RESEARCH ARTICLE / *Araştırma Makalesi*

Could Eosinophil Cationic Protein Be A Useful Biomarker In The Diagnosis of COVID-19?

Eozinofil Katyonik Protein, COVID-19 Tanısında Kullanışlı Bir Biyobelirteç Olabilir mi?

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Geliş Tarihi / Received : **05.11.2020** Kabul Tarihi / Accepted : **03.04.2021**

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(Sakarya Tıp Dergisi / ***Sakarya Med J*** **2021, 11(2-):328-336) DOI: 10.31832/smj.821617**

Abstract

Objective	Covid-19 disease is diagnosed by moleculer, serologic or radiological methods. However, these diagnostic methods cannot be reached everywhere or take too much time to result. So, we need for effective diagnosis of Covid-19 patients with simple and easy accessible laboratory biomarkers. Therefore, we investigated the diagnostic performance of Eosinophil Cationic Protein (ECP) in Covid-19.
Materials and Methods	Our study is a retrospective case-control study. The recorded clinical, laboratory and radiological data of 30 patients who were diagnosed with Covid-19, between 15 March and 15 June 2020, were compared with 30 healthy person by using appropriate statistical methods.
Results	Both patients and conrols included 10 (33.3%) females and 20 (66.6%) males with a mean age of 57.2 ± 15.46 and 60.07 ± 20.59 respectively. Eosinophil counts of the patients at admission were significantly lower than the controls (p <0.001). Eosinophil counts one week after admission were increased significantly compared to the admission levels (p= 0.004). ECP values of the patients one week after admission were significantly lower than controls and decreased compared to the admission values (p= 0.023, p< 0.001respectively). When the ECP values one week later were evaluated according to the ROC curve analysis, the control group whose cut off value was 88.67 ng / mL has been found to have 46.7% sensitivity, 93.3% specificity and AUC = 0.740 (p = 0.025; 95% CI: 0.558-0.922).
Conclusion	ECP test; can be useful in the rapid screening of patients with Covid-19-like symptoms but who are Covid-19 negative, and in separating them from Covid-19 patients.
Keywords	COVID-19; Diagnosis; ECP; Eosinopenia; Lymphopenia; Neutropenia

Öz

Amaç	*Covid-19 hastalığı moleküler, serolojik veya radyolojik yöntemlerle teşhis edilmektedir. Ancak, bu teşhis yöntemlerine her yerde ulaşılamaz veya sonuçlanması çok fazla zaman almaktadır. Bu nedenle Covid-19 hastalığının tanısında etkin, basit ve kolay erişilebilir laboratuvar biyobelirteçlerine ihtiyaç duyulmaktadır. Bu çalışmada Covid-19'da Eozinofil Katyonik Proteinin (ECT) tanı kriteri olarak kullanılabilirliği değerlendirilmiştir.*
Gereç ve Yöntemler	*Retrospektif olarak yapılan bu çalışmamıza 15 Mart-15 Haziran 2020 tarihleri arasında Covid-19 tanısı almış 30 olgu ile kontrol grubu olarak sağlıklı 30 olgu dahil edilmiştir. Tüm olguların demografik, klinik ve biyokimyasal parametreleri istatistiksel açıdan t-test ve ROC eğrisi analizleri ile değerlendirilmiştir.*
Bulgular	*Olguların %33,3'ü kadın ve %66,6'sını erkek olup, Covid-19 tanılı olguların yaş ortalaması 57,2 ± 15,46 iken, kontrol grubunun ise 60,07 ± 20,59'dur. Hastaların ilk tanı aldıklarındaki eozinofil sayılarının kontrol grubuna göre daha düşük olduğu(p<0,001) ve hastaneye yatışından bir hafta sonrasındaki eozinofil sayılarının ilk tanı aldıkları zamanki sayılarına göre anlamlı düzeyde arttığı gözlenmiştir (p=0,004). Ayrıca, hastaların hastaneye yatışından bir hafta sonra ECP değerlerinin kontrol grubuna kıyasla düşük olduğu (p=0,023) ve hastaneye yatışıyla azaldığı belirlenmiştir (p<0,001). Bir hafta sonraki ECP değerleri ROC eğrisi analizine göre değerlendirildiğinde cut off değeri 88,67 ng/mL olan kontrol grubunun %46,7 duyarlılık, %93,3 özgüllük ve AUC=0,740 (p=0,025; %95 CI: 0.558-0.922) değerine sahip olduğu bulunmuştur.*
Sonuç	*ECP testi; Covid-19 benzeri semptomları olan ancak Covid-19 negatif hastaların hızlı bir şekilde taranmasında ve Covid-19 hastalarından ayrılmasında faydalı olabileceği düşünülmektedir.*
Anahtar Kelimeler	*COVID-19; Tanı, ECP; Eozinopeni; Lenfopeni; Nötropeni*

INTRODUCTION

Covid-19 disease caused by coronavirus SARS-Cov2 has been officially named Coronavirus 2019 (COVID-19) by the World Health Organization (WHO) as of February 2020. It has turned into a pandemic that has caused 30 million cases and more than 1,000,000 casualties worldwide. Despite many studies, we still do not have very detailed information about how the virus emerged, how it caused such damage to the lungs of patients, and the long-term results of recovering patients.

Recently, eosinophils have been shown to have various other functions, such as immunoregulatory and antiviral effects, as well as powerful pro-inflammatory effects in many diseases such as Covid-19 disease. Due to the proinflammatory properties of eosinophils, serum levels have been observed to correlate with the clinical course of the disease. Eosinophils normally constitute 1-3% of the leukocytes in the circulation. Serum levels may change in some diseases such as Covid-19.[1,2] Eosinophils achieve their pro-inflammatory effects through granules in which cytotoxic proteins such as major basic protein, eosinophil peroxidase, eosinophil cationic protein (ECP) and eosinophil neurotoxin (EDN) are packaged, which are one of the basic molecules in the human body.[3]

Serum ECP levels were found to be increased in patients with chronic inflammatory respiratory disease compared to healthy controls.[4] Serum ECP values have also been reported to increase in acute bacterial and viral infections.[5] Although it can also be found in small amounts in neutrophils and monocytes, ECP is mainly caused by eosinophils and the pathogenesis of eosinophil-mediated clinical conditions, in particular Covid-19, is typically associated with ECP.[6]

Molecular (rt-PCR) and radiological (CT) diagnosis of patients with Covid-19 and similar symptoms take a long time and these two groups are very confused. Indicators that will enable a faster diagnosis are urgently needed. In this study, we aimed to investigate the diagnostic performance of ECP in Covid-19 disease in order to identify laboratory biomarkers that can be obtained simply and quickly to distinguish suspected COVID-19 patients from those with similar symptoms.

MATERIAL and METHODS

Our study is a retrospective case-control study. Clinical Research Ethics Committee of Tokat Gaziosmanpasa University Medical School approved our study with the number 20-KAEK-198 on 09.07.2020. Although the gold standard of diagnosis in Covid-19 is reverse transcriptase polymerase chain reaction (RT-PCR), we also included patients diagnosed with other diagnostic methods like serologic tests or computerized tomography (CT). Our patient group included 30 Covid-19 patients diagnosed with any of those diagnostic methods and admitted to our hospital between 15 March and 15 June 2020. They were compared with 30 healthy controls paired with patients in terms of age and gender. Patients; those who have undergone bypass operation within the last month, those with a history of metabolic, malignant and rheumatic diseases and pregnants were not included in the control group.

All data of the patients were obtained retrospectively from archived medical file materials. The collected data includes demographic information, clinical medical history, accompanying diseases, signs and symptoms, laboratory findings and radiological imaging findings. The data of the hospitalization day of the patient was determined as "Admission day data" of the study. The data obtained at the end of one week after hospitalization were determined as "first week data". Radiological images were classified as atypical, intermediate and typical apperance according to the compatiblity with the findings of Covid-19.

The samples to be used to determine serum ECP levels were obtained from samples sent to the central laboratory for routine biochemical analysis. No extra samples were taken from the patients for the purpose of the study

and no data were used except hospital and laboratory data processing records. Serum samples of the Covid-19 patient group were taken on hospital admission and one week later. Serum ECP levels in samples of both patient and control groups were measured by the commercial kit of YH Biosearch Laboratory Company, Shanghai, China, using the Enzyme Linked Immuno Sorbent Assay (ELISA) method in accordance with the kit package insert.

Descriptive analyzes give information about the general characteristics of the study groups. The data of continuous variables are as mean ± standard deviation; Data on categorical variables are given as n (%). When comparing the means of quantitative variables between groups, the Significance test of the Difference Between Two Means was used for the normally distributed variable, and the Mann Whitney U test was used for the non-normally distributed variable. For within-group comparison, the significance test of the difference between the two partners was used for the normally distributed variable, and the Wilcoxon test was used for the non-normally distributed variable. The chi-square test is used to evaluate whether there is a relationship between qualitative variables. Paired t test is used for relations between quantitative variables. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance of ECP in Covid-19 disease. When p counts were calculated less than 0.05, it was regarded statistically significant. Ready-made statistics software was used for calculations (SPSS 22.0 Chicago, IL, USA).

RESULTS

Both of our patient and control groups consisted of 10 (33.3%) women and 20 (66.6%) men with a mean ages of 57.2 ± 15.46 and 60.07 ± 20.59 respectively. PCR tests of 20 (66.6%) patients were positive, while that of 4 (13.3%) patients was negative. Serologic tests were positive in 24 (80%) patients. While the result of 24 (92.3%) patients who underwent computed tomography (CT) imaging was evaluated as compatible with the disease, 2 (6.7%) of the patient was evaluated as negative. On admission; 22 (73.3%), 22 (73.3%), 10 (33.3%) and 24 (80%) of the patients had fever, coughing, dispnea and malaise respectively. On admission; 26 (86.7%) of patients were clinically in mild-moderate and 4 (13.3%) of them were in severe condition. On mid-treatment; 22 (73.3%) of patients were clinically in mild-moderate and 8 (26.7%) of them were in severe condition. After a week of treatment; 24 (80.0%) of patients were clinically in mild-moderate and 6 (20.0%) of them were in severe condition. 4 (13.3%), 2 (6.7%), 6 (20.0%), 2 (6.7%) and 2 (6.7%) of the patients had chronic lung disease, Diabetes Mellitus, Hpertension, Cardio-Vascuar Disease, and malignant comorbidities, respectively. While 3 (10%) of the patients lost their lives during the treatment process, 27 (90%) patients recovered and discharged. The qualitative variable distributions according to the group are shown in Table 1.

In our study, ECP2 levels of one week after admission were significantly lower than those of controls and ECP2 levels of one week after admission were low compared to ECP1 levels of on admission (p=0.023 and p<0.001 respectively). When the ECP values one week later were evaluated according to the ROC curve analysis, the control group whose cut off value was 88.67 ng / mL has been found to have 46.7% sensitivity, 93.3% specificity and AUC = 0.740 (p = 0.025; 95% CI: 0.558-0.922). The eosinophil counts (EO1) of the patients on admission were found to be significantly lower than the controls (p <0.001). There was a significant increase in eosinophil levels (EO2) one week after admission, compared to the admission levels (EO1) (p= 0.004). A reliable demonstrator of eosinopenia, ratio of neutrophil to eosinophil on admission (NEU/EO1) was significantly higher than one week later (NEU/EO2) (p= 0.041). White Blood Cell (WBC1) counts on admission were significantly lower than controls (p=0.007). Neutrophil (NEU1) counts on admission and one week later (NEU2) were significantly lower than those of controls (p=0.009, p=0.041, respectively). Lymphocyte (LYM1) counts on admission and one week later (LYM2) were

Table I. Distribution of qualitative variables of patient group		
Variables		n (%)
Gender	Female	10(33,3)
	Male	20(66,7)
Discharge	Discharged	27(90.0)
	Passed Away	3(10.0)
Chronical Lung Disease (CLD)	None	0(86.7)
	Present	4(13.3)
Diabetes Mellitus (DM)	None	28(93,3)
	Present	2(6,7)
Hypertension (HT)	None	0(80.0)
	Present	6(20.0)
Cardio-Vascular Disease (CVD)	None	28(93,3)
	Present	2(6,7)
Malignancy	None	28(93,3)
	Present	2(6,7)
Serological Test Positivity	Negative	6(20.0)
	Positive	24(80.0)
Polimerase Chain Reaction (PCR)	Negative	4(13,3)
	Positive	20(66.6)
Computed Tomography (CT)	Incompatible	2(6,7)
	Compatible	24(92,3)
Clinical Condition (Admission)	Mild-Moderate	26(86,7)
	Critical-Severe	4(13,3)
Clinical Condition (Mid-Treatment)	Mild-Moderate	22(73,3)
	Critical-Severe	8(26,7)
Clinical Condition (After a week)	Mild-Moderate	24(80)
	Critical-Severe	6(20)
Fever	None	8(26,7)
	Present	22(73,3)
Dispnea	None	20(66.6)
	Present	10(33.3)
Coughing	None	8(26,7)
	Present	22(73.3)
Malaise	None	6(20.0)
	Present	24(80.0)
Data were expressed in numbers and percentages. Pearson's chi-square test was used.		

significantly lower than those of controls and admission levels were significantly lower than those of one week later (p=0.001, p=0.033, and p=0.022, respectively). Monocyte counts on admission (MO1) and one week later (MO2) were significantly lower than those of controls (p= 0.010 and p= 0.049 respectively). Basophil counts on admission (BAS1) and one week later (BAS2) were significantly lower than those of controls (p< 0.001 and p< 0.001 respectively). Platelet counts on admission (PLT1) were significantly lower than those of controls and one week later (p= 0.006

and p= 0.001, respectively). The distribution of quantitative variables according to the group is shown in Table 2.

In Figure 1; ROC analysis of ECP2 is shown.

Table II. Distribution of quantitative variables by groups

	Group				
	Control		Patient		p_1
	Mean±SD	Median[Q1-Q3]	Mean±SD	Median[Q1-Q3]	
Age (Year)	60,07±20,59	66[42-75]	57,2±15,46	59[46-69]	0,670
ECP1 (ng/mL)	238,76±301,87	152,94[98,41-210,39]	177,02±124,52	116,91[109,12-282,45]	0,713*
ECP2 (ng/mL)	238,76±301,87	152,94[98,41-210,39]	102,60±59,73	98,41[53,61-133,46]	0,023*
p_2		0,999**		0,001**	
EO1(x103/µL)	0,16±0,14	0,09[0,06-0,24]	0,04±0,03	0,04[0,02-0,07]	<0,001*
EO2(x103/µL)	0,16±0,14	0,09[0,06-0,24]	0,15±0,1	0,12[0,06-0,21]	0,935*
p_2		0,999**		0,004**	
NE1(x103/µL)	8,15±7,64	4,97[3,43-11,48]	3,55±1,15	3,32[2,47-4,63]	0,009*
NE2(x103/µL)	8,15±7,64	4,97[3,43-11,48]	4,84±3,48	3,43[2,63-4,92]	0,041*
p_2		0,999**		0,394**	
LYM1(x103/µL)	2,07±0,95	1,92[1,32-2,88]	1,08±0,52	0,87[0,65-1,39]	0,001
LYM2(x103/µL)	2,07±0,95	1,92[1,32-2,88]	1,39±0,69	1,56[0,74-1,85]	0,033
p_2	0,999		0,022		
MO1(x103/µL)	0,63±0,38	0,51[0,38-0,87]	0,35±0,1	0,33[0,27-0,4]	0,010
MO2(x103/µL)	0,63±0,38	0,51[0,38-0,87]	0,41±0,16	0,38[0,26-0,49]	0,049
p_2	0,999		0,096		
BAS1(x103/µL)	0,08±0,05	0,08[0,04-0,1]	0,03±0,02	0,03[0,02-0,04]	<0,001*
BAS2(x103/µL)	0,08±0,05	0,08[0,04-0,1]	0,03±0,02	0,03[0,02-0,04]	<0,001*
p_2	0,999			0,859**	
WBC1(x103/mL)	11,09±7,89	9,22[6,55-13,43]	5,05±1,24	5,07[4,02-6,12]	0,007
WBC2(x103/mL)	11,09±7,89	9,22[6,55-13,43]	6,81±3,2	5,95[4,28-7,6]	0,062
p_2	0,999		0,059		
PLT1	233,8±82,11	193,8[179,9-280]	160,74±47,34	169,6[127,2-186,7]	0,006
PLT2	233,8±82,11	193,8[179,9-280]	261,51±100,87	253,9[210,7-332,4]	0,416
p_2	0,999		0,001		
EO1 %	1,69±1,45	1,04[0,67-2,62]	1,01±0,73	0,96[0,52-1,14]	0,113
EO2 %	1,69±1,45	1,04[0,67-2,62]	2,27±1,59	2,61[0,63-3,81]	0,307
p_2		0,999**		0,041**	
NE1 %	66,97±16,57	63,94[52,08-82,71]	69,68±10,24	72,1[61,68-73,6]	0,594
NE2 %	66,97±16,57	63,94[52,08-82,71]	66,12±14,61	66,09[54,79-68,93]	0,882
p_2	0,999		0,226		
LY1 %	24,3±14,31	23,46[9,5-37,27]	21,59±9,03	20[17,47-30,88]	0,540
LY2 %	24,3±14,31	23,46[9,5-37,27]	24,51±12,57	26,27[17,4-34,18]	0,967
p_2	0,999		0,273		
NE1/E01	84,98±81,99	69,33[22,87-104,14]	123,48±86,1	96[51,44-178]	0,174
NE2/EO2	84,98±81,99	69,33[22,87-104,14]	60,81±70,74	24,67[17,15-77,08]	0,285
p_2		0,999**		0,041**	

Data were presented as mean ± standard deviation or median, quartile1, quartile3. p1: *: Mann Whitney U test was used. For others, the significance test of the difference between the two means was used. p2: **: Wilcoxon test, for others the difference between two spouses. ECP: Eosinophil Cationic Protein, EO: Eosinophil, NE: Neutrophil, LYM: Lymphocyte, MO: Monocyte, BAS: Basophil, WBC: White Blood Cell, PLT: Platelet. Annex'1' at the end of parameters refers to 'value at admission' while '2' refers to 'one week after'.

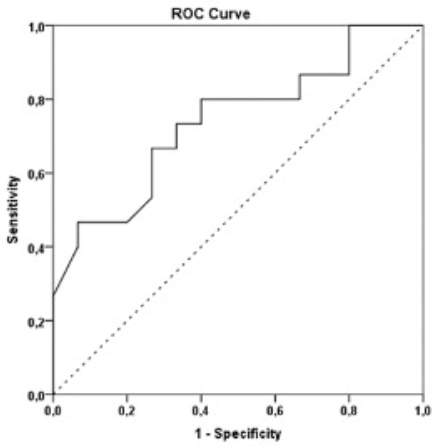

Figure I. ROC Analysis of ECP2

DISCUSSION

Preclinical studies show that eosinophils have the ability to recognize and respond to respiratory viruses and regulate the antiviral response.[7] The role of eosinophils in inflammation is also noticeable in Covid-19 disease. Since the beginning of the Covid-19 pandemic, a low amount of eosinophils (<0.01x109 / L) or eosinopenia was seen in most hospitalized patients in all patient series and was associated with the severity of the disease.[8] Most of the patients experience a very mild, self-limiting upper respiratory tract infection. However, severely ill patients show clinical symptoms specific to Covid-19, which can lead to death, such as widespread pneumonia, cytokine storm, severe eosinopenia, lymphopenia, endotheliitis, thrombo-embolic complications and multi-organ failure causing acute respiratory distress.[9] The reduction of eosinophils in Covid-19 patients may be associated with high SARS-Cov 2 viral load and consumption of SARS-Cov2-initiated eosinophil granule protein.

Eosinophils are activated after being drawn to the inflammation site and release some mediators that are toxic to tissues. These are either proteins stored in granules such as eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), eosinophil protein / eosinophil derived neurotoxin (EDN) and major basic protein (MBP)) or reactive oxygen radicals.[10] Eosinophils also produce a wide variety of cytokines, chemokines and lipid mediators and therefore, in addition to being an effector cell, they also play an immunoregulatory role in inflammatory processes and participate in tissue modification.[11,12]

In line with the existing literature, our patients showed eosinopenia at the time of admission and eosinophil counts increased at the end of first week of treatment compared to the admission levels. Some studies have used absolute eosinophil values to demosntrate eosinopenia. However, since the absolute eosinophil values may vary between different laboratories, we preferred to calculate the Neutrophil / Eosinophil ratio (NE / EO) instead of the absolute eosinophil value in order to achieve standardization in our results. The NE1 / EO1 at the time of admission was significantly higher than the ratio of one week later NE2 / EO2 (p: 0.041) showing eosinopenia is more prominent at admission.

ECP is one of the few highly basic proteins found in eosinophil granules and can neutralize viruses.[13-15] It is a ribonuclease 3 consisting of a single polypeptide chain, belonging to the RNAse superfamily. In vitro ECP secretion is induced by secretagogues such as immunoglobulins, complement factors and serum opsonized particles.[16,17] The mechanism of action to kill target cells is its capability to create transmembrane pores and channels. Many inflammatory clinical conditions are related to the amount of ECP secretion. High levels of ECP have been found in the body fluids of patients in allergic and other inflammatory diseases, indicating the involvement of eosinophils in these processes.

As a result of our study, it was observed that the ECP2 values one week later admission were significantly lower in patients compared to controls (p= 0.023). In addition, it was observed that the values of the one week later (ECP2) were significantly lower than the admission (ECP1) values (p< 0.011). ECP2 values of one week later distinguished

Covid-19 negatives from positive patients with a sensitivity of 46.7%, specificity of 93.3% and a cut-off value of ≤ 88.67 ng / mL.

Our study is the first, we encountered, in the literature to reveal the change in serum ECP values during the disease process (on admission to the hospital and one week later of treatment). Therefore, we compared our results with the studies of ECP in inflammatory diseases and viral infections so far.

Suzuki et al.in their study found that the peripheral eosinophil count and serum levels of ECP and IL 5 were significantly increased in sensitized acute asthma attacks compared to those who were not sensitized.[18] Zimmerman et al.in their studies showed that children with atopic asthma had higher eosinophil and ECP levels than non-atopic children.[19]

Paganelli et al.in their study, they conducted a study that included 22 seropositive HIV patients who presented with allergic symptoms for the first time at different stages of the disease or with acute exacerbation of an atopic problem, and 25 non-atopic healthy individuals, 20 individuals with recurrent acute or viral infections and 29 HIV-seropositive individuals without atopy as a control group.[20] Serum ECP levels of HIV-positive patients with or without atopy were found to be significantly higher. ECP was also increased in control patients with infection. Temporary ECP elevation is expected at the onset of bacterial infections.[1,21]. Since ECP is also increased in atopic diseases, it was also found to be high in HIV patients with allergic symptoms. Because of ECP is also increased in HIV, it was also found to be high in non-atopic HIV patients.

Choi et al. in their study, they investigated the relationship between RSV-induced lower airway eosinophilic inflammation and TNF-a.[21] They sampled nasal lavage fluid (NLS) of 60 patients and 20 healthy controls. TNF-α, IL-8, GM-CSF, IFN-gamma and ECP levels were found to be significantly higher in the RSV group compared to the controls. It was observed that ECP and GM-CSF levels increased only in the RSV group. All these results demonstrated a significant association of RSV bronchiolitis and eosinophilic inflammation.

The rapid diagnosis of Covid-19 is important in distinguishing suspected cases from patients with Covid-19-like symptoms. Covid-19 diagnosis is made by methods take a long time to result and cannot be accessed in every health facility. In previous studies it has been shown that eosinophils neutralize viruses, especially by means of a basic proteins such as ECP. According to our results; ECP test can be useful in the rapid screening of patients with Covid-19-like symptoms but who are Covid-19 negative, and in separating them from Covid-19 patients.

Since our study is retrospective and the sample size is small. Our results need to be validated with larger prospective cohorts.

CONCLUSIONS

In Covid-19 patients; neutropenia, lymphopenia, and eosinopenia were observed. Lymphopenia and eosinopenia were positively correlated. Eosinopenia on admission appears to be higher than baseline after one week, which seems to be associated with good outcome. It is thought that ECP may be an easy, accessible and rapid biomarker to help in differentiation of Covid-19-negative patients from positive ones compared to other moleculer, serologic and radiologic diagnostic methods.

Acknowledgment

We thanks to our laboratory and hospital data processing staff for their great contribution.

Conflicts of Interest

All authors state that there is no conflict of interest.

Ethical Consent

We obtained ethical consent of Tokat Gaziosmanpasa University Faculty of Medicine Clinical Researches Ethical Committee 09.07.2020 with the code of 20-KAEK-198.

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