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Research Article / Araştırma

Comparison of alternative acute phase reactants in the evaluation of the prognosis of COVID-19 patients

COVID-19 hastalarının prognozunu değerlendirmede alternatif akut faz reaktanlarının karşılaştırılması

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ABSTRACT

Aim: Acute phase reactants (APR) and their release pattern is important in cytokine storm related with poor prognosis in COVID-19 patients. The cytokine storm is basically caused by interleukin-6 (IL-6). However, a variety of APRs are thought to be related to disease severity. The present study is focused on evaluation of alternative acute phase reactants in COVID-19 patients. **Materials and Methods:** 121 participants were included in the study. They were divided in to 3 groups as IL-6 level < 35 pg/ml (group 1) , IL-6 level > 35 pg/mL (group 2) , and healthy controls (group 3) . Levels of altenatice APRs neopterin, adenosine deaminase (ADA) and Chitotriosidase were evaluated in study groups together with routinely studied inflammation markers. **Results**: Neopterin values were significantly different in all study groups. Chitotriosidase levels were similar bewteen group 1 and group 2 while there was a statistically significant difference between group 1 and group 3, group 2 and group 3 and also a difference in comparison of all groups together. ADA levels were only significantly different between group 1 and group 3. Among the study parameters, neopterin showed moderate correlation wtih IL-6. Neopterin also showed week moderate correlations with NLR and fibrinogen. **Conclusion**: Neopterin can be a candidate APR and a prognostic marker for COVID-19. It can can be accepted as a marker of poor prognosis, lung damage, and high morbidity in COVID-19, alongside IL-6.

ÖZ

Amaç: COVID-19 hastalarında kötü prognozla ilişkili sitokin fırtınasında akut faz reaktanları (APR) ve bunların salım modeli önemlidir. Sitokin fırtınasına temel olarak interlökin-6 (IL-6) neden olur. Bununla birlikte, çeşitli APR'lerin hastalık şiddeti ile ilişkili olduğu düşünülmektedir. Bu çalışma, COVID-19 hastalarında alternatif akut faz reaktanlarının değerlendirilmesine odaklanmıştır. **Gereç ve Yöntem:** Çalışmaya 121 katılımcı dahil edildi. IL-6 düzeyi < 35 pg/ml (grup 1), IL-6 düzeyi > 35 pg/mL (grup 2) ve sağlıklı kontroller (grup 3) olmak üzere 3 gruba ayrıldı. Altenatice APRs neopterin, adenozin deaminaz (ADA) ve Chitotriosidase seviyeleri rutin olarak çalışılan inflamasyon belirteçleri ile birlikte çalışma gruplarında değerlendirildi. **Bulgular**: Neopterin değerleri tüm çalışma gruplarında anlamlı olarak farklıydı. Kitotriosidaz düzeyleri grup 1 ve grup 2 arasında benzer iken, grup 1 ile grup 3, grup 2 ile grup 3 arasında istatistiksel olarak anlamlı bir fark ve ayrıca tüm grupların bir arada karşılaştırılmasında fark vardı. ADA seviyeleri sadece grup 1 ve grup 3 arasında anlamlı olarak farklıydı. Çalışma parametreleri arasında neopterin, IL-6 ile orta derecede korelasyon gösterdi. Neopterin ayrıca NLR ve fibrinojen ile haftalık orta düzeyde korelasyonlar gösterdi. **Sonuç**: Neopterin, COVID-19 için aday bir APR ve prognostik bir belirteç olabilir. IL-6 ile birlikte COVID-19'da kötü prognoz, akciğer hasarı ve yüksek morbidite belirteci olarak kabul edilebilir.

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Anahtar Kelimeler: COVID-19, Akut Faz Reaktanları, Neopterin, Adenozin Deaminaz, Kitotriosidaz

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INTRODUCTION

COVID-19, caused by SARS-CoV2 virus, is a mortal disease which has caused a global pandemic. The virus infects the lower respiratory tract and causes pneumonia in patients with symptoms as in SARS infection, but still becomes a fatal disease of hyperinflammation and respiratory failure (1). In response to infection, the liver synthesizes large amounts of acute phase proteins (APP). The acute phase response is a reaction triggered by impaired homeostasis caused by various changes in the body (2).

Acute respiratory distress syndrome (ARDS) is a cause of mortality in COVID-19 patients (3). One of the key elements of ARDS is cytokine storm, causing an exeggerrated systemic inflammation with the release of proinflammatory cytokines from immune modulator cells. Cytokine storm causes a severe inflammatory immune response which contributes to ARDS, multi-organ failure and eventual death in SARS-CoV-2 cases (4). COVID-19 disease has been associated with high levels of acute phase reactants that rise in severe hyperinflammation triggered by the cytokine storm. The inflammatory response is critical in disease pathogenesis and the cytokine storm causes poor prognosis in COVID-19 (5). For this reason, acute phase reactants have an important role in diagnosis and follow-up of Covid-19 patients.

CRP, Fibrinogen, ferritin, procalcitonin, D-Dimer and Neutrophile/lymphocyte raito (NLR) are routinely used inflammatory markers in COVID-19 patients. Besides these, Interleukin-6 (IL-6) has come to the front in both progression and treatment in COVID-19 patients. (IL-6) is a proinflammatory and multifunctional cytokine. It triggers antibody production for secondary immune response and elevates the synthesis of APPs like C-reactive protein (CRP) and fibrinogen. This makes IL-6 a prominent cytokine especially on infected mucosa. (6,7). Besides this, a positive correlation between elevated IL-6 levels and respiratory dysfunction was detected in COVID-19 patients, especially in those with advanced stage lung dysfunction in, which also tirggers cytokine storm, a mortal medical situation (8). There are seevral publications which use IL-6 > 35 pg/mL as the cut-off for risk of mortality and admission to the intensive care unit (ICU) in COVID-19 patients (9,10).

Adenosine deaminase (ADA) is an enzyme that functions in the metabolism of adenine nucleotides. This enzyme plays an important role in lymphocyte and monocyte maturation and activation. Therefore, ADA can be used as a biomarker of cellular immune response (11). Lymphocytopenia is basically seen in ADA deficiency, suggesting that ADA has a critical role in lymphocyte proliferation (12). As is known, COVID-19 disease is a viral disease that acts on T lymphocytes; It is characterized by pulmonary infiltration and thrombus formation. In this context, we believe that the determination of ADA level in patients can be related to the prognosis and severity of disease.

Neopterin is included cellular immune system and is secreted by macrophages, monocytes, and dendritic cells. Neopterin indicates proinflammation and increased oxidative stress (13,14). Neopterin is seen as a sensitive indicator of T lymphocyte-macrophage interaction (15). During acute viral infections, increased levels of neopterin was observed, which is associated with disease activity. Neopterin elevations have been detected in infections with hepatitis viruses, Epstein-Barr, measles, mumps, varicella, rubella, and influenza viruses (16). Up to date, there is no reported study to measure neopterin level in COVID-19 disease.

Chitotriosidase has also been shown to be expressed in various cells of the immune response such as neutrophils, osteoclasts, and Kuppfer cells. In development of acute or chronic inflammation, the activity of chitotriosidase increases greatly (17). Evidence suggests important roles of this enzyme in host immunity, for it's high concentration in anatomical regions like lungs and gut where there is sustained exposure to microorganisms (18). The involvement of COVID-19 disease at the cellular level has not been fully understood, and the fact that chitotriosidase will be among the markers thought to be associated with the course of infection may shed light on disease progression and the formation of different treatment approaches.

It has been a matter of curiosity how the acute phase reactants described above change in Covid-19 patients, who progress with lung inflammation, coagulation disorders during the disease, and often accompanied by bacterial inflammation in addition to viral infection. The aim of our present study is to evaluate the levels of ADA, neopterin and chitotriosidase together, with routine inflammation markers and IL-6 to show the possible roles of these biomarkers on disease prognosis. To the best of our knowledge, there has been no study investigating this test profile together in Covid-19 patients.

MATERIALS AND METHODS

The study was approved by the local ethics committee by the approval number (2021-11) and conducted according to the Decleration of Helsinki. A written informed consent was obtained from all participants.

Study population

121 subjects were included in the study and 3 study groups were gathered accordingly:

- PCR-positive COVID-19 patients with IL-6 levels ≤ 35 pg/mL (n = 45)
- PCR-positive COVID-19 patients with IL-6 levels > 35 pg/mL (n = 45)
- PCR-negative control subjects (n=31)

Sample collection and preparation

Venous blood samples were collected from all participants into serum tubes. Samples were centrifuged at 3500 rpm for 15 minutes and seperated sera were aliquoted into eppendorf tubes and stored at -80 °C until the day of analysis.

Analysis of samples

IL-6 levels were measured with Beckman Coulter Access autoanalyzer by chemiluminescent immunoassay method. CRP levels were detected with Beckman Coulter AU5800 autoanalyzer by immune-turibidimetric method. D-dimer and Fibrinogen were measured with Sysmex CS-2500 autoanalyzer by particle-enhanced immunoturbidimetric assay. NLR was dirven from complete blood count carried out by Beckman Coulter DxH 900 analyzer using VCS principle. Ferritin levels were masured with Beckman Coulter DxI 600 analyzer using immune chemiluminescence method.

Chitotriosidase levels were detected with optimized flourometric method first defined by Guo, 1995. ADA levels were measured by spectrophotometric method defined by Guisti, 1974. Neopterin levels were detected by High Performance Liquid Chromatography (HPLC) in our laboratories.

Statistical analysis

All statistical analyses were carried out with IBM SPSS 22.0 programme. Normality test was performed with Shapiro-Wilk test. Parametric data were expressed as mean±SD, and nonparametric data were expressed as median (min.-max.). Bonferoni and Kruskal-Wallis tests were used when comparing the data of the three groups, and the results with $p<0.017$ were considered significant. T-Test and Mann-Whitney U test were used for pairwise group comparisons. Correlation analysis was performed between the parameters. $p<0.05$ was accapted as the level of statistical significance.

RESULTS

90 patients and 31 control group individuals were included in the study. Patient group was divided in to two, according to IL-6 levels at admission. No statistically significant difference was found between age and gender distribution of the study groups. Study parameters ADA, neopterin and chitotirosidase were compared between three groups. Data is summarized in Table 1. Neopterin values were significantly different in all three study groups. Chitotriosidase levels were similar bewteen group 1 and group 2 while there was a statistically significant difference between group 1 and group 3, group 2 and group 3 and also a difference in comparison of all groups together. ADA levels were only significantly different between group 1 and group 3. All p values and comparisons ara summarized in the corresponding table.

We also compared the levels of routinely measured infection and sepsis parameters beween two patient groups. We did not measure these parameters in control group as these are routinely followed up in inpatient COVID clinics. All of the routinely studied parameters were significantly different between two study groups. The results are summarized in Table 2.

A correlation analysis was also done and significant results are indicated in Table 3. Among the study parameters, neopterin showed moderately signficant positive correlations with IL-6, NLR and fibrinogen (R and p values are given in Table 3).

DISCUSSION

SARS-CoV2 infection can be divided into 3 stages: I. Asymptomatic phase, in which the causative virus can or cannot be detected; II. Non-severe symptomatic phase with upper respiratory tract involvement; and III. A severe and fatal disease in the presence of hypoxia, and acute respiratory distress syndrome (ARDS) with ‘ground glass’ infiltration of the lung and high viral load (19). ARDS is the primary cause of mortality in COVID-19 disease like in SARS and MERS (3). Cytokine storm is a remarkable phenomenon in ARDS, which causes uncontrolled systemic inflammatory response by the release of proinflammatory cytokines and chemokines to the blood stream. This in turn triggers a severe inflammatory immune response that contributes to ARDS, multi-organ failure and eventual death in SARS-CoV-2 cases (4). COVID-19 disease has been associated with high levels of acute phase reactants that occur in severe hyperinflammation triggered by the cytokine storm. The inflammatory response plays a critical role in COVID-19 disease and cytokine storm increases the severity of disease (5). For this reason, acute phase reactants have an important place in the diagnosis and follow-up of Covid-19 patients. IL-6 has found to be the major cytonkine responsible from cytokine storm. So, in time; a classification of the severity of disease according

Table 1. Comparison of study parameters between groups

				p values			
Parameter	IL-6<35 (n=45)	IL-6>35 (n=45)	Control (n=31)	G1/G2	G1/G3	G2/G3	G1/G2/G3
Age(Years)	54.40±14.36	56.00±10.93	54.65±11.49	1.000	1.000	1.000	0.812
Gender (F/M)	24/21	22/23	15/16	1.000	1.000	1.000	0.887
Neopterin	2.78 (1.58-7.68)	4.59 (0.15-75.37)	1.76 (1.01-4.53)	0.006	0.001	0.001	<0.001
Chitotriosidase	175.75±94.62	175.32±94.53	89.24±60.85	1.000	<0.001	0.001	<0.001
ADA	22.32±37.41	12.12±6.24	8.82±9.85	0.139	0.048	1.000	0.041

p<0.05 is accepted as statistical signficance. Significant differences are repressented with boldtype. G1: IL-6<35, G2: IL-6>35, G3: Control

Table 2. Comparison of infection parameters between groups

Parameter	IL-6<35 (n=45)	IL-6>35 (n=45)	p değerleri
IL-6 (pg/mL)	8.32 (0.92-30.99)	117.91 (37.68-1624)	<0.001
CRP (mg/L)	18.95 (0.80-271.94)	135.15 (6.26-661.06)	<0.001
NLR	3.54 (0.85-80.75)	12.90 (1.10-122.88)	<0.001
D-Dimer (mg/L)	0.46 (0.20-10.57)	2.13 (0.32-13.49)	<0.001
Fibrinogen (mg/dL)	425.32±136.37	501.16±176.31	<0.001
Procalcitonin ng/mL)	0.070 (0.010-3.24)	0.914 (0.050-98.34)	<0.001
Ferritin (ng/mL)	200.60 (9.70-1500)	441.35 (59.70-1500)	0.002

p<0.05 is accepted as statistical signficance. Significant differences are repressented with boldtype.

Table 3. Correlation analyses between study parameters

		CRP	NLR	D-Dimer	Fibrinojen	Procalcitonin	Ferritin	Neopterin
IL-6	Corr. Coe.	0.685**	0.581**	0.674**	0.235*	0.729**	0.317**	0.308*
	p	<0.001	<0.001	<0.001	0.034	<0.001	0.003	0.012
CRP	Corr. Coe.		0.532**	0.565**	0.532**	0.771**	0.441**	
	p		<0.001	<0.001	<0.001	<0.001	<0.001	
NLR	Corr. Coe.			0.548**		0.592**	0.378**	0.340**
	p			<0.001		<0.001	0.001	0.007
D-Dimer	Corr. Coe.					0.622**	0.306**	
	p					<0.001	0.006	
Fibrinojen	Corr. Coe.							0.296*
	p							0.021
Procalcitonin	Corr. Coe.						0.482**	
	p						<0.001	
Chitotriosidase	Corr. Coe.							0.261*
	p							0.048
ADA	Corr. Coe.							0.304*
	p							0.013

**. Correlation is significant at the 0.01 level. *. Correlation is significant at the 0.05 level. Corr. Coe.: Correlation Coefficient

to IL-6 levels has been settled. It is now known that IL-6 production is increased by viral load, especially in poor prognosis of COVID-19 cases (20). As the disease progresses, CD4+ T lymphocytes are converted to pathogenic Th1 cells, and this in turn stimulates the release of granulocyte-macrophage CSF and other cytokines causing inflammation. Monocytes are also activated with higher IL-6 levels (21). We designed the present study by dividing the patient group into 2 by predetermined IL-6 cutoff levels.

We compared levels of the study parameters in 3 groups. We've found that neopterin levels were significantly different in all three groups. The values were lowest in the control group and highest in the group with IL-6 > 35 pg/mL. Chitotriosidase levels did not show a significant difference between two patient groups according to IL-6 levels. But there were significant differences between both group 1 and group 3 and group 2 and group 3 (data shown in Table 1). ADA levels were highest in Group 1 (Il< 35 pg/mL) while there was a decrease in Group 2. But the difference between ADA levels of Group 1 and Group 2 was not statistically significant. Only group 1 and group 3 showed significant difference in terms of ADA levels. There was also a non-significant difference of the ADA levels of three groups.

We can conclude that our findings can show the most meaningful change in neopterin levels. During acute viral infections, increased levels of neopterin have been observed, which is associated with disease activity. They also found that 96% of patients with viral Lower respiratory Tract Infections (LRTIs) had elevated serum neopterin levels (>10 nmol/L). Serum neopterin levels were monitored serially in patients with SARS virus and revealed that all patients studied (n = 129) had elevated neopterin levels on day 9 (22). COVID-19 disease is also included in the Corona virus group family that causes SARS type disease, and for our knowledge this is the first report that examined the neopterin level in COVID-19 disease. Neopterin levels determined in patients will be of great value in the severity of involvement and in the follow-up of LRTI and disease severity.

Chitotriosidase is expressed at lower levels in macrophages of healthy subjects. It has also been shown to be expressed in different cell types involved in immune response. During the development of inflammatory disorders, the enzymatic activity of chitotriosidase increases in a great manner (17). Recently, it has been reported that the enzyme plays a role in pathogenesis of pulmonary fibrosis, bronchial asthma, COPD and pulmonary infections. Lung infection progresses when there is inflammation in the lung caused by pathogenic microorganisms like bacteria, viruses, fungi and parasites. The role of chitotriosidase in infection has been evaluated (23,24). Evidence suggests that this enzyme has important roles in host immunity, as it is highly concentrated in anatomical regions like lungs and gut where there is sustained exposure to microorganisms (18). The involvement of COVID-19 disease at the cellular level has not been fully understood, and the fact that chitotriosidase will be among the markers thought to be associated with the course of infection may shed light on disease progression and the formation of different treatment approaches.our findings support that Chitotriosidase levels are elevated in COVID-19 patients. We did not find a significant difference when compared together with IL-6 levels. This can be explained with different mechanismss of action between IL-6 and chitotriosidase as they are released from different cell types. Besides this, these are only measurements in admission, there might have been a significant change in chitotriosidade levels in progressed disease over a prolonged follow-up.

ADA levels were only different among group 1 and group 3. No significant change was observed in the group with IL-6 levels > 35 pg/mL. In the context of inflammation, plasma ADA levels rise in response to increased adenosine levels. Cytokine production by neutrophils and monocytes was restored with a high plasma ADA concentration. ADA also has an effect on regulatory T lymphocyte function, inhibiting adenosine-mediated activation of these cells (25). Improvement in regulatory T lymphocyte formation is also promoted by deamination of adenosine and memory and effector T cells. As ADA activity is also high in monocytes and macrophages during intracellular infections caused by the release of adenosine, serum ADA is assumed to originate mostly from these cells (26, 27). As is known, COVID-19 disease is a viral disease that acts on T lymphocytes; It is characterized by pulmonary infiltration and thrombus formation. In this context, we believe that the determination of ADA level in patients may be related to the prognosis and severity of the disease. However in routine follow ups, ADA levels are both studied in serum and pleural fluids. And the most compromising ADA elevations are seen in pleural fluids rather than serum. In this study, we only studied serum specimens. May be in future studies, ADA levels in pleural fluids of COVID-19 patients will show a more correlated result with IL-6 levels and disease progression.

We also made correlation analyses with the routine inflammation parameters and our study parameters. There were strong positive correlations betwen IL-6 and procalcitonin, CRP, D-dimer and NLR (data shown in table 3). Among the study parameters, neopterin showed moderate correlation wtih IL-6. Neopterin also showed week moderate correlations with NLR and fibrinogen.

These results also make neopterin a promising biomarker of severe inflammation in COVID-19 patients.

Our study has sure some shortcomings. First of all, the study population is limited. Second of all, the methods we studied ADA, neopterin and chitotriosidase were manually registered. So there can be some inconveniences during measurement of parameters.

COVID-19 pandemic has affected millions of people worldwide. For now it seems to be under control but nwe mutations and alterations in the nature of SARS viruses keeps us alerted so that anytime the diseases symptoms may become severe and devastating again. So, search for new biomarkers of disease progression is still important. As conclusion, this study can be accepted as a preliminary work offering the evaluation of new and novel inflammatory markers in progression of COVID-19 disease and disease severity. And neopterin is seem to come to the front as a promising inflammatory biomarker.

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