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The importance of neopterin in COVID-19: the prognostic value and relation with the disease severity

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SUMMARY

Coronavirus Disease 2019 [COVID-19], caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], has rapidly evolved into a global health emergency. Neopterin [NPT], produced by macrophages when stimulated with interferon [IFN-] gamma, is an important cytokine in the antiviral immune response. NPT has been used as a marker for early assessment of disease severity in different of diseases. The main cause of NPT production is the pro-inflammatory cytokine IFN. Macrophage activation has also been revealed to be linked with disease severity in SARS-CoV-2 patients. We demonstrate the importance of NPT in the pathogenesis of SARS-CoV-2 and suggest that targeting of NPT in SARS-CoV-2 infection may be critical in the early prediction of disease progression and provision of timely management of infected individuals.

Keywords : SARS CoV-2; Neopterin; COVID-19; Prognosis

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2] infection has been spreading rapidly around the world since it's first appeared in China in late 2019. The data show that approximately percent 80 of COVID-19 patients have mild disease percent 20 require hospitalization, and approximately percent 5 need intensive care admission [1]. COVID-19 has a poor prognosis in elderly, male patients and, in patients with comorbidities such as diabetes, cardiovascular disease, or Chronic Obstructive Pulmonary Disease [COPD] [2-5]. In patients infected with SARS-CoV-2, hyper-inflammation and coagulopathy are known to be associated with disease severity and death [6]. Elevated levels of inflammatory markers, including C-reactive protein, ferritin, D-dimer, inflammatory cytokines, and chemokines, and elevated neutrophil to lymphocyte ratios are associated with disease severity and mortality from COVID-19 [6]. High levels of circulating cytokines, profound lymphopenia, substantial mononuclear cell infiltration in the lungs and other organs have been reported in severe cases compared to mild COVID-19 cases [6]. Previous studies have shown that in severe cases, the proportion of mononuclear phagocytes increased and the composition of macrophages changed in favor of monocyte-derived macrophages [6]. As a result, high levels of cytokines linked to macrophage activation including interferon- [IFN-], have been reported in SARS-CoV-2 patients [7]. NPT produced by macrophages on stimulate with IFN-, a cytokine important in the antiviral immune response. Serum NPT levels reflect the activation phase of the cellular immune system, which is important in the pathogenesis and progression of various diseases [8]. Previous studies have shown an association between serum NPT levels and prognosis in certain viral infections, such as influenza, human immunodeficiency viruses, hepatitis C virus, and dengue fever virus [9-11]. High levels of circulating cytokines have been reported in patients with severe COVID-19. Therefore, targeting of NPT in SARS-CoV-2 infection may be important for early prognosis of disease progression and timely treatment of infected patients. Serum NPT levels have been measured to assess the immune activation in several diseases, but only a few studies have been conducted on individuals infected with SARS-CoV-2. Therefore, this review is intended to elucidate the importance of NPT as a diagnostic and prognostic marker in COVID-19 patients.

LITERATURE REVIEW

Overview of Neopterin: biosynthesis, mechanisms of tryptophan and oxidative

In the present pandemic, it is frequently observed that cytokine storm occurs in patients with COVID-19 infection. When respiratory epithelial tissue is infected by COVID-19 infection, inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12, TNF- and other chemokines locally realized. subsequently, monocytes, macrophages, neutrophils, DCs, and NK cells are recruited by cytokines resulting in activation CD4+ and CD8+ T cells to synthesis IFN- and TNF-, which induce lung injury. Furthermore, high production IL-2, IFN-, GM-CSF, and TNF- leads to anemia by macrophage activation and erythro-phagocytosis [92,102]. IFN- is considered as a glycosylated protein of 25 kDa [103]. It is well established that IFNs are categorized into three categories; type I [IFN], type II [IFN] and type III [IFN][104].

IFN is produced mainly by natural killer [NK] cells, natural killer T cells [NKT], activated lymphocytes such as CD4 T helper type 1 [Th1] cells and CD8 cytotoxic T cells, B cells, and professional antigen-presenting cells [APCs] [105-110]. It is now apparent that Janus activated kinases [JAKs] and STAT1 signal is trigger by binding IFN to IFNAR1 and IFNAR2 receptors. Attaching of IFN to IFNARs result in activation of tyrosine kinases JAK1 and JAK2 phosphorylating the transcription factor STAT1 to form dimer then dimers translocate to the nucleus and bind GAS to stimulate the transcription of these genes; for example: IFN stimulate expression of immunoglobulin Fc receptors on phagocytes and improve expression of MHC antigens facilitating antigen presentation to T lymphocytes [111, 112]. TNF is classified as non-glycosylated protein which has 157 residues [113] secreted by macrophages/monocytes. TNF gene is located on chromosome 6 [50]. TNF plays a verity of roles in cell, for example; viral replication, cell growth modulation, tumorigenesis, and inflammation process. [114-117].

The expression of TNF gene is controlled by

Fig. 1. Graphical abstract.

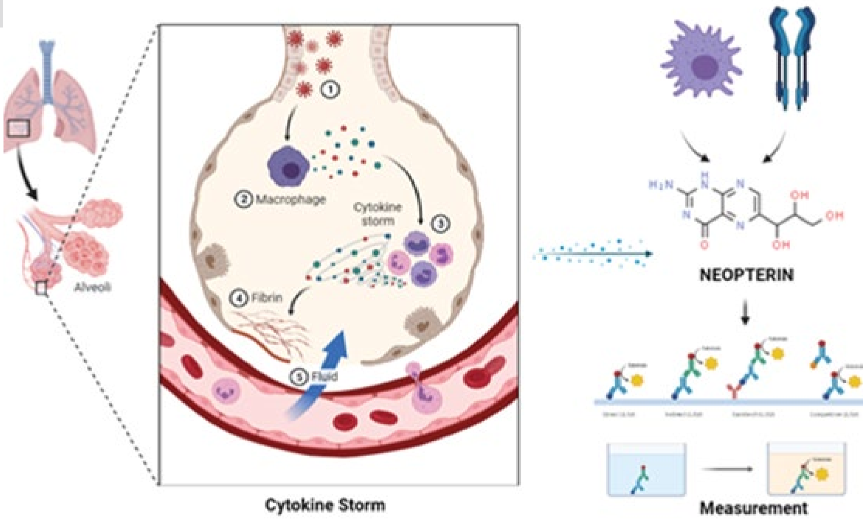
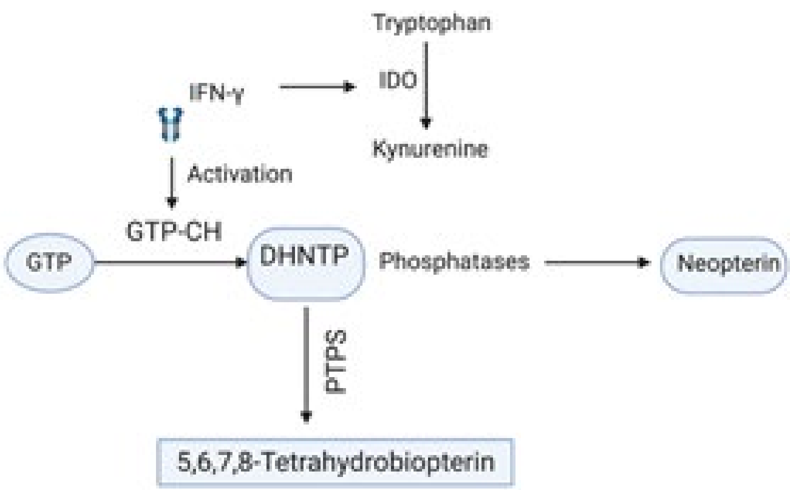


Fig. 2. Biosynthesis of neopterin.



nuclear factor kappa b [NFB] andnuclear factor activated T cells [NF-AT] [115,116] TNF signals through TNF recep- tor 1 [TNFR1] and TNF receptor 2 [TNFR2] [118]. Both pro-inflammatory and pro-apoptotic pathway are triggered by the binding of the ligand soluble TNF- and transmembrane to the TNF receptor [TNFR1] and TRAF2, respectively. TNFR1 stimulate NFB, MAPK and Caspase-8 inducing inflammation, tissue degeneration, apoptosis. On the other hand, TRAF2 can activate MKLK leading to necroptosis [119,120]. Interleukin: Interleukin [IL] refers to a class of cytokine prominently secreted by leukocytes [121]. ILs regulates numerus of function such as: stimulation and differentiation of immune cells, proliferation, maturation. IL not only act as pro-inflammatory agent but also have anti-inflammatory properties [121]. Mature IL-6 has 185 amino acids. The gene of IL-6 is located at chromosome 7 p21. This pleotropic cytokine exerts numerous functions such as: inflammation, immune response, and hematopoiesis which are produced from T cells, macrophages, endothelial cells, fibroblasts and monocytes [122]. Binding of IL-6 to its receptor initiates cascades of signaling through JAK/STAT3 stimulating the transcription of several factors such as: other cytokines and adaptor proteins [123]. Takentogether, Interleukins, TNF and IFN play inseparable role in cytokinestorm.

Association of Neopterin with the severity of COVID-19: Statins, one of the best-selling prescription drug class HMG-CoA reductase enzyme inhibitors in the US, is known to have a favorable safety profile; they contain the world's best selling prescription drug atorvastatin. When looking at their biochemical effects, the uncommon effects of statins that extend far beyond the lipid profile and components such as LDL-C, HDL-C and triglycerides ranging from nitric oxide and inflammatory markers to polyunsaturated fatty acids [124]. Since statins in the lipid-lowering drug class are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase [125], many at risk [126] including young/old, male/female individuals. It has well-documented benefits for moderate to high cardiovascular disease [124].

To SARS-CoV-2 patients with a compromised cardiovascular system and comorbidities including various cardiovascular diseases and hypertension may then become inflicted with acute respiratory distress syndrome and increased mortality. Statin can be given to the patient in the manufacturing field and office, where AR is "little and needs little in intensive care. In addition, in another study, the continued use of statins in patients with COPD had to be cautious about intubation. In addition to its benefits in existing techniques in the technology used in practice, it can also prove new roles that can benefit and can be achieved from technologies derived from anti-inflammatory, anti-thrombodultic, immuno-thrombodultic and immuno-thrombodulatory and methods of sampling science. Still not explicitly applicable to the conversation, some hospital statins are therefore included in education from COVID-19 [2]. In addition, an analysis of in-hospital deaths in 8910 COVID-19 patients from Asia, Europe, and North America demonstrated a positive prognosis for statin use. At the same time, statins positively affect the endothelium under stress, since viral use increases the endothelial damaging rendering thrombotic value [4]. If one person has something else across the U.S. due to COVID-19 more than 10,000, from admission to use, other prior use, comorbid conditions, hospital and bear controlled more than 40% in the next and severely over 40. The result was associated with a greater than 25% risk of developing severe symptoms. The observations and teaching that statins were not considered as ingredients still indicate preliminary information [125-127].

Some research results show that the statin effect is not significant for COVID-19 when the comparative data of users and non-users are examined. This is mainly because statin users with COVID-19 disease are shown to have a greater baseline risk driven by older age and higher cardiovascular comorbidity burden. This could in theory hide the potential protective effect of statins in this particular subset of patients [128]. For this reason, multivariate analyzes can give more positive results than univariate analyzes. While it is known that there is a 30% reduction in fatal or severe COVID-19 infection according to multivariate meta-analyses; does not confirm a significant lack of protection in the data reported in the univariate meta-analysis among statin users [128,129].

Low-Density Lipoprotein (LDL); ApoB is a large

Tab. 1. Concentration of neopterin levels in some diseases.

Disease	Neopterin concentration in the patient	Neopterin concentration in the healthy/mild	P value
Behcet 's disease	111.27 ± 37.49 nmol/L	76.77 ± 38.27 nmol/L	P<.001
Psoriasis vulgaris	2.26 ± 1.92 ng/ml	1.19 ± 0.18 ng/ml	P=0.001
Dermatomyositis	IQR 13·9–35·2 nmol/l	IQR 2·9–5·6 nmol/l	P<0·001
Prostat cancer	0.71 AUC	0.75 AUC	P<0.001
Lung cancer	2.66-13.54 nmol/L	3.36-51.70 nmol/L	P=0.004
Brucellosis	79.07 ± 34.9 nmol/l	39.71 ± 23.4 nmol/l	P=0.002
Polycystic ovary syndrome	7.5-49.5 nmol/L	6.5-12.9 nmol/L	p<0.05
Breast cancer	1.2-12.0 nmol/L	0-23.6 nmol/L	P<.05
Graves' disease	5.7+/- 2.4	4.1+/- 1.7 4.0+/- 1.5	p<0.01
Gastrointestinal cancer	4.84 ± 0.74	1.57 ± 0.13	p<0.001
Thyroid diseases	7.14 ± 5.95 nmol/l	4.10 ± 1.70 nmol/l	p<0.0l
Renal carcinoma	7.09 +/- 1.99 nmol/litre	2.87+ 0.59 nmol/litre	P<0.05
Crohn's disease	302+/- 15 nmol/mol	163+/- 8 nmol/mol	P<0.001
Rheumatoid arthritis	11.46 ± 3.56 nmol/L	4.74 ± 1.98 nmol/L	P<0.0001

particulate molecule with a molecular weight of 2,000 kDa, consisting of triacylglycerol, free cholesterol, cholesteryl ester and phospholipid molecules. LDL, which contains 1600 cholesterol esters and 170 molecules of triglycerides in its core, consists of 700 phospholipid molecules and 600 cholesterol molecules in the surrounding layer. In its outer layer, there is apo B100 molecule. Half of LDL fatty acids consist of Polyunsaturated Fatty Acids (PUFA). PUFAs are protected from oxidation by antioxidants. Oxidized LDL (ox-LDL) exposed to oxidative stress and inflammation is seen in various diseases resulting in the presence of oxidative stress and reactive oxygen derivatives. High concentration of ox-LDL initiates cellular changes resulting in cell death; ROS formation, caspase, protein kinase activation, calcium homeostasis and proapoptotic/ antiapoptotic gene expression change [130]. NPT a pyrazinopyrimidine compound, is used as a very popular biomarker, especially in important pathologies in which cellular immune mechanisms are activated [131]. Since high NPT production is associated with increased production of Reactive Oxygen Species (ROS) and low serum antioxidant concentrations such as alpha-tocopherol, NPT can also be considered as a marker of ROS generated by the active cellular immune system. Therefore, NPT measurements can predict not only the extent of cellular immune activation, but also the extent of oxidative stress [132,168].

Hypochlorous acid (HOCl), an important inorganic bactericidal compound of innate immunity, is effective against a wide variety of microorganisms [133]. Stabilized at pH 3.5–5.5, HOCl is a weak acid that interacts with structural proteins or viral material to inactivate microorganisms [134]. HOCl is known as the most potent oxidant produced by neutrophils and is a potent microbicidal agent within these cells. Because of its chemical nature, HOCl has never been used as a medicine to treat infection. A remarkable feature of the immune system is its ability to initiate an effective response against invading pathogens by deploying a group of highly reactive chemicals, including oxidized halogens, oxidizing radicals, and single oxygen (Figure 1) [135]. HOCl is currently a disinfectant approved under different brands by the US Environmental Protection Agency for SARS-CoV-2. HOCl, which interacts with structural proteins such as the capsid or surface compounds of viruses, lipid envelope and DNA/RNA materials, HOCl with concentrations as low as 20 ppm has been found to be effective in disinfecting surfaces including porous rayon. In addition, it is not toxic to humans and has been found to be a disinfectant 80-200 times more effective than standard disinfection procedures [134].

The current data show that HOCl oxidizes NH2 to form NPT. NH2 is described as an antioxidant and a powerful radical scavenger. NPT remains stable at neutral pH, while NH2 is oxidized to 7, 8-dihydroxyantopterine in oxygen-saturated solution. Oxidizing agents in acidic solution, for example MnO2 or I2, leave the NH2 side chain unaffected and selectively oxidize the 7, 8-dihydro structure of NH2 to form NPT.

The mechanism of oxidation remains unclear. The reaction mixture not only has a balance of hypochlorite and free acid, but also has oxidizing properties of dissolved chlorine (Cl2) resulting from the decomposition of HOCl. However, when HOCl content is quantified spectrophotometrically, the oxidative potential of Cl is not included. This may explain why the amount of NPT formed exceeds the amount of HOCl administered. Since

Tab. 2. Some studies on neopterin.

Year	Number of patients	Finding
2020	34(mild diseases, N=15) (Sever diseases, N=19)	All of the severe cases had elevated neopterin concentrations (>9.1 nmol/L).
2020	103(mild diseases, N=93) (Sever diseases, N=10)	Serum neopterin levels were higher in severe COVID-19 disease patients than those in mild cases.
2020	115	Elevated neopterin levels were significantly associated with disease severity.
2020	6	CSF neopterin (median 43.0 nmol/L) was increased in all patients.

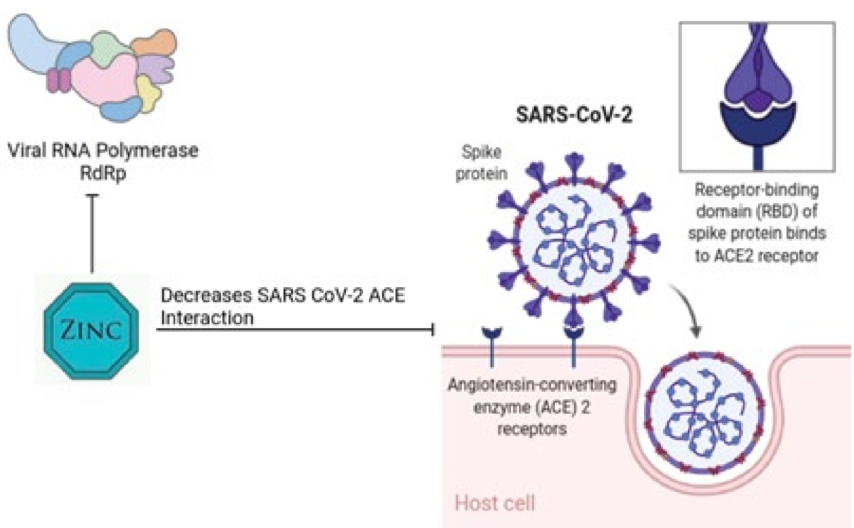


Fig. 3. Zn can inhibit ACE2 expression by reducing of sirtuin1 Also Zn is able to suppress Replication of virus genomic and Translation of virus protein.

the quantification of NPT by fluorescence detection is selective and sensitive in one study, the rate of formation of NPT was monitored. NH2 is a non-fluorescent compound. The UV/Vis signal is an overlap of NH2 and NPT, and apart from electrochemical detection, no suitable HPLC method is known to separate these two compounds. It was also concluded that alternative quantification of NH2 after iodine oxidation after HOCl oxidation is impossible due to additional products formed. NPT is thought to act instead as a pro-oxidant, depending on conditions such as the nature of the oxidant, pH, or absence/presence of iron ions. Evidence is provided for the first time that reactive species can act on the NPT/NH2 ratio independently, thereby altering the redox modulatory properties of these pteridines. A dynamic ratio has been noted in conformity with the idea that pteridines are redox modulators rather than a static model of stable NPT/NH2 excretion. HOCl has been shown to increase the oxidative potential in the local microenvironment by increasing the NPT-mediated prooxidative potency and decreasing the antioxidative capacity of NH2. A conversion of the NPT/NH2 ratio was also found, with NPT concentrations sometimes found higher than NH2 concentrations compared to NH2 alone [135].

In recent years, COPD has been defined as an inflammatory disease with systemic consequences. COPD may also predispose individuals to the presence of other comorbidities, such as arterial hypertension, diabetes, and cardiovascular disease, which can potentially affect the outcome and severity of COPD. Therefore, the coexistence of associated diseases is common and may affect COPD disease progression and prognosis. According to the stated experience, higher NPT levels have been found in patients with cardiac and renal diseases, and these can be expressed as reflecting attacks of viral etiology [136]. It is supported by data that mortality and NPT after pneumonia are risk factors for respiratory tract infection and cardiovascular events. The first line of these observations may have clinical implications when assessing COPD severity and exacerbation [137].

NPT can be potentially expressed as a promising inflammatory mediator. It has been reported to act as a mediator of cell immunity against intracellular pathogens such as viruses, parasites and intracellular bacteria. It is widely accepted that COPD is associated with an increased systemic inflammatory response compared to controls, and this inflammatory response is reported in patients with stable COPD at higher levels of NPT when compared to control groups [138]. NPT is released from monocytic cells after stimulation with interferon gamma (IFN-γ) as a well-established biomarker of cellular activation. IFN-γ also promotes the degradation of tryptophan in the kynurenine pathway, which produces several neuroreactive metabolites, including quinolic acid, which may contribute towards neurological disorders [139]. Briefly, NPT is an oxidized form of dihydroneopterin during antioxidant reactions in which high levels of NPT in serum and other biological fluids are associated with high production of ROS and induction of oxidative stress (OS) during intense activation of cellular immunity [73]. High concentrations of NPT have been reported to be detected in every neuro-COVID patient studied according to studies [140]. NPT was elevated in cerebrospinal fluid samples of patients with COVID-19 and neurological abnormalities [139]. Also, the serum level of NPT can distinguish viral infection of the lower respiratory tract from a bacterial one, it can be noted a twofold higher increase in its viral state compared to bacterial infection. In brain damage caused by COVID-19, NPT levels were found to be high in cerebrospinal fluid (CSF) from patients [73].

It is accepted that uveitis patients with co-morbidities such as diabetes mellitus, hypertension and cardiovascular disease are at higher risk if they develop COVID-19. Asymptomatic retinal complications of SARS-CoV-2 infection have also been reported, but the prevalence is unknown. Research currently points to studies describing uveitis, retinitis, retinal vasculitis, and optic disc involvement in animals after coronavirus infection [141]. No reports of COVID-19-associated uveitis have been published to date, but thin retinal microvascular pathology and small lesions have been described in the ganglion cell and inner plexiform layers [142].

NPT plasma level has been measured in many autoimmune diseases. Due to the overstimulation of monocyte/macrophage cells by T lymphocytes in patients with RA, NPT may be an indicator of both cellular and innate immune activity in these patients. Higher NPT concentrations have been shown to be associated with increased cardiovascular risk in the general population. As is known, cardiovascular disorders are one of the most important causes of mortality in patients with RA. Studies have shown that NPT levels increase with age in both RA and control groups; In addition, it was found that RA patients increased with disease onset age and disease duration. The reason for higher NPT levels in male RA patients is not clear, but it can be stated here that higher anti-CCP antibody contributes to increased inflammation and NPT levels in these patients [143,144].

Association of Neopterin with symptoms in COVID-19 patients: NPT is an independent prognostic factor for COVID-19 sever ty [56]. It appears in the blood before the onset of clinical symptoms, rises in acute stages of viral infection, and is linked to severe dyspnea, a more extended hospitalization period, and other complications [73]. While Covid19 is generally identified as pulmonary infection, it brings disturbances to various organ systems in the body with their related symptoms. The association of non-pulmonary clinical signs and symptoms with NPT in patients with COVID-19 has not been thoroughly investigated. Some scarce studies reported the probable association of NPT in body fluids with gastrointestinal, neurologic, and renal signs and symptoms [73].

The pooled prevalence of gastrointestinal (GI) symptoms (including nausea, vomiting, diarrhea, abdominal pain, and anorexia) in patients with confirmed COVID-19 was 18% with diarrhea being the most significant [145] Some patients show gastrointestinal symptoms (e.g., nausea and diarrhea) as an initial manifestation of the disease [146] and patients with a severe form were more likely to experience GI symptoms.

Fecal NPT is assumed as a surrogate of cellular viral immune response and may be an indicator of intestinal inflammation in COVID-19 patients [10, 147]. SARS-CoV-2 can impose injuries to the gut mucosa by its ability to infect and replicate in the enterocytes. Intestinal epithelial cells express two critical proteins for SARS-CoV-2 cell entry, simultaneously: ACE2, and transmembrane serine protease [148], make the oral-fecal route a potential route for infection [147].

In a study on 37 hospitalized COVID-19 patients (Non-ICU setting) with a median age of 62 years and a high level of C-reactive protein (evidence for systemic inflammation), fecal NPT values were elevated (more than 614.7 ng/g) in comparison with control healthy subjects. Seventeen patients who had GI symptoms (diarrhea and/or nausea and/or vomiting) demonstrated even higher NPT values in the stool. This subgroup of patients was also found to have elevated serum C-reactive protein concentration and body temperature on the day of stool sampling compared with the low NPT group, suggesting the presence of systemic inflammation. The fecal NPT did not significantly differ according to the type of the GI sign or symptoms. The infected cells (including enterocytes) release selected cytokines and chemokines that induce intestinal inflammation and underlie GI symptoms [147].

Considering that the results of this study are based on a limited sample size, and SARS-COV-2 RNA was confirmed in only 35% of the patients, we should sound a note of caution about such findings. As SARS-CoV-2 infection is closely related to previous SARS in several aspects, it is assumed that SARS-CoV-2 RNA may have an ability to spread into the CNS via the membrane-bound ACE2, resulting in clinical neurological signs and symptoms [141]

NPT is an informative biomarker of central nervous system immune activation in various viral infectious settings, including HIV-1 infection and influenza [148, 152]. NPT level in the serum and cerebrospinal fluid (CSF) increased in 6 patients with moderate to severe COVID-19 infection who also presented neurological disorders. Neurologic symptoms were encephalopathy, extreme fatigue, memory loss, personality changes, moderate neck stiffness, photophobia, somnolence, dysgeusia, disorientation [141]. High CSF NPT may be inspired by a forceful systemic inflammatory response induced by SARS-CoV-2 infection [149]. This observation may outline the COVID-19-induced CSF inflammation and brain injury [73,141]. There is still considerable ambiguity about the pathophysiological basis of profound elev ated CSF NPT in COVID-19 infection and its use as a prognostic factor for neurological symptom development [149].

All we know about the role of NPT in COVID-19-induced acute kidney injury are in the light of studies evaluating NPT in severe COVID-19 setting. The severe form may be accompanied by acute kidney injury in about half of the cases [150]. Even though it is reported that elevated serum creatinine and blood urea concentrations are associated with high serum NPT, some other studies failed to provide a meaningful correlation in severe COVID-19 cases [76]. Many studies believed that high serum NPT concentrations related to the severity of the infection, deteriorated renal function, and higher temperature upon hospital admission [56]. Therefore, future studies on the current topic are required to elucidate the exact role of NPT in the clinical symptoms of patients with COVID-19 infection.

Measurement of Neopterin in COVID-19: NPT is one of the measurable prognostic substances which are produced by the immune system in the human. Recently, due to its cost- effective and easily detectable features, NPT has become a very important marker for usage in the clinic to predict disease progression. Because the high amount of NPT mirrors extremely activated cellular immunity, It has been used for the diagnosis of several diseases and their treatment selections [10, 151]. Since the 19th-century [14], NPT levels were detected and often used as a progression prediction marker for the diseases. Especially, In infectious diseases like bacterial parasitic and viral, detection of NPT levels became highly useful in terms of the monitoring activation of cellular immunity [153,154]. Currently, we are facing the COVID-19 viral infection and useful information about the disease and its progression has become very important. Several articles showed that measuring NPT levels can guide to observing the infection degree of COVID-19 prognosis.

One of the first studies for detecting the usefulness of NPT levels in COVID-19, Ozer et al. showed that the NPT levels found 46 nmol/L in patients who have coronavirus and this result pointed to the fact that the patients have COVID-19 NPT levels much higher than the people have no viral infection or have mild COVID-19 [56]. Additionally, other studies support these findings with similar results. For instance, Bellmann-Weiler and her colleagues used 115 patients' serum samples to measure NPT levels and they found that the NPT levels were similar to the first study which is above 40 nmol/L. Moreover, they concluded that the high amount of NPT [45 nmol/L] can be useful for the early prediction of high- risk group COVID-19 patients [77]. In clinic usage, NPT has mostly been detected in serum and urine [155]. Also, shown that it could be measured in the cerebrospinal fluid [156] and saliva [157] as well and besides this, some studies detected NPT in the synovial fluid [158] and pancreatic secretion [159-169]. Measurement of NPT is immensely simple in body samples and it can be made with several techniques. Table 4 represents all studies that were measure and point to the importance of NPT levels in the COVID-19. According to the table, ELISA has been the first choice for measuring the levels of NPT. ELISA is one of the labeled immunoassays and simply this technique uses the antibody-antigen interactions as an immunocomplex to detect the desired molecule in the sample.

Generally, a particular molecule binds to its antibody that contains special binding sites for its specific antigen. Also, the antibodies can be detected with the ELISA tests [170]. For the detection and measurement of NPT, the ELISA test contains rabbit-anti-NPT that is antibody binding sites for both sample NPT and enzyme-attached antigen. These antigen-antibody complexes then bind to the specific surface of the test for detection. Due to its flexibility, the ELISA test can apply and design for various diseases. The test uses up to 96 well plates and this allows one to do look at the multiple samples at the same time [162]. Thus a lot of samples can observe and the results can be obtained in a little time. Also, its usage is very simple then doesn't need special learning. The other advantageous usage of ELISA is its sensitivity and specificity [163]. With a small sample size, desired substances can be detected through specific antigen-antibody interactions. Additionally, the test has some drawbacks. While applying fluid samples it doesn't need pretreatment but non- fluid samples like stool need be pretreatment for the test. One of the studies represent in the Table 4 used the stool sample to measure NPT levels. They made some dilution processes before the applying test on the samples. Then they used the supernatant of the samples for test respectively [147]. There are other potential methods that measure and detect NPT. Lately, their usage did not present in COVID-19 infection but they used it for measuring NPT levels in several diseases and infections. The technique RIA is one of the labeled immunoassays [163]. Different from the ELISA, the RIA technique uses radioactive isotopes rather than enzymes as a label. Although the procedure is similar to ELISA, RIA has some differences and drawbacks [160] such as, in the RIA test due to its labeled radioactive isotopes, the trained people need for the preparation and does the experiment. Also, the storage and disposal of radioactive substances require special procedures that must do carefully. Most importantly, if these isotopes are not disposed of in the right way, they can cause radiation hazardous. Notwithstanding it has some difficulties, The RIA test is successful for the detection of biomarkers. S´anchez-Regan˜a et al. concluded that the determination of NPT could be done with the RIA and results showed that the RIA is highly accurate [161].

Another potentially used technique for the measurement of NPT is HPLC that is uses the liquid sample mixture, several pumps, and columns to specify biological substances. Additionally, the detector of the HPLC system is enabled to determine substances quantitatively [163]. Although the use of High-Pressure Liquid Chromatography [HPLC] for detecting fluorimetric signals has been widely used, many of the procedures described have practical limitations. This is mainly due to the difficulty in detecting contaminant peaks in blood samples. Carru et al. used the longer column in their experiment. In these conditions, the NPT concentration achieved with phosphate buffer was totally resolved from impurities. The concentration achieved with water as eluents were also decreased by about 20% wing to several features of NPT, the measurement techniques should choose carefully. The specificity of ELISA enables it to detect NPT not only in serum samples but also in urine and other body materials. Conversely to ELISA, the HPLC method should be used to detect NPT, mostly in urine samples in terms of being NPT levels very low in the serum rather than urine [164]. Also, the high fluorescent feature makes NPT easily detectable in the urine samples by HPLC. Furthermore found that the NPT detection with RIA was uncertain in the urine samples [18]. Therefore they conclude that the RIA should just be used for the measurement of NPT in serum samples. Recently, biosensors have become promising devices for the measurement of NPT. Also, with the fastly growing human population, the demand for fast and accurate point of care biosensor devices increased. Biosensors are highly useful analytic devices with several good features such as portability, simplicity, and the best-desired feature its specificity [164]. As a chemosensor, Sharma et al. used the molecular imprinting method that generates an artificially synthesized receptor polymer for the NPT. They showed that their molecularly imprinted film was sensitive and also give a chance to differentiate NPT analogs from samples [165,173]. The specification of progression of COVID-19 patients is highly possible through the measurement of NPT levels. Therefore, the demand for improved measurement techniques for NPT has become important for the characterization of the disease severity and infectious degrees of patients who have the SARS COV-2 virus.

Prognostic value of Neopterin in COVID-19: There is incomplete evidence about prognostic biomarkers that could ad- vantage physicians to categorize COVID-19 cases that are likely to improve a poor outcome. In COVID-19 patients, it is recognized that overexcited inflammation and coagulopathy are related with death in patients and disease severity. The results showed that compared with mild cases of COVID-19, high levels of circulating cytokines, profound lymphopenia, and significant infiltration of mononuclear cells into the lungs and other organs occur in very severe inflammatory conditions [166]. High rates of circulating biomarker such as cytokines were described in severe COVID-19 patients. The serum rates of the immune motivation NPT have revealed to be of predictive value in patients with SARS-CoV-1 [15, 164] and Early studies suggest that serum NPT may be useful in classifying SARS-CoV-2 patients [56, 76]. It has also been shown that high levels of cytokines associated with macrophage activation, including IFN-, are present in patients with SARS-CoV-2 [7]. Also proved based on different reports that raised kynurenine/ tryptophan ratio are usual in COVID-19 and associate narrowly with elevated NPT levels, and like NPT also kynurenine/ tryptophan is related with undesirable results [76]. The same observations have been made in other infections, such as HIV-1 [14]. Overall, the IFN-induced immune response to viral in- fections may lead to increased NPT concentrations as well as increased tryptophan degradation and increased kynurenine to tryptophan ratio [13]. According to the different results of the studies, various scenarios have been presented about the role of neoprene and how it increases in people with COVID-19. Most are related to the role of antioxidants in controlling ROS [14, 167]. These include a variety of vitamins, especially vitamin B, so that a decrease in vitamin B levels is associated with an increase in homocysteine and NPT levels in people with the disease [164, 161,168]. It is also one of the possible mechanisms related to iron levels. If the amount of inflammatory factors in the blood increases, iron may be more likely to be stored [ferritin], which the results of some studies prove the same, and the amount of NPT is associated with an increase in ferritin [162, 163, 166, 170]. NPT formed by macrophage cells on motivation with IFN-, which is a main factor in the antiviral immune reaction, therefore it can be used to forecast the severity of disease in COVID-19 cases [56]. In patients with infection diseases, improved NPT levels were known in body fluid samples like saliva, urine, blood and CSF, e.g., during cytokine therapies but also in diseases that are related with stimulation of the T-helper-1 immune cells such as autoimmune pathologies, mycobacterial infections and numerous types of tumor cells and with viral infections including SARS-CoV-1 and HIV-1 and recently also in COVID-19 with SARS-CoV-2 [15,62,78,165,172]. The results of studies have shown that serum levels of NPT are closely related to the severity of COVID-19, with levels starting to rise from the 3-4 day of SARS-CoV-2 infection, being correlated with severe dyspnea, Take a long stay hospital and other complications [73]. The other measurement of NPT levels is able to prepare valuable data in patients with current COVID-19 disease. Higher NPT levels emerge to describe to an epidemic and widespread infection and thus to an improved infectious condition, whereas a normal or very low NPT is revealing for quiet infection lacking or existence of fewer active infection [76]. Nevertheless, further studies are needed to confirm this conclusion, which is still in the early stages.

Challenges and future perspectives: COVID-19 is considered as a cytokine storm and affects multi-organ inflammatory infection. The mortality rate of this pulmonary and systemic injury is ascertained by the severity of inflammation and coagulation. Due to this, prevention, early diagnosis in corporation with effective therapeutic interventions is urgently needed for saving lives. NPT is an early critical marker for the progression and severity of immune disease or may be useful together with the several inflammatory markers to suggest a diagnosis of SARS-CoV-2. It is also postulated as a sensitive marker of oxidative stress which could decrease inflammation through suppressing NF-B signaling and NLRP3 inflammasomes. Other studies indicated that, NPT contribute with high produc- tion of ROS and NF-B, which lead to pro-inflammatory gene rise including inducible nitric oxide synthase [iNOS] and trigger inflammatory processes. Furthermore, we need to consider that the elevated level of NPT may be related to other pathological conditions or inflammation- related diseases not only confined to COVID-19, such as RA, nephropathy, neuropsychiatric anomalies or cancers. Within this view, further studies are required to address the exact role of NPT in the clinical symptoms of patients with COVID-19 infection. Also, It is important to highlight that among the knowledge gaps of COVID-19 there are diagnostic errors with laboratory testing as well as their interpretation in patient management. While, NPT appears in the blood before the onset of clinical symptoms; it considered as an independent prognostic factor for COVID-19 severity. However, what appears to issue from this evaluation is that NPT values have significantly enhanced in individuals with severe SARS-CoV-2 infection in comparison with those with milder forms of the disease. Therefore, it could be logical to assume immediate measurement of cellular immune activation marker namely NPT in patients and subsequently a longitudinal monitoring, so as to identify a subgroup of patients with progressive inflammatory situation.

CONCLUSION

In conclusion, NPT level have a significant correlation with the severity of COVID-19 and can be considered as a macrophage activation and sensitive indicator to predict disease risk. Further studies should also be planned to clarify whether targeting of NPT in SARS-CoV-2 infection may be critical in the early assessment of disease progression and prognosis of infected patients.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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