Efficacy of copeptin in distinguishing COVID-19 pneumonia from community-acquired pneumonia

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Abstract
The clinical symptoms of community-acquired pneumonia (CAP) and coronavirus disease 2019 (COVID-19)-associated pneumonia are similar. Effective predictive markers are needed to differentiate COVID-19 pneumonia from CAP in the current pandemic conditions. Copeptin, a 39-aminoacid glycopeptide, is a C-terminal part of the precursor pre-provasopressin (pre-proAVP). The activation of the AVP system stimulates copeptin secretion in equimolar amounts with AVP. This study aims to determine serum copeptin levels in patients with CAP and COVID-19 pneumonia and to analyze the power of copeptin in predicting COVID-19 pneumonia. The study consists of 98 patients with COVID-19 and 44 patients with CAP. The basic demographic and clinical data of all patients were recorded, and blood samples were collected. The receiver operating characteristic (ROC) curve was generated and the area under the ROC curve (AUC) was measured to evaluate the discriminative ability. Serum copeptin levels were significantly higher in COVID-19 patients compared to CAP patients (10.2 ± 4.4 ng/ml and 7.1 ± 3.1 ng/ml; p < .001). Serum copeptin levels were positively correlated with leukocyte, neutrophil, and platelet count (r = −.21, p = .012; r = −.21, p = .013; r = −.20, p = .018; respectively). The multivariable logistic regression analysis revealed that increased copeptin (odds ratio [OR] = 1.183, 95% confidence interval [CI], 1.033–1.354; p = .015) and CK-MB (OR = 1.052, 95% CI, 1.013–1.092; p = .008) levels and decreased leukocyte count (OR = 0.829, 95% CI, 0.730–0.940; p = .004) were independent predictors of COVID-19 pneumonia. A cut-off value of 6.83 ng/ml for copeptin predicted COVID-19 with a sensitivity of 78% and a specificity of 73% (AUC: 0.764% 95 Cl: 0.671–0.856, p < .001). Copeptin could be a promising and useful biomarker to be used to distinguish COVID-19 patients from CAP patients.

KEYWORDS
biochemical analysis, coronavirus, pathogenesis, research and analysis methods, respiratory tract, SARS coronavirus, virus classification
1 | INTRODUCTION

A series of unexplained cases of pneumonia were detected in Wuhan, China, in December 2019. The disease, which was found to develop as a result of a novel type of coronavirus, could not be brought under control despite the rapid measures of the Chinese government and spread all over the world. The coronavirus study group of the International Committee on Taxonomy of Viruses named the active virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and World Health Organization named the disease it caused coronavirus disease 2019 (COVID-19). A total of more than 90 million COVID-19 cases and more than 2 million deaths have been reported worldwide as of January 15, 2021.

Copeptin is an arginine-vasopressin (AVP) glycopeptide composed of 39 amino acids, and it is derived from the C-terminal part of pre-pro-AVP, which is the AVP precursor molecule. Copeptin is released from the neurohypophysis simultaneously by osmotic or hemodynamic stimulation with AVP and its plasma levels correlate well. AVP is an antidiuretic and vasoconstrictive hormone. It shows the endogenous stress response and its release is increased by stimuli, such as hypotension, hypoxia, hyperosmolarity, acidosis, and infections. However, its circadian rhythm, short half-life, and being an unstable molecule make it impossible to use it as a biomarker. Copeptin is a more stable peptide and its level in the blood can be easily detected.

Community-acquired pneumonia (CAP) is a pulmonary parenchymal infection acquired outside of a healthcare setting and it is one of the leading causes of morbidity and mortality worldwide. Bacterial infections are responsible for most of the CAP and the most commonly detected pathogens are Streptococcus pneumoniae, Haemophilus influenzae, atypical bacteria, and viruses. The clinical symptoms of CAP and COVID-19-associated pneumonia are generally similar. The gold standard test used to confirm the diagnosis of COVID-19 disease is the reverse transcriptase polymerase chain reaction (RT-PCR). However, it has been reported that the sensitivity of RT-PCR may not be high enough for the early diagnosis and treatment of patients. In addition, these tests may not be available in a state of emergency and it takes time for the result to come out. It has been demonstrated in various studies that thoracic computed tomography (CT), which is easily accessible in many hospitals, is a useful test that can be used in the diagnosis of COVID-19 pneumonia. However, one of the biggest problems in current pandemic conditions is the difficulty of performing CT scans for every patient who is suspected of pneumonia due to excessive patient load. In addition, thorax CT may not provide a clear distinction between COVID-19 and pneumonia due to other factors in every case. Peripheral ground-glass opacities observed on thoracic CT are characteristic for COVID-19 pneumonia and have a high sensitivity. However, this measurement has low specificity in distinguishing COVID-19 from other types of pneumonia, and false-positive cases are not rare.

It has been shown that some laboratory tests, such as leukocyte count, lymphocyte count, and C-reactive protein (CRP) used routinely, can be useful in distinguishing COVID-19 pneumonia from CAP. Copeptin levels are known to increase with infectious stimuli. It has been shown in the studies that serum copeptin levels increase in infectious diseases, such as CAP, ventilator-associated pneumonia, lower respiratory tract infections, and sepsis, and this increase is associated with poor prognosis. However, no studies have been found in the literature until now that evaluates the effectiveness of copeptin in distinguishing COVID-19 pneumonia from CAP.

This study aims to measure serum copeptin levels in COVID-19 pneumonia and CAP patients, to analyze the power of copeptin in predicting COVID-19 pneumonia, and to investigate the relationship of copeptin with various inflammatory markers.

2 | MATERIAL AND METHOD

2.1 | Design of the study and the subjects

This study included consecutive patients with COVID-19 pneumonia or CAP who were admitted to the Pandemic or Chest Disease Clinics in the Faculty of Medicine of Firat University between October 2020 and December 2020. Patients older than 18 years were included in the study. The present study was carried out at a tertiary university hospital, which is the primary referral center for patients with COVID-19 in the region.

COVID-19 pneumonia diagnosis was defined as a SARS-CoV-2 positive real-time RT-PCR from a nasal and/or throat swab together with clinical symptoms and radiological results (chest radiography and/or CT) suggesting COVID-19 pneumonia according to the national guideline of COVID-19 in China.

The diagnosis of CAP was determined based on evidence of pulmonary infiltrates on chest imaging (chest radiography and/or CT) together with the presence of lower respiratory tract infection symptoms. CAP cases were diagnosed according to the American Thoracic Society/Infectious Diseases Society of America 2019 guideline. All patients with CAP had negative RT-PCR results for SARS-COV-2. Also, patients whose chest radiography and/or CT results were typical for COVID-19 pneumonia were not included in the study, even if their PCR tests were negative.

Clinical parameters and demographic data were documented. After the questioning of the medical histories and physical examinations of the subjects, blood samples were collected from patients diagnosed with COVID-19 and CAP before the treatment.

Patients with acute myocardial infarction, acute coronary syndrome, heart failure, renal failure, peripheral artery disease, chronic obstructive pulmonary disease, interstitial lung disease, any organ malignancy or immunosuppression (HIV infection, solid organ or stem cell transplantation, or any immunosuppressive treatment), and pregnancy were excluded from the study.

The study was conducted in accordance with the Helsinki Declaration, and it was approved by the Ethical Committee of the
2.2 | Measurement of serum copeptin levels

The serum was separated by centrifuging the samples at 4000 g for 10 min and freezing at −80°C for further analysis. The serum copeptin levels were measured using a double-antibody sandwich enzyme-linked immunosorbent assay kit (Catalog No.: 201-12-5463 Human copeptin Elisa Kit: Sunred Biological Technology Co. Ltd.). The assay sensitivity was 0.067 ng/ml. The inter-assay and intra-assay calculation values were <12% and <10%, respectively. The detection range of copeptin was 0.07-20 ng/ml.

2.3 | Statistical analysis

The statistical analyses were conducted by using IBM SPSS Statistics 21 (Statistical Product and Service Solutions version 21, authorization code: d91314f638c364094170) software. The results were presented as mean ± SD. The statistical significance level was determined to be \( p < .05 \). The Student \( t \) test was used for comparing two independent samples. A one-way analysis of variance test was conducted for multiple sample comparisons. In addition, the Tukey test was conducted to determine the importance of any significant difference detected. The \( \chi^2 \) test was used to compare the gender distribution between the groups, while the Pearson correlation test was used in the evaluation of the parametric values. Binary logistic regression analyses were used for univariate and multivariate analysis to assess which variables were predictive of COVID-19 pneumonia, and odds ratios (ORs) were calculated with a 95% confidence interval (CI). The cut-off value for copeptin was determined by using the “receiver operating characteristic” (ROC) analysis method, and sensitivity and specificity values for copeptin were determined according to this value. “Area under curve” (AUC) value was determined with the ROC curve. The minimum required sample size was estimated as 26 for each group based on large effect size (Cohen’s \( d = 0.80 \)) expectation between groups in terms of copeptin levels (\( \alpha = .05, 1 - \beta = .80 \)). Gpower package version 3.6.1 was used for sample size estimations.

3 | RESULTS

3.1 | Comparison of basic demographic and laboratory data

The study population consists of 98 hospitalized patients with COVID-19 pneumonia and 44 hospitalized patients with CAP. The median age was 59.3 years, and 62.2% of the patients were men for COVID-19 patients. The median age was 66.6 years and 63.8% of the patients were men for CAP patients. No statistically significant difference was determined among the two groups in terms of sex (\( p = .87, \chi^2 = 0.025 \)) while the ages of patients in CAP were significantly higher compared to COVID-19 patients (\( p = .02 \)). Patients with COVID-19 showed a significantly lower leukocyte, neutrophil, lymphocyte, and platelet count compared to CAP patients in terms of complete blood count parameters (\( p = .018 \) for lymphocyte, \( p < .001 \) for others).

An analysis of the basic biochemical data of patients revealed that the COVID-19 group had significantly higher aspartate transaminase (AST) and D-dimer levels compared to the CAP group (\( p < .001 \) and \( p = .019 \); respectively).

An analysis of cardiac and inflammatory markers revealed that creatine kinase (CK) and CK-MB levels were significantly higher (\( p = .006 \) and \( p = .001 \); respectively) and procalcitonin levels were significantly lower in the COVID-19 group (\( p = .012 \)).

Additionally, oxygen saturation (SaO2) levels were significantly lower in the COVID-19 group compared to the CAP group (\( p < .001 \)). The demographical and laboratory data of the COVID-19 group and the CAP group are presented in Table 1.

3.2 | Evaluation of serum copeptin levels

The mean serum copeptin levels of COVID-19 and CAP patients were 10.2 ± 4.4 ng/ml and 7.1 ± 3.1 ng/ml, respectively. Serum copeptin levels were significantly higher in the COVID-19 group compared to the CAP group according to these results (\( p < .001 \)). Figure 1 shows the serum copeptin levels of the two groups.

3.3 | Correlation analysis

There was a negative correlation between the serum copeptin levels and leukocyte, neutrophil, and platelet count (\( r = -.21, p = .012; r = -.21, p = .013; r = -.20, p = .018 \) respectively) (Figure 2).

3.4 | Logistic regression analysis

The results of binary logistic regression analysis of the potential predictors of COVID-19 pneumonia are shown in Table 2. The univariable logistic regression model showed the following parameters had statistical significance, including age (OR = 0.974; 95% CI, 0.953–0.996; \( p = .02 \)), copeptin (OR = 1.292; 95% CI, 1.126–1.482; \( p < .001 \)), leukocyte count (OR = 0.803; 95% CI, 0.726–0.887; \( p < .001 \)), platelet count (OR = 0.991; 95% CI, 0.987–0.995; \( p < .001 \)), procalcitonin (OR = 0.625; 95% CI, 0.403–0.972; \( p = .04 \)), AST (OR = 1.055; 95% CI, 1.024–1.088; \( p < .001 \)), and CK-MB (OR = 1.038; 95% CI, 1.010–1.067; \( p = .008 \)). The multivariable logistic regression model indicated that increased copeptin (OR = 1.183; 95% CI, 1.033–1.354; \( p = .015 \)) and CK-MB (OR = 1.052; 95% CI, 1.013–1.092; \( p = .008 \)) levels and decreased leukocyte count (OR =
**TABLE 1** Comparison of the demographic and laboratory data of COVID-19 pneumonia and community-acquired pneumonia groups

|                      | COVID-19 pneumonia (n = 98) | Community-acquired pneumonia (n = 44) | p   |
|----------------------|-----------------------------|--------------------------------------|-----|
| Age, years           | 59.3 ± 18.2                 | 66.6 ± 14.8                          | .02 |
| Sex, male, n (%)     | 61 (62.2)                   | 28 (63.6)                            | .87 |
| SaO2, %              | 86.8 ± 5.3                  | 90.1 ± 4.1                           | <.001|
| Complete blood count |                            |                                      |     |
| Leukocyte, ×10^9/L   | 6.7 ± 3.9                   | 10.6 ± 4.3                           | <.001|
| Neutrophil, ×10^9/L  | 5.1 ± 3.8                   | 8.2 ± 4.3                            | <.001|
| Lymphocyte, ×10^9/L  | 1.1 ± 0.6                   | 1.5 ± 0.9                            | .008|
| Hemoglobin, g/dl     | 13.5 ± 1.9                  | 13.6 ± 2.0                           | .64 |
| Platelet, ×10^9/L    | 191.2 ± 88.8                | 275.7 ± 102.4                        | <.001|
| Biochemical markers  |                            |                                      |     |
| Urea, mg/dl          | 44.3 ± 24.3                 | 50.6 ± 36.4                          | .22 |
| Creatinine, mg/dl    | 0.92 ± 0.36                 | 0.95 ± 0.5                           | .73 |
| ALT, U/L             | 30.6 ± 19.3                 | 26.1 ± 17.5                          | .19 |
| AST, U/L             | 38.1 ± 18.6                 | 25.9 ± 13.2                          | <.001|
| LDH, U/L             | 346.3 ± 149.6               | 305.5 ± 113.4                        | .1  |
| D-dimer, mg/L        | 1.38 ± 1.47                 | 0.88 ± 0.42                          | .019|
| Inflammatory markers |                            |                                      |     |
| CRP, mg/L            | 71.4 ± 63.9                 | 90.1 ± 63.8                          | .11 |
| Procalcitonin, mg/L  | 0.38 ± 0.74                 | 0.90 ± 1.74                          | .012|
| Cardiac markers      |                            |                                      |     |
| CK, U/L              | 155.6 ± 192.1               | 93.0 ± 72.4                          | .006|
| CK-MB, U/L           | 32.7 ± 31.1                 | 19.5 ± 11.7                          | <.001|
| Copeptin, ng/ml      | 10.2 ± 4.4                  | 7.1 ± 3.1                            | <.001|

Note: Bold values are statistically significant values (p < .05). Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; CK, creatine kinase; LDH, lactate dehydrogenase; SaO2, oxygen saturation.

The results of the present study indicate that serum copeptin levels were significantly higher in the COVID-19 group compared to the CAP group. Furthermore, multivariable logistic regression analysis revealed that increased copeptin level was an independent predictor of COVID-19 pneumonia. In addition, copeptin was found to have a reasonable sensitivity (78%) and specificity (73%) in distinguishing COVID-19 patients from CAP patients.

**DISCUSSION**

The results of the present study indicate that serum copeptin levels were significantly higher in the COVID-19 group compared to the CAP group. Furthermore, multivariable logistic regression analysis revealed that increased copeptin level was an independent predictor of COVID-19 pneumonia. In addition, copeptin was found to have a reasonable sensitivity (78%) and specificity (73%) in distinguishing COVID-19 patients from CAP patients.

CAP is characterized by symptoms, such as fever, cough, sputum production, chest pain, and shortness of breath, as well as new pulmonary infiltrates on radiological examinations. COVID-19 disease often affects the lower respiratory tract and causes pneumonia. The clinical symptoms of CAP and COVID-19 associated pneumonia are generally similar. However, it is very important to distinguish COVID-19 pneumonia from CAP in current pandemic conditions and isolate these patients as it may cause significant public health problems. Also, early recognition of COVID-19 patients and hospitalization of severe forms are vital due to different treatment approaches and high mortality rates. It has been observed in some recent studies that various biomarkers, such as leukocyte count, lymphocyte count, red cell distribution width (RDW), procalcitonin, sedimentation, and CRP, have beneficial effects in distinguishing COVID-19 pneumonia from CAP.11,12 Patients with COVID-19 pneumonia were found to have significantly lower leukocyte, neutrophil, and lymphocyte counts compared to patients to CAP in our study. In addition, procalcitonin levels were found to be lower in the COVID-19 group, while there was no statistical difference between the two groups in terms of CRP levels. But these results are not surprising. Different inflammatory responses are expected in infections with different types of pathogens, and this may explain important differences in laboratory data. Bacterial infections are often the main pathogen in CAP patients, and these patients have higher leukocyte counts, neutrophils, and procalcitonin levels.21,22 In addition, previous studies have shown that lymphopenia is a typical feature in COVID-19 patients and may be related to the severity of the disease.20,23 In addition, a negative correlation was found between copeptin levels and the number of leukocytes, neutrophils, and platelets in our study. A positive correlation was found between disease severity and copeptin levels in the CAP patients in a previous study. No classification of severity was made for both pneumonia groups in our study. However, correlations between copeptin levels and leukocyte, neutrophil, and platelet counts seem to be related to disease severity.

One of the most important problems in COVID-19 patients is the dynamic changes in platelet count and platelet-related parameters. There is no evidence that the SARS-CoV-2 virus has its own procoagulant effects. The coagulopathy observed in COVID-19 patients is likely the result of a severe inflammatory
response and endothelial dysfunction. Patients with COVID-19 pneumonia usually have mild thrombocytopenia due to platelet depletion. In addition, there are various coagulation abnormalities, particularly high levels of fibrinogen and D-dimer. It is known that there are significant associations between COVID-19 severity and high D-dimer level and low platelet count. Yu et al. found that the D-dimer level was significantly higher in COVID-19 patients and was associated with inflammation in their study evaluating D-dimer levels in patients with COVID-19 and bacterial pneumonia. D-dimer levels were found to be significantly higher in COVID-19 patients in our study than in CAP patients in our study, consistent with current literature.

Angiotensin-converting enzyme 2 receptors play a very important role in the pathogenesis of the virus. Myocardial damage is one of the important pathogenic features of COVID-19, and it is known that cardiac biomarkers are increased, especially in those with severe disease. In addition, it was determined that patients with high CK and CK-MB levels were at significantly increased risk of serious illness or intensive care unit admission.
CK-MB levels were significantly higher in COVID-19 patients compared to CAP patients in our study, consistent with the literature.

The physiological functions of AVP in regulating fluid balance, vascular tone, and endocrine stress response are well known. Copeptin is released simultaneously with AVP from the neurohypophysis due to osmotic, hemodynamic, and stress-related stimuli. Copeptin release is stimulated by many physiological and pathological stimuli, such as pain, infection, hypoglycemia, hypoxemia, and others.
exercise, stroke, and shock. Evidence suggests that copeptin is superior to cortisone in determining stress levels. Copeptin has been shown to have an active role in lung diseases, such as pneumonia, and in being superior to traditional inflammatory markers as a prognostic marker in CAP patients. It was determined in a study conducted in children that serum copeptin levels were higher in children with pneumonia compared to the healthy control group, and copeptin was a reliable marker that can be used to evaluate the severity and prognosis of pneumonia in this disease group. Similarly, Du et al. reported that copeptin reflected the severity of pneumonia in children and was associated with pneumonia complications. Copeptin has also been shown to be a useful biomarker for predicting severity and complications in pneumonia patients in studies conducted in adults. Seligman et al. determined that copeptin levels gradually increased with the severity of sepsis and that copeptin was an independent predictor of mortality in VIP in their study evaluating 71 VIP patients. Müller et al. found that the copeptin concentration was significantly higher in the control group and that patients diagnosed with CAP had the highest copeptin concentration in patients with acute bronchitis and acute exacerbation of COPD in their study comparing copeptin values in various etiologies of lower respiratory tract infection. It was found in this study that as the severity of pneumonia increased, copeptin levels increased, and copeptin levels were significantly higher in patients who died compared to those who survived. The importance of copeptin in COVID-19 patients and its value as a biomarker in distinguishing COVID-19 pneumonia from CAP remains unknown. Our study is the first study conducted in this field and the results were quite striking in our study. Copeptin levels were found to be significantly higher in COVID-19 patients compared to CAP patients in our study. It is known that copeptin levels increase due to hemodynamic, osmotic, or inflammatory reasons. It was determined that copeptin levels increased as the severity of the disease and sepsis increased in pneumonia patients. COVID-19 may cause the involvement of different organs and systems such as the lung, liver, kidney, heart, gastrointestinal, hematological, and nervous system. High mortality in infected patients is associated with diffuse lung involvement and multiple organ failure. It is known that COVID-19 causes multiorgan involvement, has a more severe course, and has more common lung involvement compared to CAP. It was determined that COVID-19 patients have higher intensive care unit admission, development of acute respiratory distress syndrome, mechanical ventilation attachment, and mortality rates compared to CAP patients. Therefore, hemodynamic and osmotic disorders are expected to be more severe in COVID-19 patients. Hemodynamic and osmotic stimuli may have increased copeptin release more due to changes in blood pressure and plasma osmolality in these patients. In addition, it is known that endotoxins and inflammatory markers with increased levels during respiratory tract infections stimulate AVP secretion. Cytokine storm is known to be one of the most important features of COVID-19 pneumonia and is associated with the severity and mortality of the disease. Inflammatory markers and cytokines were found to be higher in COVID-19 patients compared to CAP patients. This excessive cytokine response and inflammatory response that develops in COVID-19 patients may contribute to the increase in copeptin level. In addition to these, it is known that gas exchange in the lungs during lower respiratory tract infections causes changes in the AVP system. In addition, AVP release may be induced by several other factors, such as acidosis, pain, hypoxia, or neuroendocrine stress. Severe hypoxemia may be seen in patients with COVID-19 pneumonia due to loss of lung perfusion regulation and hypoxic vasoconstriction in addition to intrapulmonary shunt. Hypoxemia is a common result in patients with COVID-19 pneumonia and is independently associated with hospital mortality. It was determined in our study that SaO2 levels were lower in COVID-19 patients compared to CAP patients. Conditions such as hypoxia and pain that develop in the case of severe pneumonia in addition to the aforementioned conditions may also stimulate the release of AVP and simultaneously copeptin from the neurohypophysis.

The diagnostic value of routine laboratory tests in distinguishing COVID-19 pneumonia from CAP was evaluated by ROC analysis in a study. Pan et al. determined that RDW, mean corpuscular hemoglobin concentration (MCHC), and hemoglobin have a good discriminatory ability in the prediction of COVID-19 pneumonia with ROC analysis. It was observed in this study that when the cut-off value for RDW with the highest AUC (0.87) was taken as 13.35, it distinguished COVID-19 pneumonia with 79.8% sensitivity and 84.6% specificity. Similarly, the value of copeptin in distinguishing COVID-19 pneumonia has been evaluated with ROC analysis in our study. When the optimal cut-off value of copeptin in terms of distinguishing COVID-19 pneumonia from CAP was determined as 6.83 ng/ml, its sensitivity and its specificity were found to be 78% and 73%, respectively. Also, it is shown that copeptin was found an independent predictor of COVID-19 pneumonia according to multivariable logistic regression analysis. Copeptin may be a simple and useful marker that can be used to distinguish COVID-19 pneumonia from CAP, has reasonable sensitivity and specificity, and gives quick results according to the results obtained from our study. However, our study is the first study conducted in this field, and studies with larger series are needed to support the findings of our study. There were some limitations to this study. The primary limitation of our study is the lack of follow-up data. The importance of copeptin in these disease groups could be demonstrated more clearly if the serum copeptin levels were also examined during the follow-up and posttreatment period. Second, the value of copeptin in critical patients could not be determined since patients requiring intensive care were not included in the study. Lastly, the number of patients in the CAP group in our study is relatively low and the healthy control group was not included in the study.

In conclusion, it was determined in this study that serum copeptin levels were higher in COVID-19 pneumonia patients compared to CAP patients, and copeptin distinguished COVID-19 pneumonia with a reasonable level of sensitivity and specificity. Copeptin can be a useful biomarker that can be used for distinguishing COVID-19 pneumonia patients from CAP patients.
CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conception and design of the study: Mutlu Kuluoztürk, Erdal In, and Selda Telo. Acquisition of data: Mutlu Kuluoztürk, Ayşegül A. Geçkil, Selda Telo. Analysis and interpretation of data: Erdal In and Ercan Karabulut. Drafting the article: Erdal In, Mutlu Kuluoztürk, and Ayşegül A. Geçkil. Revising it critically for important intellectual content: Erdal In and Ercan Karabulut. Final approval of the version to be submitted: Erdal In, Mutlu Kuluoztürk, Selda Telo, Ercan Karabulut, and Ayşegül A. Geçkil.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The database used and/or analyzed during the current study is not publicly available but can be available from the corresponding author on reasonable request.

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