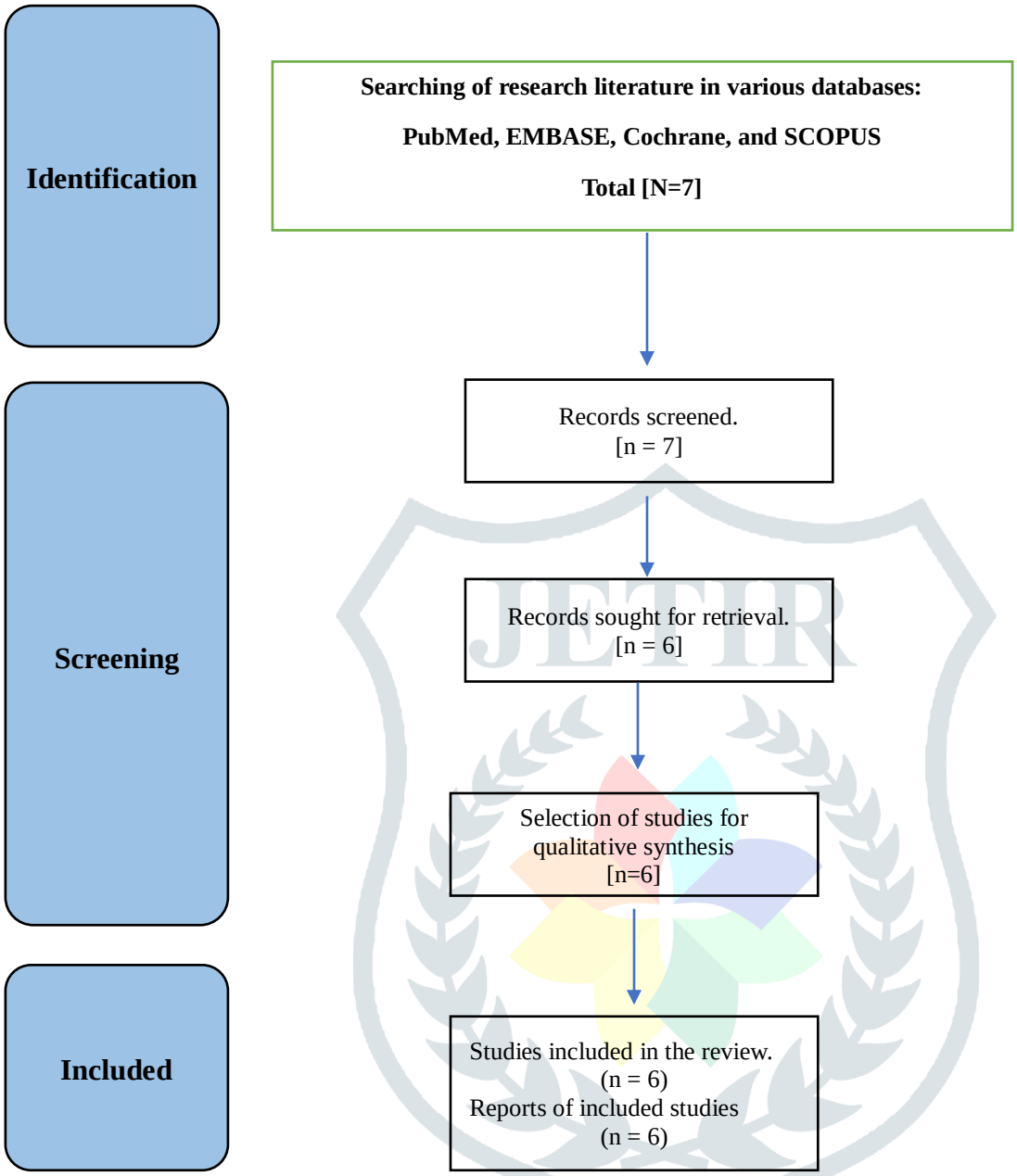

Figure 1 PRISMA Flowchart for systematic review as per database and literature search.

3. Utility of Neopterin in SARS-COV-2 Infection

Neopterin also known as (6-(D-erythro-1′, 2′, 3′-trihydroxypropyl)-pterin) works as an immune activation marker and it is reported to have high concentrations in many inflammatory stages. It has been seen that before antibodies are released the serum neopterin level correlates with the disease [20].

NPT is involved in various redox reactions occurring in the human body [23]. Its synthesis takes place in vivo from GTP and monocytes, macrophages, dendritic cells, and endothelial cells play a vital role in its formation. Interferon stimulation is the major factor behind its activation and formation. When the serum NPT level is elevated, it will regularly reactive oxygen species by regulating intracellular signaling mechanisms in the body. There are changes produced at the m-RNA level as well and it is considered as an indicator of oxidative stress as well.

One of the recent studies suggested that in acute viral stages, the level of NPT is highly increases, and before clinical symptoms set in it starts appearing in the acute stages. Clinical studies suggested that when cell-mediated immunity is involved the concentration of serum neopterin level above the cut-off value of ≤ 10 nmol/l is observed in irregular conditions [4]. They illustrated that in various viral infections, the serum NPT levels were elevated and in the case of HIV also it is identified as a prognostic marker when defining infection progression [18,27].

Mıstanoglu et al. [19] reported the usability of neopterin in SARS-CoV-2 patients when there is uncontrolled activation of monocytes and macrophages in the human body. They included 100 patients in their study out of which 41 were males and 59 females were included. They suggested independent variables to demonstrate the disease severity. Among all the variables NPT levels appeared to be the new biomarker to define severity in SARS-CoV-2.

Similarly, **Robertson et al**. [24] investigated the potent role of neopterin. They compared two groups, patients with mild and severe infections. They deduced that neopterin levels in severely diseased individuals were high two times as compared to the individuals showing mild symptoms. They took repetitive measurements for the study and proved that NPT levels were high for a long duration and took time to return to normal when severely affected. When compared with mild patients the levels returned to normal levels quickly. Magnus et al. stated that neopterin acts as one of the CSF inflammatory biomarkers when diagnosing neurological signs and symptoms in SARS-CoV-2 patients [12].

In another study, **Al-Kuraishy et al.** [1] mentioned that neopterin should be considered as an independent prognostic marker to define COVID-19 severity. They stated that NPT levels rise from the 3rd day of infection and are associated with various symptoms like dyspnoea, longer hospital admission, and other complications. Likewise, **Ozger et al.** [22] reported that the patients with severe COVID-19 had higher levels of NPT than mild ones when they were admitted to the hospital, and it increased four times when compared with the healthy population.

Chauvin et al. [5] reported that high neopterin levels would predict fatality in SARS-CoV-2-infected patients. They measured blood neopterin levels using the ELISA technique. They quantified serum NPT levels from healthy donors and COVID-19-affected individuals. Their study concluded that when the infection was severe NPT levels were elevated in such cases due to immune reactions taking place in the body and when the patients were admitted to the hospital neopterin concentration was measured and it proved to be a severe hallmark which identified high-risk population that needs advanced monitoring and medical care. **Rashmi et al.** [23] reported prognostic value and relation with the disease severity. They studied neopterin levels to help in predicting the severity of COVID-19 because of macrophage activation and interferon stimulus.

Hailemichael et al. [12] have reported the study that neopterin serves as a promising biomarker for COVID-19 infection. They informed that Macrophage activation is linked with SARS-CoV-2 severity and immunopathology of SARS-CoV-2 is associated with an exacerbation of immune response.

Neopterin so far has been observed as a potential silent disease marker and a broad-spectrum tool to understand the pathogenicity. Hence, disease severity is not linked alone to viral infection but exaggerated immune response is also responsible for the same.

Most of the systematic reviews and meta-analyses did not confirm the cause of NPT elevation in serum and whether its effects prove to be advantageous or detrimental in the present scenario. However, **Yan et al.** [29] reported that high NPT levels counteract endothelial dysfunction in COVID-19 patients, and they are protective in such cases.

Table 1 illustrates the summary of data extracted on the same parameters from different studies for neopterin in SARS-CoV-2 infection.

Author	**Mıstanoglu et al. [19]**	**Ozger et al. [22]**	**Robertson et al.[24]**	**Chauvin et al. [5]**
Place of study	Turkey	Turkey	Sweden	France
Number of patients involved in the study	100 41: male 59: female	134	34	610 256- healthy donors 374 – COVID-19 patients
Sample taken	Serum	Serum	Serum	Serum
Identification of High-risk patients	Yes	Yes	Yes	Yes
Serum Neopterin levels considered	Yes	Yes	Yes	Yes
Types of patients	Mild to severe	Moderate to severe	Mild to severe	Healthy and severely ill
Limitations	Limited sample size and serum neopterin measurement follow-up values.	NA	Measurements of Creatinine in mild cases	NA

Table 1 Summary of data extracted for Neopterin levels in SARS-CoV-2 infections from various studies.

II. Limitations and Future Perspectives

This systematic review and meta-analysis provide a convincing finding but still, the limitations need to be addressed. Variability will be introduced in the analysis by the use of different study designs, patient groups, and other measurement methods. NPT levels can be assessed in human serum as well as body fluids by clinicians but to overcome the limitations further research and a standardized protocol for neopterin assessment in the context of SARS-CoV-2 is needed and it will establish a more appropriate way for the examination before hospital admission of the patients.

Figure 2 represents the chart of AUC values obtained from the reaction operating curve from two different research literature viz Mıstanoglu **et al.** [19] **and Ozger et al.** [22]**.**

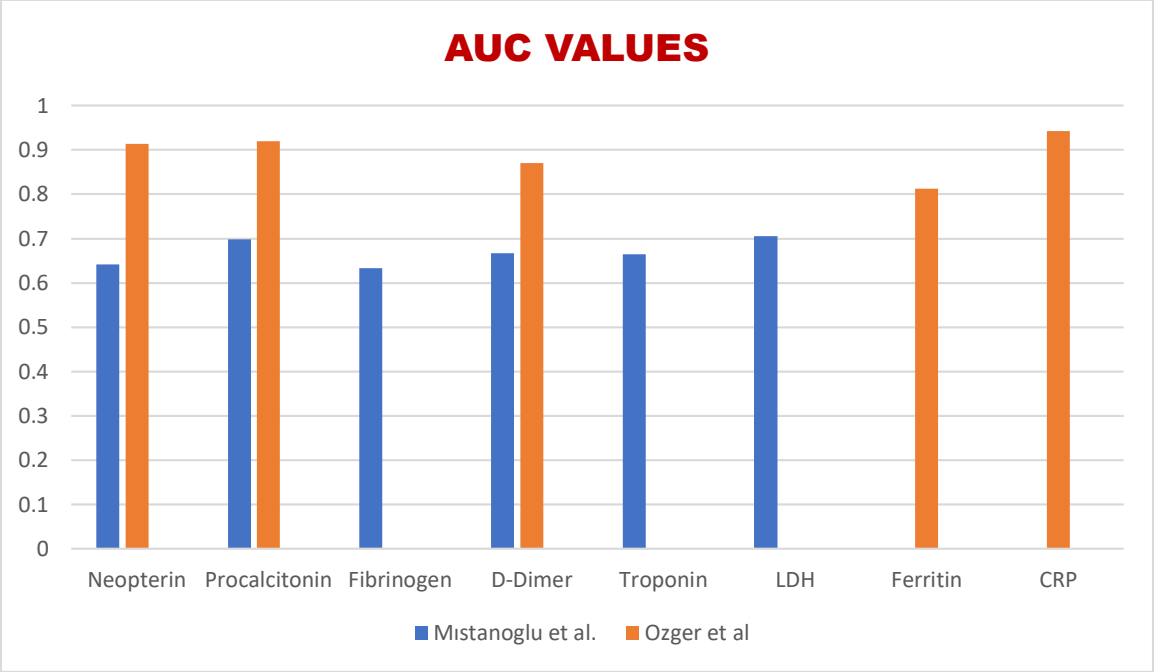

Figure 2: AUC values in the ROC curve from two different studies demonstrating the severity of the disease.

III. Conclusion

Neopterin (NPT) might be a potential prognosis biomarker for SARS-Cov-2 and it helps to identify high-risk patients and determine disease severity at the earliest so that adverse and fatal outcomes will be reduced by close monitoring and advanced treatment strategies. To determine the potential of neopterin as an important biomarker of COVID-19 large-scale and standardized studies are needed to authenticate the same. It can be used for identifying high-risk patients and accordingly, the treatment decisions should be made. Clinical trials and mandatory studies are essential to evaluate the serum NPT levels and their correlation with SARS-CoV-2 infection severity. This will allow us to make fast and precise decisions that will help the scientific world in dealing with some deadly diseases and will prevent population morbidity.

Funding None

Declarations

Conflict of interest - The authors declare that they have no conflicts of interest.

REFERENCES:

1. Al-Kuraishy, H. M., Al-Gareeb, A. I., Alzahrani, K. J., Cruz-Martins, N., & Batiha, G. E. (2021). The potential role of neopterin in Covid-19: a new perspective. *Molecular and cellular biochemistry*, *476*(11), 4161–4166. https://doi.org/10.1007/s11010-021-04232-z
2. Bellmann-Weiler R, Lanser L, Burkert F, et al. Neopterin predicts disease severity in hospitalized patients with COVID-19. *Open Forum Infect Dis*. 2020. doi: 10.1093/ofid/ofaa521
3. Berdowska A, Zwirska-Korczala K. Neopterin measurement in clinical diagnosis. *J Clin Pharm Ther*. 2001;26(5):319–329. doi: 10.1046/j.1365-2710.2001. 00358.x
4. Chan CPY, Choi JWY, Cao K-Y, et al. Detection of serum neopterin for early assessment of dengue virus infection. *J Infect*. 2006;53(3):152–158. doi: 10.1016/j.jinf.2005.11.008
5. Chauvin, M., Larsen, M., Quirant, B., Quentric, P., Dorgham, K., Royer, L., Vallet, H., Guihot, A., Combadière, B., Combadière, C., Barallat, J., Mayaux, J., Luyt, C. E., Mathian, A., Amoura, Z.,

Boddaert, J., Armestar, F., Gorochov, G., Martinez-Caceres, E., & Sauce, D. (2021). Elevated Neopterin Levels Predict Fatal Outcome in SARS-CoV-2-Infected Patients. *Frontiers in cellular and infection microbiology*, *11*, 709893. https://doi.org/10.3389/fcimb.2021.709893

6. Chen, G., Wu, D., Guo, W., Cao, Y., Huang, D., Wang, H., et al. (2020). Clinical and Immunological Features of Severe and Moderate Coronavirus Disease 2019. *J. Clin. Invest.* 130 (5), 2620−2629. doi: 10.1172/JCI137244

7. Eisenhut M. Neopterin in diagnosis and monitoring of infectious diseases. *J biomark*. 2013;2013:1–10. [PMC free article] [PubMed] [Google Scholar]
8. Firth CA, Laing AD, Baird SK, Pearson J, Gieseg SP. Inflammatory sites as a source of plasma neopterin: measurement of high levels of neopterin and markers of oxidative stress in pus drained from human abscesses. *Clin Biochem*. 2008;41(13):1078–1083. doi: 10.1016/j.clinbiochem.2008.06.008
9. Fuchs D, Avanzas P, Arroyo-Espliguero R, Jenny M, Consuegra-Sanchez L, Kaski J. The role of neopterin in atherogenesis and cardiovascular risk assessment. *Curr Med Chem*. 2009;16(35):4644–4653. doi: 10.2174/092986709789878247 [PubMed] [CrossRef] [Google Scholar]
10. Goyal N, Kashyap B, Singh NP, Kaur IR (2017) Neopterin and oxidative stress markers in the diagnosis of extrapulmonary tuberculosis. Biomarkers 22(7):648–653

11. Grabherr, F., Effenberger, M., Pedrini, A., Mayr, L., Schwärzler, J., Reider, S., Enrich, B., Fritsche, G., Wildner, S., Bellmann-Weiler, R., Weiss, G., Scholl-Bürgi, S., Müller, T., Moschen, A., Adolph, T. E., & Tilg, H. (2021). Increased Fecal Neopterin Parallels Gastrointestinal Symptoms in COVID-19. *Clinical and translational gastroenterology*, *12*(1), e00293. https://doi.org/10.14309/ctg.0000000000000293

12. Hailemichael, W., Kiros, M., Akelew, Y., Getu, S., & Andualem, H. (2021). Neopterin: A Promising Candidate Biomarker for Severe COVID-19. *Journal of inflammation research*, *14*, 245–251. https://doi.org/10.2147/JIR.S290264

13. Hara S, Sanatani T, Tachikawa N, Yoshimura Y, Miyata N, Sasaki H, et al. Comparison of the levels of neopterin, CRP, and IL-6 in patients infected with and without SARS-CoV-2. Heliyon 2022; 8: e09371.

14. Heurich, A., Hofmann-Winkler, H., Gierer, S., Liepold, T., Jahn, O., Pöhlmann, S. (2014). TMPRSS2 and ADAM17 Cleave ACE2 Differentially and Only Proteolysis by TMPRSS2 Augments Entry Driven by the Severe Acute Respiratory Syndrome Coronavirus Spike Protein. *J. Virol.* 88 (2), 1293–1307. doi: 10.1128/JVI.02202-13

15. Hoffmann, M., Kleine-Weber, H., Pöhlmann, S. (2020). A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. *Mol. Cell.* 78 (4), 779–784.e5. doi: 10.1016/j.molcel.2020.04.022

16. Lescure, F.-X., Bouadma, L., Nguyen, D., Parisey, M., Wicky, P.-H., Behillil, S., et al. (2020). Clinical and Virological Data of the First Cases of COVID-19 in Europe: A Case Series. *Lancet Infect. Dis.* 20 (6), 697−706. doi: 10.1016/S1473-3099(20)30200-0

17. Lugnier C, Al-Kuraishy HM, Rousseau E. PDE4 inhibition as a therapeutic strategy for improvement of pulmonary dysfunctions in Covid-19 and cigarette smoking. *Biochem Pharmacol*. 2021;185:114431. doi: 10.1016/j.bcp.2021.114431.

18. Mildvan D, Spritzler J, Grossberg SE, et al. Serum neopterin, an immune activation marker, independently predicts disease progression in advanced HIV-1 infection. *Clin Infect Dis*. 2005;40(6):853–858. doi: 10.1086/427877

19. Mıstanoglu Ozatag, D., Korkmaz, P., Keskin, H., & Koçak, H. (2023). The usability of neopterin in determining disease course in COVID-19. *Saudi medical journal*, *44*(8), 767–772. https://doi.org/10.15537/smj.2023.44.8.20230365

20. Murr C, Fuith L, Widner B, Wirleitner B, Baier-Bitterlich G, Fuchs D. Increased neopterin concentrations in patients with cancer: indicator of oxidative stress? *Anticancer Res*. 1999;19(3A):1721–1728. [PubMed] [Google Scholar]

21. Murr C, Widner B, Wirleitner B, Fuchs D. Neopterin as a marker for immune system activation. *Curr Drug Metab.* 2002; 3:175–187. doi: 10.2174/1389200024605082

22. Ozger, H. S., Dizbay, M., Corbacioglu, S. K., Aysert, P., Demirbas, Z., Tunccan, O. G., et al. (2021). The Prognostic Role of Neopterin in COVID-19 Patients. *J. Med. Virol.* 93 (3), 1520−1525. doi: 10.1002/jmv.26472.

23. Rasmi, Y., Heidari, N., Kübra Kırboğa, K., Hatamkhani, S., Tekin, B., Alipour, S., Naderi, R., Farnamian, Y., & Akca, I. (2022). The importance of neopterin in COVID-19: The prognostic value and relation with the disease severity. *Clinical biochemistry*, *104*, 1–12. https://doi.org/10.1016/j.clinbiochem.2022.03.002

24. Robertson, J., Gostner, J. M., Nilsson, S., Andersson, L. M., Fuchs, D., & Gisslen, M. (2020). Serum neopterin levels about mild and severe COVID-19. *BMC infectious diseases*, *20*(1), 942. https://doi.org/10.1186/s12879-020-05671-7

25. Sheikh, A., Sheikh, A., Sheikh, Z., Dhami, S., Sridhar, D. (2020). What's the Way Out? Potential Exit Strategies From the COVID-19 Lockdown. *J. Glob Health* 10 (1), 010370. doi: 10.7189/jogh.10.010370

26. Webb BJ, Peltan ID, Jensen P, Hoda D, Hunter B, Silver A et al. Clinical criteria for COVID-19-associated hyperinfammatory syndrome: a cohort study. Lancet Rheumatol 2020; 2: e754– e763

27. Wirleitner B, Schroecksnadel K, Winkler C, Fuchs D. Neopterin in HIV-1 infection. *Mol Immunol*. 2005;42(2):183–194. doi: 10.1016/j.molimm.2004.06.017

28. Yadav AK, Sharma V, Jha V. Association between serum neopterin and inflammatory activation in chronic kidney disease. *Mediators Inflamm*. 2012;2012. doi: 10.1155/2012/476979

29. Yan JQ, Tan CZ, Wu JH, Zhang DC, Chen JL, Zeng BY, Jiang YP, Nie J, Liu W, Liu Q, Dai H. 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):123–131. doi: 10.1007/s11010-013-1634-6.

30. Zheng B, Cao KY, Chan CPY, et al. Serum neopterin for early assessment of severity of severe acute respiratory syndrome. *Clin Immunol*. 2005;116:18–26. doi: 10.1016/j.clim.2005.03.009.