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RESEARCH ARTICLE / ÖZGÜN ARAŞTIRMA

# Is There a Relationship Between Serum Procalcitonin Level and Mortality and Disease Severity in Patients Diagnosed with COVID-19?

## COVID-19 Tanılı Hastalarda Serum Prokalsitonin Düzeyi ile Mortalite ve Hastalık Şiddeti Arasında Bir İlişki Var mı?

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**ABSTRACT**

**Objective:** Coronavirus disease (COVID-19) exhibits a spectrum of clinical conditions, ranging from mild upper respiratory tract disease to acute respiratory distress syndrome (ARDS), with hyperinflammation playing a pivotal role in the development of ARDS. Procalcitonin (PCT) serves as a biomarker indicating hyperinflammation. Our study aimed to assess the correlation between serum PCT levels and disease severity, as well as in-hospital mortality in COVID-19 patients.

**Material and Methods:** The study included patients hospitalized with COVID-19 in our clinic between November 2020 and March 2021. Demographic characteristics, vital signs, comorbidities, and laboratory parameters on the admission day were recorded. Patients were categorized into non-severe and severe COVID-19 based on disease severity. Serum PCT values were compared between these groups. Additionally, patients were further divided into discharged and in-hospital mortality groups, with serum PCT values compared between these subgroups.

**Results:** Out of 137 patients, 78 (57%) had severe COVID-19, and in severe cases, PCT values were significantly higher compared to the non-severe group ($p<0.001$). Twenty patients (14.6%) died during hospitalization, and in the in-hospital mortality group, PCT values were significantly elevated compared to the discharged group ($p=0.014$). Using a serum PCT value cut-off >0.12 to predict mortality yielded a sensitivity of 70%, specificity of 56.41%, positive predictive value (PPV) of 21.54%, and negative predictive value (NPV) of 91.67%. For predicting disease severity, a PCT value cut-off >0.124 resulted in a sensitivity of 44.87%, specificity of 27.12%, PPV of 44.87%, and NPV of 27.12%.

**Conclusion:** Our study establishes a connection between elevated PCT levels in COVID-19 patients and increased mortality and disease severity. Monitoring serum PCT levels during hospitalization may aid clinicians in the early identification of potentially severe cases.

**Keywords:** COVID-19, disease severity, mortality, procalcitonin.

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## ÖZ

**Amaç:** Koronavirüs hastalığı (COVID-19), hafif üst solunum yolu hastalığından akut solunum sıkıntısı sendromuna (ARDS) kadar değişen klinik durumlar ile seyredebilir. Hiperinflamasyon, ARDS gelişiminde önemli bir rol oynamaktadır. Prokalsitonin (PCT), hiperinflamasyonun bir göstergesi olan biyobelirteçlerden birisidir. Çalışmamız, COVID-19 nedeniyle yatan hastalarda serum PCT düzeyi ile hastalık şiddeti ve hastane içi mortalite arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

**Gereç ve Yöntemler:** Kasım 2020 ile Mart 2021 tarihleri arasında kliniğimizde yatan COVID-19 hastaları çalışmaya dahil edilmiştir. Demografik özellikler, vital bulgular, ek hastalıklar ve yatış günü laboratuvar parametreleri kaydedilmiştir. Hastalık şiddetine göre hastalar, ağır olmayan ve ağır COVID-19 olarak iki gruba ayrılmıştır. Bu iki grup arasında serum PCT değerleri karşılaştırılmıştır. Ayrıca, hastalar taburcu olanlar ve hastane içi vefat edenler olarak ikiye ayrılmış, bu iki grupta serum PCT değerleri karşılaştırılmıştır.

**Bulgular:** Çalışmaya toplam 137 hasta dahil edilmiştir. Ağır COVID-19 tanısı olan hasta sayısı 78 (%57) olup, ağır hastalarda PCT değerleri ağır olmayan gruba göre daha yüksek bulunmuş ve fark istatistiksel olarak anlamlı saptanmıştır (p<0.001). Toplam 20 (%14.6) hasta vefat etmiştir. Hastane içi vefat eden grupta, taburcu olan gruba göre PCT değerleri daha yüksek bulunmuş ve fark anlamlı olarak saptanmıştır (p=0.014). Mortaliteyi tahmin edebilmek için kullanılan serum PCT değeri cut-off > 0.12 olduğunda %70 sensitivite, %56.41 spesifite, %21.54 pozitif prediktif değer (PPD) ve %91.67 negatif prediktif değer (NPD) elde edilmiştir. Hastalık şiddetini tahmin edebilmek için kullanılan PCT değeri cut-off > 0.124 olduğunda %44.87 sensitivite, %27.12 spesifite, %44.87 PPD ve %27.12 NPD elde edilmiştir.

**Sonuç:** Çalışmamız, COVID-19 tanısı ile yatırılan hastalarda serum PCT düzeylerinin yüksekliğinin mortalite ve hastalık şiddeti ile ilişkili olduğunu göstermiştir. Hastaneye yatış sırasında serum PCT düzeylerinin izlenmesi, klinisyenlerin potansiyel olarak ciddi vakaları erken tanımlamasına yardımcı olabilir.


**Anahtar kelimeler:** COVID-19, hastalık şiddeti, mortalite, prokalsitonin.

## INTRODUCTION

The Coronavirus disease (COVID-19), which appeared in 2019, is a global health problem and can progress from an upper respiratory tract infection to severe conditions such as ARDS, septic shock, and death.[1] One of the most important issues related to COVID-19 is determining the risk factors to predict the severity of the disease. Biomarkers are important for guiding management and treatment in COVID-19.[2] Procalcitonin (PCT) is one of these biomarkers that have been investigated to predict disease severity and mortality.[3] PCT is the prohormone of calcitonin and is produced by thyroid C-cells. In the case of inflammation, it is synthesized in all tissues. PCT is a biomarker in bacterial infections and disease progression and is also used in respiratory infections and sepsis outcomes.[4] An increased PCT level is usually observed in patients with bacterial infection and is often used to distinguish bacterial infections from viral infections.[5] Interleukin (IL)-6 and tumor necrosis factor (TNF)-α triggers PCT synthesis in addition to bacterial toxins.[6] IL-2 and TNF-α are increased in severe COVID-19 infections.[7] PCT level may be elevated in hyperinflammation. ARDS is clinically the most important complication of COVID-19, and PCT may be a predictor of hyperinflammation and the development of ARDS. PCT can be a biomarker to estimate mortality and severity.[8] We aimed to investigate serum PCT level, in-hospital mortality, and disease severity in COVID-19 patients.

## MATERIAL AND METHODS

The study was a single-center cohort study. A total of 137 patients hospitalized with COVID-19 disease between November 2020 and March 2021 were examined retrospectively. Patients over 18 years of age with a positive COVID-19 PCR test were included. Patients were divided as severe and non-severe COVID-19. PCT levels were compared between these two groups. Similar parameters were also compared between those who died in hospital and those who were discharged.

Patients with a respiratory rate <30/minute, $SpO_2$>%90 on room air were defined as non-severe, while a respiratory rate ≥30/minute, $SpO_2$ level below ≤%90, and bilateral diffuse pneumonia findings on chest X-ray or CT were classified as severe.

Serum PCT was analyzed by ECLIA (electrochemiluminescence immunoassay) on a Roche HITACHI Cobas e 601 (Tokyo, Japan).

The Ethics Committee approved the study (Date: 26.10.2022, Approval number: 514/236/27) and it was conducted in accordance with the Declaration of Helsinki. The need for written informed consent was waived owing to the retrospective design of the study.

### Statistical Analysis

SPSS version 25.0 software (Chicago, IL, USA) was used for analysis. The Pearson chi-square test and Mann-Whitney U test were used to assess variables between two groups. Significant cut-off values that could predict mortality and disease severity were analyzed by ROC analysis. p values less than 0.05 were considered significant.

## RESULTS

Of the 137 patients, 79 (58%) were male and 58 (42%) were female. The mean age was 59 (24-87) years. The most commonly observed symptoms were shortness of breath (75%), cough (55%), and fatigue (44%), respectively. A total of 89 (65%) patients had comorbid diseases, with hypertension (40%), diabetes (31%), and cardiovascular disease (15%) being the most common. Oxygen treatment was re-

**Table 1: General characteristics of groups**

| | Exitus (n=20) | | Discharged (n=117) | | Total (n=137) | | p |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Sex | | | | | | | |
| Male | 15 | 75 | 64 | 54.7 | 79 | 57.7 | 0.090 |
| Age/years[1] | 70.5 (54–87) | | 58 (24–85) | | 59 (24–87) | | **<0.001** |
| Saturation %[1] | 87 (69–93) | | 90 (64–99) | | 90 (64–99) | | **0.006** |
| Fever C[1] | 37.2 (36–38.8) | | 37 (36–40) | | 37 (36–40) | | 0.7 |
| Cough | 10 | 50 | 66 | 56.4 | 76 | 55.5 | 0.594 |
| Dyspnea | 16 | 80 | 87 | 74,4 | 103 | 75.2 | 0.589 |
| Gastrointestinal complaints | 3 | 15 | 13 | 11.1 | 16 | 11.7 | 0.617 |
| Chest pain | 1 | 5 | 10 | 8.5 | 11 | 8 | 0.590 |
| Fatigue | 138 | 65 | 47 | 40.2 | 60 | 43.8 | **0.039** |
| Headache | 2 | 10 | 11 | 9.4 | 13 | 9.5 | 0.933 |
| Myalgia | 5 | 25 | 28 | 23.9 | 33 | 24.1 | 0.918 |
| Comorbidities | 17 | 85 | 72 | 61.5 | 89 | 65 | **0.042** |
| Hypertension | 13 | 65 | 42 | 35.9 | 55 | 40.1 | **0.014** |
| Diabetes | 7 | 35 | 36 | 30.8 | 43 | 31.4 | 0.706 |
| Cardiovascular disease | 5 | 25 | 15 | 12.8 | 20 | 14.6 | 0.154 |
| Platelet/$10^3$ [1] | 166 (71–486) | | 204 (76–617) | | 197 (71–617) | | **0.034** |
| C-Reactive Protein (mg/L)[1] | 120.5 (20–202) | | 87.6 (1.7–277 | | 93 (1.7–277) | | 0.087 |
| Ferritin ($\mu$g/L)[1] | 526 (108–2000) | | 532 (16.7–2000 | | 531 (16.7–2000) | | 0.829 |
| D-Dimer ($\mu$g/L)[1] | 750 (240–4400) | | 700 (190–4400) | | 700 (190–4400 | | 0.549 |
| Lactate dehydrogenase (U/L)[1] | 341.5 (205–680) | | 339.5 (102–901) | | 339.5 (102–901) | | 0.873 |
| Procalcitonin (ng/ml)[1] | 0.16 (0.01–6.4) | | 0.1 (0.03–5.6) | | 0.1 (0.01–6.4) | | **0.014** |
| Troponin ($\mu$g/L)[1] | 0.01 (0.01–0.2) | | 0.01 (0–0.09) | | 0.01 (0–0.2) | | **0.001** |
| Hospitalization (days)[1] | 13.5 (4–27) | | 10 (3–37) | | 10 (3–37) | | 0.116 |
| Oxygen support | 20 | 100 | 85 | 72.5 | 105 | 76.6 | **0.008** |
| Intensive care unit admission | 19 | 95 | 11 | 9.4 | 30 | 21.9 | **<0.001** |
| Intubation | 20 | 100 | 2 | 1.7 | 22 | 16.1 | **<0.001** |

[1]: Median value (minimum-maximum).

quired for 105 (76.6%) patients, and 20 of them died during hospitalization. Oxygen support was needed for 28 (47.5%) of 59 patients with non-severe pneumonia after hospitalization. Thirty patients (21.9%) were transferred to the ICU, and 20 were non-survivors. The number of intubated patients was 22 (16%), while the in-hospital mortality rate was 20 (14.6%). Factors such as fatigue (p=0.039), comorbidity (p=0.042), the need for oxygen support (p=0.008), intensive care (p<0.001), and intubation (p<0.001) were higher in patients who died in the hospital (Table 1).

The mean age of patients who died in the hospital was higher (p<0.001). Additionally, oxygen saturation (p=0.006) and platelet values were lower (p=0.034) in this group. Furthermore, troponin and PCT levels were higher in the non-surviving group (p=0.001 and p=0.014, respectively) (Fig. 1). Leukocyte, lymphocyte, and neutrophil counts, and the number of days of hospitalization were not statistically different between the study groups (Table 1).

Patients were divided into severe and non-severe COVID-19 groups. The severe group included 78 (57%) patients with a mean age of 60.5 (min: 25 - max: 87) years. In the severe group, mean age, fever, leukocyte count, neutrophil, CRP, ferritin, PCT, and troponin levels were higher, and the difference was significant. Dyspnea, the need for oxygen support and intensive care, intubation, and mortality were higher in the severe group, and the difference was statistically significant (Table 2).

The mean PCT level was 0.35±0.90 $\mu$g/l in the study group. PCT value that may predict mortality and severe disease was examined by ROC analysis. A threshold value of >0.1205 for serum PCT in predicting in-hospital mortality yielded a sensitivity of 70%, specificity of 56.41%, PPV of 21.54%, and NPV of 91.67% (Fig. 2). When the threshold value for the estimation of serum PCT in severe disease was >0.124, the sensitivity was 44.87%, specificity was 27.12%, PPV was 44.87%, and NPV was 27.12% (Fig. 3).

**Table 2: Laboratory and clinical data according to disease severity**

| | Severe COVID-19 n=78 | | Non-severe COVID-19 n=59 | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Sex | | | | | |
| Male | 44 | 56.4 | 35 | 59.3 | 0.733 |
| Age/years[1] | 60.5 (25–87) | | 58 (24–81) | | **0.047** |
| Fever[1] | 37.2 (36–40) | | 36.7 (36–39.2) | | **0.008** |
| Cough | 45 | 57.7 | 31 | 52.5 | 0.548 |
| Dyspnea | 64 | 82 | 39 | 66.1 | **0.032** |
| Gastrointestinal complaints | 9 | 11.5 | 7 | 11.9 | 0.953 |
| Chest pain | 7 | 9 | 4 | 6.8 | 0.640 |
| Fatigue | 39 | 50 | 21 | 35.6 | 0.092 |
| Headache | 6 | 7.7 | 7 | 11.9 | 0.409 |
| Myalgia | 21 | 26.9 | 12 | 20.3 | 0.372 |
| Comorbidities | 54 | 69.2 | 35 | 59.3 | 0.229 |
| Hypertension | 33 | 42.3 | 22 | 37.3 | 0.553 |
| Diabetes | 25 | 32 | 18 | 30.5 | 0.847 |
| Cardiovascular disease | 11 | 14.1 | 9 | 15.2 | 0.850 |
| Leukocyte[1] | 7385 (1290–60100) | | 5600 (2700–12700) | | **0.001** |
| Lymphocyte[1] | 1000 (200–4310) | | 1100 (430–2760) | | **0.042** |
| Neutrophil[1] | 5860 (1790–22800) | | 3900 (1600–9120) | | **<0.001** |
| Platelet/$10^3$ [1] | 212 (71–617) | | 191 (79–486) | | 0.072 |
| C-Reactive Protein (mg/L)[1] | 117 (1.7–266) | | 63.2 (4.5–277) | | **0.001** |
| Ferritin ($\mu$g/L)[1] | 597.5 (51–2000) | | 425 (16.7–2000) | | **0.014** |
| D-Dimer($\mu$g/L)[1] | 820 (237–4400) | | 600 (190–4400) | | 0.108 |
| Lactate dehydrogenase (U/L)[1] | 376 (135–901) | | 330 (102–691) | | 0.067 |
| Procalcitonin (ng/ml)[1] | 0.13 (0.01–6.4) | | 0.09 (0.03–1.4) | | **<0.001** |
| Troponin ($\mu$g/L)[1] | 0.01 (0–0.2) | | 0.01 (0–0.06) | | **0.018** |
| Hospitalization (days)[1] | 13 (4–37) | | 8 (3–22) | | **<0.001** |
| Oxygen support | 77 | 98.7 | 28 | 47.5 | **<0.001** |
| Intensive care unit admission | 26 | 33.3 | 4 | 6.8 | **<0.001** |
| Intubation | 19 | 24.4 | 3 | 5.1 | **0.002** |
| Exitus | 17 | 21.8 | 3 | 5.1 | **0.006** |

[1]: Median value (minimum-maximum)

PCT levels were also analyzed for increasing levels. A one-unit increase in PCT increases mortality by 1.726 times in the analysis (Table 3).

**Table 3 : Logistic regression analysis of one unit increase in procalcitonin level and mortality**

| Procalcitonin | B | SE | p | OR | OR Lower | OR Upper |
|---|---|---|---|---|---|---|
| | 0.546 | 0.223 | 0.014 | 1.726 | 1.114 | 2.672 |

B: Logistic regression coefficient, SE: Standard error, OR: Odds ratio

## DISCUSSION

We found a significant relationship between serum PCT levels and mortality and disease severity in COVID-19 patients. The procalcitonin value was significantly higher in the group with in-hospital mortality. Additionally, the study revealed that individuals with a procal-

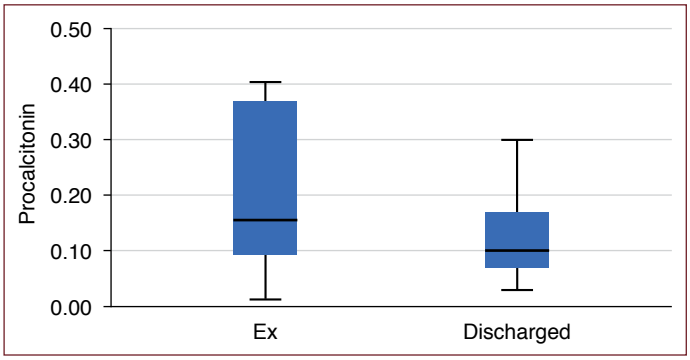
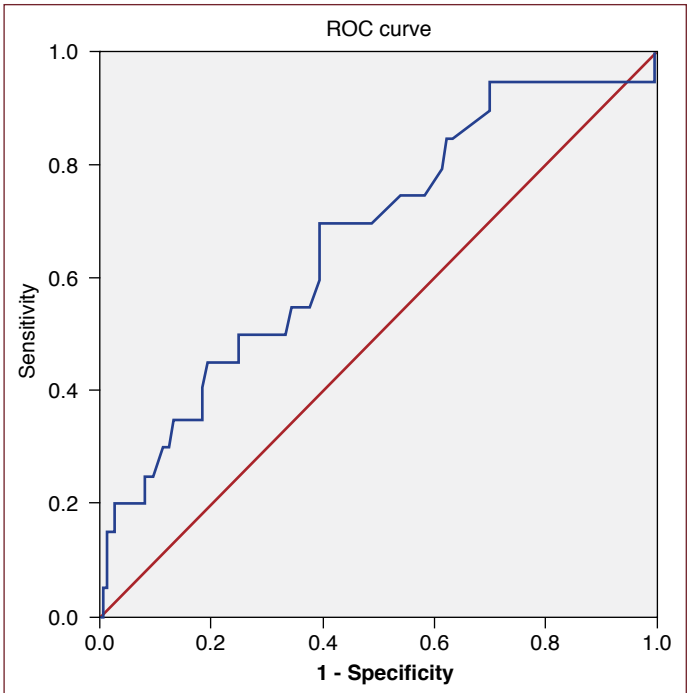



**Figure 1:** Relationship between procalcitonin and mortality.



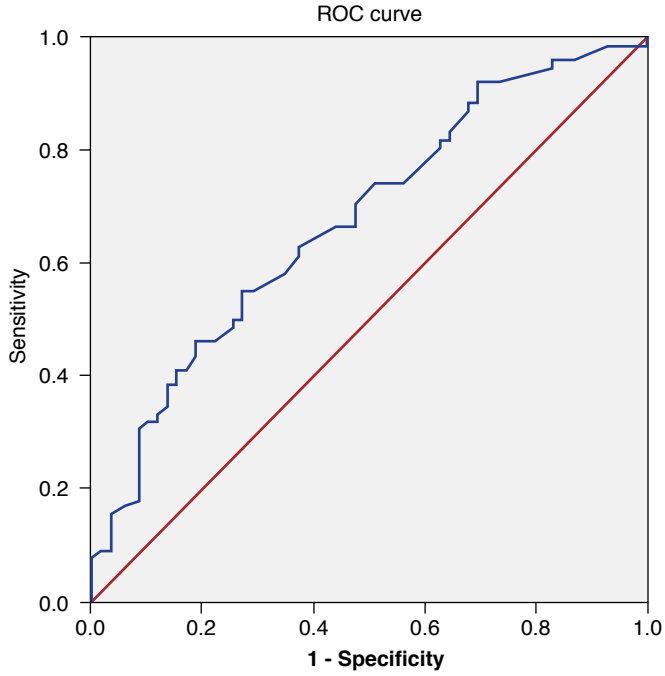

| Area | SE | p | 95% CI | | Cut-off | sen | spe | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| | | | Lower bound | Upper bound | | | | | |
| 0.672 | 0.066 | 0.014 | 0.542 | 0.802 | >0.1205 | 70.00 | 56.41 | 21.54 | 91.67 |

**Figure 2:** Evaluation of procalcitonin value to predict in-hospital mortality by ROC Analysis.

ROC: Receiver operating characteristic, SE: Standard error, CI: Convidence interval, sen: Sensitivity, spe: Specifity, PPV: Positive predictive value, NPV: Negative predictive value.

citonin value of ≤0.12 exhibit lower mortality. The severe group had significantly higher procalcitonin values compared to the non-severe group. However, a significant cutoff value for procalcitonin associated with disease severity could not be identified.

In-hospital mortality was higher in COVID-19 patients with advanced age, basal serum PCT, and troponin levels. Advanced age has been reported as an important independent determinant of mortality in COVID-19 diseases. In our study, increasing age was also associated with mortality.




| Area | SE | p | 95% CI | | Cut-off | sen | spe | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| | | | Lower bound | Upper bound | | | | | |
| 0.678 | 0.046 | **<0.001** | 0.589 | 0.768 | >0.124 | 44.87 | 27.12 | 44.87 | 27.12 |

**Figure 3:** Evaluation of procalcitonin value to predict disease severity by ROC analysis.

A study by Shyam-Sundar et al.[9] showed a relationship between troponin and mortality in COVID-19 cases. In another study of 2716 COVID-19 cases conducted by Case et al.,[10] in-hospital mortality was found to be higher in patients with elevated troponin levels (12.2%; p<0.001). In our study, in-hospital mortality was also higher in patients with a high troponin level (p=0.001).

Procalcitonin, a precursor to calcitonin, is typically synthesized and released by thyroid parafollicular C cells and remains usually undetectable in the physiological state. However, in the presence of inflammatory cytokines (IL-6, TNF-α) and bacterial endotoxins, elevated levels can be secreted from extrathyroidal tissues.

The primary mechanism of clinical worsening in COVID-19 patients is the cytokine storm. Proinflammatory cytokines such as IL-1β, IL-6, IL-10, G-CSF, IL-8, IL-17, TNF-α, and IFN-gamma were found to be increased in COVID-19 patients and were associated with disease severity, multiple organ failure, and mortality. IL-6 and other cytokines may trigger PCT. A positive correlation between PCT levels and disease severity and clinical impairment was also reported.[11]

High PCT level and mortality association were reported by Huang et al.[12] PCT level has good discriminating power in predicting mortality and disease severity. PCT can help identify serious cases and reduce mortality with early treatment.[3] Our study showed a correlation between PCT values, disease severity, and mortality.

Shen et al.[13] reported that PCT elevation is a potential biomarker for assessing the severity of COVID-19 and predicting prognosis.

Another study by Feng et al.[14] found that PCT elevation was strongly associated with both mortality and intensive care unit admission.

Twe et al.[15] showed that the optimal PCT cutoff point of 0.2 ng/mL is useful for predicting mortality. In the study where Zhang et al.[16] evaluated 221 cases of COVID-19, 23 cases with a PCT level of >0.17ng/mL were hospitalized in the intensive care unit, and 9 cases with a PCT level of >1ng/mL died, and the remaining cases had lower PCT levels. It has been noted that a higher PCT level indicates a worse prognosis and is associated with severity.

This study has limitations. Firstly, it was a single-center and retrospective study. Secondly, the number of cases was limited, and clinical data were restricted.

## CONCLUSION

Our results indicated that PCT elevation was correlated with mortality and disease severity in COVID-19 patients. PCT levels at admission may help physicians to identify severe disease early and guide clinical decisions. PCT measurement in COVID-19 cases can be used as a prognostic laboratory biomarker for critical conditions. Further studies are needed to understand the role of PCT in predicting mortality and disease severity in COVID-19 patients.

### Disclosures

**Ethics Committee Approval:** The study was approved by The Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (date: 26.10.2022, number: 514/236/27).

**Author Contributions:** Concept – B.Z.E.; Design – B.Z.E., E.D.; Supervision – N.K., E.D.; Fundings – B.Z.E., E.D.; Materials – S.Ş.C., N.K., E.D.; Data Collection and/or Processing – B.Z.E., S.Ş.C., N.K.; Analysis and/or Interpretation – E.D., B.Z.E.; Literature Search – B.Z.E., E.D.; Writing – B.Z.E., E.D.; Critical Reviews – S.Ş.C., N.K., E.D.

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