High Serum Progranulin Levels in COVID-19 Patients: A Pilot Study

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Abstract—In this study, we aimed to determine whether the progranulin level in serum predicts the course and severity of the disease in COVID-19 (+) patients and whether it can be used as a biomarker in these patients. Therefore, we sampled 61 people infected with COVID-19, and the cases were divided into the following groups: asymptomatic, noncomplicated, moderate, and severe. Concentrations of progranulin, TNF-α, IL-6 from in serum obtained from all participants were measured using commercially available ELISA kits, as well as WBC, PLT, NE, LY, ALT, AST, Hb, PCT, and CRP were examined with clinical analyzer. All measurements obtained for the patient samples were compared with those of 20 healthy individuals. The serum progranulin concentration was statistically higher in the COVID-19 (+) patient group than in the control group of healthy individuals [112.6 $\pm$ 54.8, 0.0 (0.0-54.2 pg/ml, respectively $p = 0.000$)]. ROC analysis was performed to evaluate the progranulin potential as a biomarker for COVID-19 (+) patients. A larger AUC (0.931 $\pm$ 0.08) value and a more significant p-value for progranulin than for CRP ($p = 0.000$) was detected. As a result, we believe that progranulin reaches high levels in the COVID-19 disease and may be a determinant in diagnosis and prognosis, and may be a better biomarker than CRP.

INTRODUCTION

Coronavirus disease of 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with substantial pulmonary disorders, and extrapulmonary manifestations, including thromboembolism, bleeding, myocardial injury, renal failure, gastrointestinal symptoms [1]. The spectrum of clinical presentations ranges from asymptomatic, mild courses, or severe and life-threatening diseases requiring intensive care treatment [2]. As the COVID-19 epidemic intensifies, there is an urgent need to identify clinical and laboratory predictors for progression towards severe and fatal forms of this disease.

Interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) are important members of the cytokine network with both anti-inflammatory and pro-inflammatory

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Abbreviations: COVID-19, Coronavirus disease of 2019; CRP, C-reactive peptide; IL-6, interleukin-6; PRGN, progranulin; TNF-α, tumor necrosis factor-α.
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effects. Dysregulated cytokine production promotes development of autoimmune disorders or simply persistence of infection, leading to the maintenance of a chronic pathological inflammatory state [3]. IL-6 is a proinflammatory cytokine that stimulates acute phase responses, hematopoiesis, and specific immune reactions. Recently, it has been reported that IL-6 is responsible for high mortality rate in COVID-19 [4]. Among the many cytokines studied, TNF-α was noted to be particularly important as it is located upstream of the inflammation cascade and has many complex functions in the immune system [5].

Progranulin (PGRN), also known as the granulin-epithelin precursor, proepithelin [6], acrogranin [7], and epithelial transforming growth factor, is a glycoprotein composed of tandem repeats of 12 cysteine modules, called the granulin or epithelial domain. PGRN, a pleiotropic growth factor, is known to play an important role in maintaining and regulating homeostatic dynamics of normal tissue development, proliferation, regeneration, and host-defense response, and therefore has been widely studied in infectious diseases, wound healing, tumorigenesis, neuroproliferative and degenerative diseases [8]. Interactions between PGRN and inflammation are complex. PGRN binds receptors for TNF-α and inhibits downstream TNF-α signaling. PGRN blocks the ability of TNF-α to stimulate, among other effects, neutrophil respiratory burst. PGRN is therefore considered as anti-inflammatory factor [9].

C-reactive protein (CRP) is one of the nonspecific acute phase response proteins synthesized in liver with participation of the IL-6 pathway. Its increased level serves as a biomarker of inflammation, infection, and tissue damage [10, 11]. Serum CRP concentrations have been found to rise in COVID-19 (+) patients in the studies [12-14].

COVID-19 is a new infectious disease for which current laboratory markers are not available to assess severity of the disease. For this reason, objective of this study was to investigate whether the progranulin levels predict the course and severity of the disease in the COVID-19 (+) patients and whether it can be used as a biomarker in these cases.

MATERIALS AND METHODS

Materials. Patients and healthy people were selected from the patients who visited the Department of Infectious Diseases, Atatürk University Research Hospital. The groups consisted of COVID-19 (+) patients and control group with similar demographic characteristics. COVID-19 infection was diagnosed by the real-time polymerase chain reaction (RT-PCR) test through examination of nasopharyngeal and oropharyngeal samples taken from the patients. Healthy volunteers with demographic characteristics similar to the patients, with negative for RT-PCR test and without any complaints were included in the control group. All samples were taken after approval of the study by the clinical research ethics committee (No: B.30.2.ATA.0.01.00/411). All COVID-19 cases were managed according to the national guidelines. COVID-19 patients were divided into the following groups: asymptomatic (AG, no symptom, no pulmonary involvement in chest imaging studies), noncomplicated (NCG, patients with symptoms such as fever, muscle, joint pain, cough and sore throat, and no respiratory distress − respiratory rate per minute <24, $SpO_2 > 93\%$ in room air, and normal chest X-ray and/or lung tomography), moderate (MG, patients with symptoms such as fever, muscle, joint pain, cough and sore throat, respiratory rate <30/min, $SpO_2 > 90$ in room air, and mild to moderate pneumonia signs on chest X-ray or tomography), and severe (SG, patients with symptoms such as fever, muscle, joint pain, cough and sore throat, with tachypnea (≥30/min), SpO_2 level below ≤90% in room air, and bilateral diffuse pneumonia signs on chest X-ray or tomography). On the first day of their admission, blood was taken from the patients in the MG and SG groups. These were also patients who took various antiviral drugs (Tamiflu, Plaquanil, Favipavir) and did not have chronic diseases (such as COPD, tuberculosis, or AIDS). Patients using immunosuppressive drugs or receiving chemotherapy were not included in the study. Healthy volunteers were adults over 18 years of age who were similar in age to the patient group, had normal physical examination findings and normal results of routine tests, were not pregnant, and did not have chronic diseases (such as COPD, tuberculosis, or AIDS). All of COVID-19 (+) patients in the severe group were patients treated in the intensive care unit (ICU) and nine patients were ventilated. At the beginning of the study, blood was taken from 95 people and they were included in the study. However, considering the inclusion/exclusion criteria, four people younger than 20 years old, eight people whose serum samples were hemolyzed, and two people who had COVID-19 (−) test in the PCR retest were excluded from the study, and the study was carried out with total of 81 people.

Examination of biochemical and clinical profile. Blood samples were taken from the patients admitted to our hospital. While some of the blood samples were sent to the hospital laboratory for routine analysis, another portion was sent to the Atatürk University, Faculty of Medicine, Medical Biochemistry Department Research laboratory for testing Il-6, TNF-α, and PGRN. Serum Il-6, TNF-α, and PGRN concentrations in the samples from each patient were recorded, along with the information on their age, gender, comorbid characteristics, and biochemical parameters (ALT, AST, WBC, NE, LY, PLT, Hb, PCT, and CRP).

Serum IL-6, TNF-α, and PGRN analysis. Serum TNF-α concentrations were measured using a human-specific sandwich enzyme-linked immunosorbent assay

(Hu TNF-α ELISA kit; Cat. No. KE00154, AuthentiKine, USA). Serum IL-6 concentrations were measured using a human-specific sandwich enzyme-linked immunosorbent assay (Hu IL-6 ELISA kit; Cat. No. KE00139, AuthentiKine). Serum PGRN concentrations were measured using a human-specific sandwich enzyme-linked immunosorbent assay (Hu PGRN ELISA kit; Cat. No. MBS163502, MyBioSource, Belgium). IL-6, TNF-α, and PGRN analyses were performed using a microplate reader (XS Powerwave, BioTEK, USA).

Statistical analysis. IBM SPSS 20.0 software package was applied for data analysis in the study. Data were presented as mean, standard deviation, minimum, maximum, percentage, and number. The Kolmogorov–Smirnov test was used to determine whether the continuous variables were normally distributed. In comparisons between the two independent groups, Independent Samples *t*-test was used for the data with normal distribution, and Mann–Whitney-U test was used in other cases. In the comparison of continuous variables with more than two independent groups, the ANOVA test was used when normal distribution condition was met, and the Kruskal–Wallis test was used, when it was not. Pearson correlation analysis was used for the data with normal distribution, and Spearman correlation analysis was used for other data.

Receiver operating characteristic (ROC) analysis test was employed to determine whether the continuous variable could be used in the diagnosis and to determine the cut-off value, positive predictive value (PPV), negative predictive value, and area under the curve (AUC). Statistical significance level for all data was set at $p < 0.05$.

RESULTS AND DISCUSSION

Demographic characteristics and radiological images of the COVID-19 (+) patient group and the healthy control group are given in Table 1. There was no statistical difference between the mean age of the combined patient group and the control group ($p = 0.997$). 49.3% of the 81 participants were female, 50.7% were male.

While progranulin was detected in only 4 of 20 subjects in the control group, it was not detected in only 6 of 61 subjects in the patient group. Since absorbance of the samples where progranulin levels could not be detected was the same as the blank, concentration of progranulin in these samples was evaluated as 0.00 mg/liter. Serum progranulin concentration was statistically higher in the COVID-19 (+) patient group than in the healthy control group ($p = 0.000$). There was no statistical difference between the progranulin levels in the COVID-19 (+) subgroups ($p = 0.078$). Boxblot graph of both COVID-19 (+) patient subgroups and healthy control group are given in Fig. 1. There was a significant difference in the TNF-α and IL-6 levels between the patient and the control groups or the patient subgroups ($p = 0.000$). No difference in the biochemical data was observed between the COVID-19 (+) subgroups in ALT, AST, WBC, NE, LY, PLT, Procal, and Hb values. There was a significant decrease in the NE, LY, and PLT values and a significant increase in the Hb values in the combined patient group compared to the healthy group. On the other hand, the CRP concentration was significantly different both between the patient and control group and between COVID-19 (+) subgroups. Data on biochemical parameters of all groups are presented in Table 2.

No significant correlation was observed between the levels of progranulin and other parameters in the COVID-19 (+) patient group. In the COVID-19 (+) subgroups, positive correlation was observed with CRP ($r = 0.474$, $p = 0.017$) in the MG group of patients, and negative significant correlation with PLT in the severe group of patients ($r = -0.578$, $p = 0.038$) (Fig. 2). On the other hand, when all participants were considered, significant positive correlation was observed between the progranulin and the TNF-α and IL-6 levels ($r = 0.260$, $p = 0.018$, $r = 0.461$, $p = 0.000$, respectively) (Fig. 3).

ROC analysis was performed to evaluate potential of progranulin as a biomarker for COVID-19 (+) patients. It detected a larger AUC value and a more significant

Table 1. Demographic characteristics and parameters of radiologic imaging for the control group and patients with COVID-19 (+)

Variables	PG					HCG ($n = 20$)
	AG ($n = 10$)	NCG ($n = 13$)	MG ($n = 25$)	SG ($n = 13$)	Total PG ($n = 61$)	
Age (year)	39.4 ± 14.1	38.1 ± 17.1	53.0 ± 18.1	59.0 ± 13.8	48.8 ± 18.4	48.9 ± 15.9
Gender (female/male)	6/4	9/4	11/14	4/9	30/31	10/10
Radiological parameters (N/GG/GG+C)	8/2/0	8/4/1	1/20/4	0/4/9	17/30/14	–
Survival (alive/ex)	10/0	13/0	25/0	6/7	54/7	–

Notes. PG, COVID-19 (+) patient group; AG, asymptomatic group; NCG, noncomplicated group; MG, moderate group; SG, severe group; HCG, healthy control group; N, normal; GG, ground glass; GG+C, ground glass + consolidation.

Table 2. Biochemical parameters of the healthy control group and the patients with COVID-19 (+)

Variables	PG						HCG (n = 20) mean ±SD or median (min-max)	p^2-value
	AG (n = 10) mean ±SD or median (min-max)	NCG (n = 13) mean ±SD or median (min-max)	MG (n = 25) mean ±SD or median (min-max)	SG (n = 13) mean ±SD or median (min-max)	p^1-value	Total PG (n = 61) mean ±SD or median (min-max)		
PRG (pg/ml)	112.8 ± 58.8	94.5 ± 52.5	132.8 ± 39.1	91.6 ± 70.2	0.078	112.6 ± 54.8	0.0 (0.0-54.2)	0.000
TNF-α (pg/ml)	22.4 ± 8.9	23.1 ± 4.3	26.2 ± 7.1	34.3 ± 7.6	0.00	26.68 ± 8.1	18.8 ± 4.5	0.038
IL-6 (pg/ml)	25.1 ± 13.0	38.9 ± 8.4	67.8 ± 18.8	92.1 ± 12.2	0.00	60.15 ± 27.59	20.27 ± 10.9	0.000
ALT (U/liter)	36 (13-79)	17 (10-37)	20 (7-80)	20 (10-43)	0.392	20 (7-80)	27 (11-93)	0.796
AST (U/liter)	27.0 ± 12.2	27.3 ± 8.4	24.1 ± 7.8	30.9 ± 9.1	0.194	26.7 ± 9.1	28.1 ± 20.0	0.700
WBC (×10³)	8.3 ± 1.7	6.4 ± 3.1	6.2 ± 2.8	6.1 ± 1.2	0.140	6.6 ± 2.5	8.5 ± 2.8	0.050
NE (×10³)	5.01 ± 1.7	5.0 ± 0.3	5.4 ± 0.2	5.8 ± 2.5	0.065	5.5 ± 2.5	5.2 ± 2.1	0.035
LY (×10³)	1.8 ± 0.5	1.7 ± 1.0	1.4 ± 0.9	1.2 ± 0.4	0.153	1.5 ± 0.8	2.3 ± 1.1	0.000
PLT (×10³)	240 (191-281)	240 (154-385)	240 (135-408)	192 (51-291)	0.238	227 (51-408)	280 (166-616)	0.000
Hb (g/dl)	15.6 ± 1.9	14.8 ± 2.1	14.7 ± 1.7	14.6 ± 0.9	0.366	14.8 ± 1.7	13.2 ± 2.6	0.002
CRP (mg/liter)	3.5 (3.1-47.0)	3.1 (3.1-53.1)	3.2 (3.1-66.1)	30.5 (3.0-192.0)[a,b,c]	0.015	3.7 (3.0-192.0)	1.2 (0.0-5.38)	0.000
PCT (ng/ml)	0.047 ± 0.1	0.049 ± 0.1	0.043 ± 0.1	0.039 ± 0.2	0.47	0.044 ± 0.0	–	–

Notes. PG, COVID-19 (+) patient group; AG, asymptomatic group; NCG, noncomplicated group; MG, moderate group; SG, severe group; HCG, healthy control group; PRG, progranulin; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; WBC, white blood cell; ALT, alanine aminotransferase; Ast, aspartate aminotransferase; Hb, hemoglobin; PLT, platelet; NE, neutrophil; LY, lymphocyte; CRP, C-reactive protein; PCT, procalsitonin; SD, standard deviation; min-max, minimum-maximum; [a], $p < 0.05$ compared to AG; [b], $p < 0.05$ compared to NCG; [c], $p < 0.05$ compared to MG; p^1, comparison between COVID-19 (+) subgroups; p^2, comparison between total PG and HCG.

p-value for progranulin than for CRP. The cut-off value was 38 pg/ml for progranulin and 6 mg/ml for CRP, and positive predictive value (PPV) and negative predictive value (NPV) were calculated. The determined parameters of ROC analysis are presented in Table 3 and Fig. 4.

The course of COVID-19 disease, which causes significant health problem all over the world, varies from person to person, and, therefore, knowing the parameters to monitor the course severity and follow-up of the disease will make an important contribution to pathophysiology.
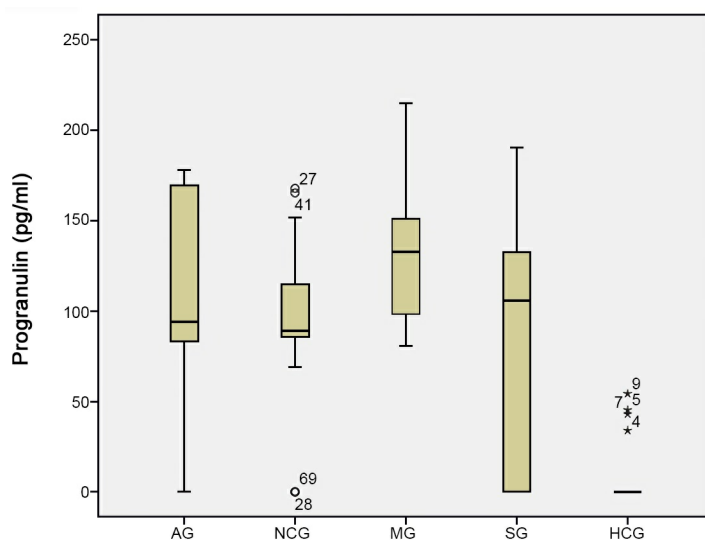

Fig. 1. Boxplot graph of serum progranulin levels in the control group and in the COVID-19 (+) patient subgroups (*p* = 0.000). Designations: AG, asymptomatic group; NCG, noncomplicated group; MG, moderate group; SG, severe group; HCG, healthy control group.
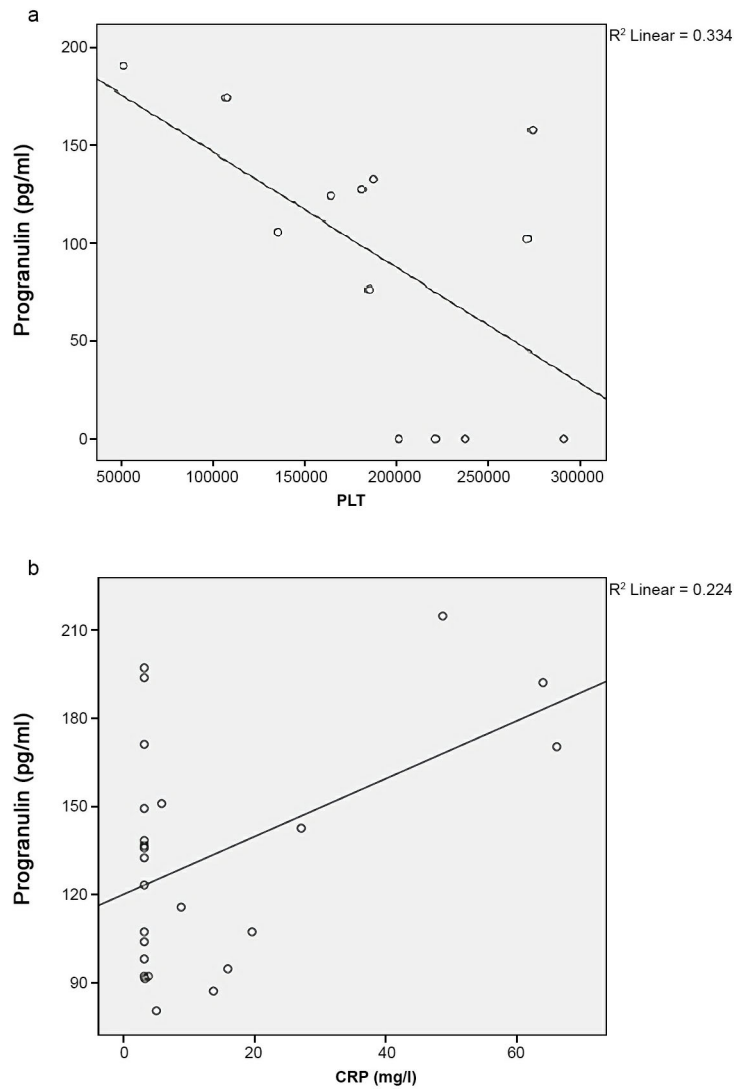
a

b

Fig. 2. a) Scatter diagram of progranulin and PLT correlation in the severe group ($R^2 = 0.334$, $r = -0.578$, $p = 0.038$); b) scatter diagram of progranulin and CRP correlation in the MG group ($R^2 = 0.224$, $r = 0.474$, $p = 0.017$).

Quantitative parameters showing the stage of development of the COVID-19 disease are extremely important for classifying patients according to the disease severity and applying effective treatment quickly. This study looked at the serum concentrations of Il-6, TNF-α, and PGRN as well as biochemical parameters in COVID-19 patients of varying severity, compared them to the parameters in healthy people, and suggested new diagnostic targets by evaluating these potentially important data.

IL-6 is rapidly produced through transcriptional and post-transcriptional mechanisms as an immune response to infection and tissue injury. Dysregulated expression of IL-6 exerts a pathological effect on chronic inflammation and autoimmunity [15]. It is commonly accepted that IL-6 plays a pivotal role in the cytokine storm induced by SARS-CoV-2 as a multifunctional mediator of inflammation and participates in the interstitial pneumonia and

ARDS observed in the severe cases of COVID-19 [16]. In the acute phase of inflammation and infection, IL-6 is produced by immune cells, especially T-helper 17 (TH17) cells in the COVID-19 patients [17]. In addition, the IL-6 production is also induced by TNF-α as a pyro-

Table 3. Data of ROC analysis for progranulin and CRP

Biomarker	AUC (CI%)	p-value	PPV (CI%)	NPV (CI%)
PRG	0.931 (87.6-98.6)	0.000	91.8 (82.3-82.4)	69.5 (52.5-82.5)
CRP	0.791 (66.8-91.3)	0.000	93.3 (79.1-88.2)	34.6 (28.7-40.9)

Designations: AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; CI, coefficient interval.
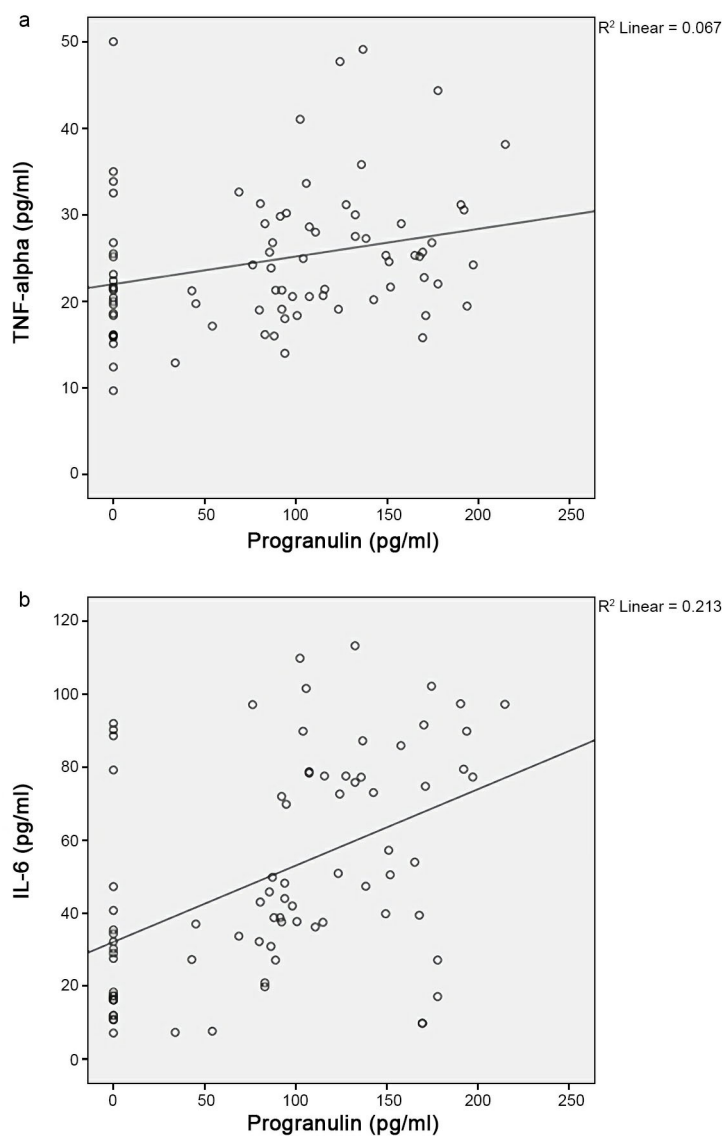
Fig. 3. a) Scatter diagram of progranulin and TNF-α concentration in the samples from all participants; b) scatter diagram of progranulin and IL-6 concentration in the samples from all participants.

genic cytokine released from immune cells in response to chronic inflammatory and autoimmune diseases, suggesting that IL-6 is a downstream effector of TNF-α [18]. Using meta-analysis of cumulative data from 24 studies, Wu et al. [19] investigated the role of inflammatory cytokines, including IL-6, IL-10, and TNF-α, in the severity and mortality of COVID-19. They reported that IL-6 levels were significantly increased in the COVID-19 patients. In another study conducted in individuals with COVID-19 disease, it was reported that plasma IL-6 levels increased with the increase in severity of the disease [20]. In our study, there was a statistically significant difference in the TNF- and IL-6 levels between the patient and control groups, as well as between the patient subgroups ($p = 0.000$).

COVID-19 patients showed higher plasma proinflammatory cytokine levels including chemokines such as IFN-γ, IL-1β, IP-10, and MCP-1, while higher concentrations of TNF-α in the severe cases requiring admission to intensive care units were found [21]. In the study, serum cytokine and chemokine levels were investigated in asymptomatic, symptomatic, and convalescent COVID-19 cases and healthy controls, and the levels of TNF-α were found to be higher in the symptomatic group as compared to the healthy controls [22].

Eight further meta-analysis studies by Wu et al. [19] investigating TNF-α levels in the circulation of the severe ($n = 725$) and non-severe COVID-19 ($n = 587$) patients showed no statistically significant difference between the groups. In our study, we could not find a sig-

nificant difference in the TNF-α values between the groups.

PGRN is a pleiotropic growth factor and immune regulatory molecule found in epithelium, bone marrow, and variety of immune cells such as T cells, dendritic cells, monocytes, and macrophages [23]. By binding to the membrane-bound receptors TNF-R1, TNF-R2, or Toll-like receptor 9, PGRN performs variety of functions in the innate and adaptive immune systems. In the adaptive immune system, PGRN is crucial for T cell regulation as it promotes differentiation of CD4$^+$ T cells into the Foxp regulatory T cells (Tregs) and protects Tregs from negative regulation by TNF-α [24, 25]. PGRN prevents regulatory NK cell cytotoxicity against antiviral T cells and inhibits lipopolysaccharide-mediated IL-6 and TNF-α secretion from macrophages [9]. In our study, PGRN was found to be at the significantly higher levels in the COVID-19 positive patients compared to the control group. When we looked at the severity of the disease, we did not observe any statistical difference between the PGRN levels ($p = 0.078$). Serum protein expression in the COVID-19 patients was examined in the literature, and there was no difference in IL-6 levels in the SARS-CoV-2 positive patients compared to the patients with similar symptoms and disease severity but negative for SARS-CoV-2, whereas a specific increase of the PGRN level has been shown [26]. Yao et al. [27] found that serum VCAM-1 and PGRN levels were higher in the patients with COVID-19 than in the healthy controls in their study of PRGN and VCAM-1 levels in the patients with COVID-19.

In the study of PGRN levels in sepsis, community-acquired bacterial pneumonia (CAP), and COVID-19, researchers discovered that the COVID-19 patients with confirmed pneumonia had significantly higher levels of PGRN than the non-COVID-19 CAP patients. They emphasized that for the COVID-19 patients with confirmed pneumonia, progranulin is even better biomarker than procalcitonin and CRP [28].

Studies have shown that CRP levels reach high values at the onset of COVID-19 disease and are determinative in diagnosis and prognosis [13, 14]. CRP is a biomarker used not only in the diagnosis of the disease, but also in determining its severity, evaluating treatment response, and predicting mortality [29]. In the multicenter retrospective study conducted by Feng et al. [12] it was reported that the CRP level increased as the clinical picture worsened and reached a significant difference in the critically ill patients in 476 cases. As a result of our ROC analysis evaluating potential of PGRN as a biomarker for the COVID-19 (+) patients, we determined that it has a larger AUC value and a more significant p-value than CRP. Thus, we believe that PGRN may be a good biomarker for COVID-19 disease.

CONCLUSIONS

COVID-19 is recognized as a global health threat, so it is essential that clinicians have access to reliable rapid pathogen testing and applicable differential diagnosis based on clinical identification during their first contact with the suspected patients. In comparison with the TNF-α and IL-6 levels, the serum level of PGRN was almost never detected in healthy people, while it was found to be very high in the COVID-19 (+) patients. It has been observed that it is more sensitive than CRP in distinguishing patients with COVID-19 from the healthy people. Furthermore, low PCT levels in the COVID-19
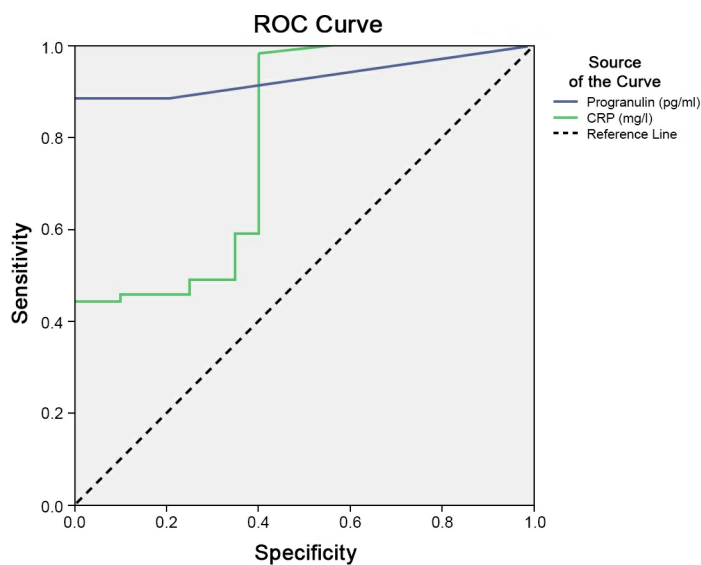

Fig. 4. ROC analysis graphic of progranulin and CRP (AUC = 0.931, $p = 0.000$ for progranulin; AUC = 0.791; $p = 0.000$ for CRP).

patients suggest that PGRN is increased due to the viral origin of the infection. We believe that progranulin levels reach high values in the COVID-19 disease and may be a determinant in diagnosis and prognosis, and may be a better biomarker than CRP.

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