Abstract. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is likely to cause uric acid dysregulation, resulting in abnormal serum uric acid concentrations. In this study, we aimed to evaluate the associations between admission serum uric acid levels and demographic, clinical and laboratory features of patients hospitalized with Coronavirus disease 2019 (Covid-19) and to explore the effect of admission serum uric acid values on clinical outcomes.

Methods. In this retrospective study, the demographic, clinical and laboratory data of patients with confirmed Covid-19 were collected from the electronic health records of the hospital. The study population was stratified according to the quartiles of serum uric acid; Quartile 1: ≤3.5 mg/dl, Quartile 2: 3.6 mg/dl to 6 mg/dl for women and 3.5 mg/dl to 7 mg/dl for men, Quartile 3: ≥6 mg/dl for women and ≥7 mg/dl for men. The outcomes were the development of acute kidney injury (AKI) and in-hospital mortality.

Results. 146 patients were included in the analysis. The median age of patients was 57 (IQR, 49-65) years and 70.5% were male. The overall median serum uric acid level on admission was 4.4 (IQR, 3.5-5.9) mg/dl. Participants in the highest serum uric acid quartile were significantly more hypertensive, and diabetics and showed significantly higher estimated glomerular filtration rate (eGFR) and troponin T levels compared to patients in the lowest serum uric acid quartile. On the other hand; patients in the lowest serum uric acid quartile were admitted with more severe disease than patients with Quartile 2. During follow-up, 19 (13.1%) participants experienced AKI and 15 (10.3%) died. There were significantly positive correlations between AKI and age, hypertension, serum creatinine (SCr), hyperuricemia, C-reactive protein (CRP) and Troponin T (r=0.263, P=0.001; r=0.192, P=0.02; r=0.182, P=0.028; r=0.235, P=0.004; r=0.219, P=0.008; r=0.236, P=0.004, respectively). A significantly negative correlation was noted between AKI and eGFR (r=−0.189, P=0.023). According to multivariate logistic regression analysis, AKI development was independently associated with CRP and hyperuricemia (OR, 1.009; 95% CI, 1.0082-1.016, P=0.009 and OR, 4.314; 95% CI, 1.190-15.633, P=0.026). The receiver operating characteristic (ROC) curve showed that the area under the curve (AUC) of the concentration of serum admission uric acid was 0.693 (95% CI 0.537–0.849, P<0.006) and the cutoff value was 5.45 mg/dl (sensitivity: 68.4%; specificity: 75.6%).

Conclusions. Hyperuricemia and increased CRP were independent risk factors for the development of AKI. Although patients with lower uric acid values developed more severe symptoms, mechanical ventilation and mortality rates were not found to be significantly different among patients with Covid-19 grouped based on admission serum uric values. Following the patients admitted with high uric acid levels closely in terms of renal functions would be helpful for early detection of AKI.

Key words: Coronavirus disease 2019, uric acid, acute kidney injury, mortality.

Conflict of interest statement. The authors declare no competing interest.
Introduction. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the novel coronavirus that causes the pandemic of coronavirus disease 2019 (COVID-19). Clinical presentations of COVID-19 can range from asymptomatic infection, self-limited influenza-like symptoms, and acute pneumonia to severe respiratory failure [1]. COVID-19 is also characterized by extra-pulmonary manifestations involving the gastrointestinal tract, the neurological and cardiovascular systems, and the kidneys [2]. Early detection of patients who are likely to develop the critical disease is fundamental to identifying high-risk patients and allocating limited resources.

Uric acid is generated as a final product of purine degradation through the normal physiological process in hepatocytes and is removed in the kidney and gut through the action of urate anion exchanger 1 (URAT1) and glucose transporter 9 (GLUT9) [3]. Serum uric acid level is a result of a counterbalance between uric acid production and excretion. Uric acid accounts for >50% of total antioxidant activity in the blood, slows cell aging through its antioxidative effect and has a protective effect against some diseases [4]. However, paradoxically, uric acid is involved in pathological inflammatory reactions by activating the renin-angiotensin system, acting as an oxidative stressor, and decreasing the bioavailability of nitrogen oxide [5]. There is a general agreement that hyperuricemia increases the risk of

Meric Oruc
mericozd@yahoo.com
stroke and death [6], cardiovascular diseases [7], gout, insulin resistance, type 2 diabetes [8, 9], and all-cause mortality [10].

Studies have shown that inflammatory cytokines are significantly higher in COVID-19 patients than in controls [11]. Inflammatory cytokines have a direct catabolic effect on skeletal muscle and cause wasting of muscles and eventually apoptosis [12]. Tissue hypoxia and cell death cause hyperuricemia, which furthers microvascular disease, inflammation, endothelial dysfunction, and kidney disease [13]. However previous studies have shown that serum uric acid concentrations were markedly lower in patients with especially severe COVID-19 disease [14-17]. Moreover, hypouricemia was found to be strongly associated with a poor prognosis in SARS-CoV-2-affected patients [18].

In this study, we aimed to evaluate the associations between admission serum uric acid levels and demographic, clinical and laboratory features of patients hospitalized with COVID-19 and to explore the effect of admission serum uric acid values on clinical outcomes.

**Materials and Methods.** Patients hospitalized in infectious diseases clinics with a diagnosis of COVID-19 between October 2020 and December 2020 were enrolled in this retrospective study. The diagnosis of COVID-19 was confirmed with at least one positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test result in cases admitted with symptoms, signs and findings (laboratory/radiological) suggestive of COVID-19, according to the national guidelines [19].

The identification and classification of patients with COVID-19 on admission to emergency departments have been based on the adaptation of the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidance. Patients were divided into mild, moderate, severe, and critically severe groups [20]. Critically severe patients followed in intensive care units were excluded from the study. Patients with acute kidney injury (AKI) and/or estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m², patients on chronic kidney replacement therapy (hemodialysis, peritoneal dialysis or kidney transplantation) and who were transferred from intensive care units were excluded. Patients with incomplete or missing serum uric acid values within 24 hours after admission were also excluded.

The source of medical records was OCTOMED (Kartal Dr. Lutfi Kirdar City Hospital Automation Program) electronic database system. The National Public Health Data Management System database was also used as an external data source, particularly to track the RT-PCR test results and to obtain data on previous creatinine values. We collected data for patient demographics, comorbidities, vital signs and laboratory test results on admission. Laboratory data consisted of measurements of lymphocyte, serum creatinine (SCr), uric acid, albumin, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, fibrinogen, D-dimer and troponin T levels. The first value of laboratory data within 24 hours of hospital admission was taken. For patients who had multiple qualifying hospital admissions, we included only the first hospitalization however outcomes were recorded according to the last hospitalization.

To examine the associations between serum uric acid levels and baseline characteristics and outcomes, the study population was stratified according to the quartiles of serum uric acid; Quartile 1: ≤ 3.5 mg/dl, Quartile 2: 3.6 mg/dl to 6 mg/dl for women and 3.5 mg/dl to 7 mg/dl for men, Quartile 3: ≥ 6 mg/dl for women and ≥ 7 mg/dl for men. The lowest level of serum uric acid was also recorded for each patient whom had at least two serum uric acid values during hospitalization.

Outcomes data were retrieved until January 2020. By the time of this analysis, all patients had either died or had been discharged from the hospital. The clinical outcomes were the development of AKI and in-hospital mortality.

**Definitions.** The date of hospital admission was accepted as the first day. Patients using antihypertensive drugs were accepted as hypertensive, while those using antidiabetic drugs were accepted as diabetic.

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [21]. AKI during hospital stay was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria [22]. The available baseline value for each patient was taken as the mean outpatient value 7-365 days prior to admission [23]. If the baseline value of SCr was not available, the lowest value during hospitalization was taken [22]. We did not use the urine output criteria to define AKI as the documentation of urine output in the electronic health record was unavailable.

Hypouricemia was defined as a serum uric acid value < 2.5 mg/dl, a cutoff previously used for the study in SARS-CoV-1 [24]. Hyperuricemia (Quartile 3) was defined as a serum uric acid value ≥ 6 mg/dl for women and ≥ 7 mg/dl for men [25].

The follow-up period started from the date of hospitalization and ended the day of discharge or in-hospital mortality.

**Statistical analysis.** Baseline characteristics were reported by serum uric acid quartiles as medians and interquartile ranges (IQRs) for continuous variables, and as counts and percentages for categorical variables. Categorical variables were compared using the chi-square test or Fisher tests. The nonparametric Kruskal-Wallis test with Bonferroni correction was used to compare groups. A Spearman’s correlation analysis was used to examine associations between AKI and the study variables. Multivariate logistic regression analysis was performed to identify risk factors. The dependent variable was AKI, and the independent variables were the other study variables. Variables were selected for regression analysis based on Spearman’s correlation analysis if P<0.05. To determine the discriminative power of admission uric acid for the development of AKI, the
area under the receiver operating characteristic (ROC) curves were calculated. All tests were performed using SPSS for Windows, version 17.0 software (SPSS Inc. Chicago, IL, USA). P values of less than 0.05 were considered statistically significant.

**Ethics.** The study protocol was approved by the Clinical Research Ethics Committee of Kartal Dr. Luťfi Kirdar City Hospital (approval date: 29.12.2021, approval number: 2021/514/216/26) The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

**Results.** A total of 146 patients were included in the study. Table 1 shows the demographic, clinical and laboratory characteristics of the study patients on admission based on serum uric acid levels.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The demographic, clinical and laboratory characteristics of the patients on admission according to serum uric acid levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Cases (n = 146)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 (49-65)</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>103 (70.5)</td>
</tr>
<tr>
<td>HT, n (%)</td>
<td>64 (43.8)</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>48 (32.9)</td>
</tr>
<tr>
<td>Time diagnosis to admission (day)</td>
<td>6 (2-8)</td>
</tr>
<tr>
<td>Fever, n (%)</td>
<td>28 (19.2)</td>
</tr>
<tr>
<td>Severe disease, n (%)</td>
<td>99 (67.8)</td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>120 (110-130)</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>70 (70-80)</td>
</tr>
<tr>
<td>Lymphocyte (×10³/µL)</td>
<td>1.0 (0.6-1.3)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.82 (0.69-0.91)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>95.4 (83.7-105.6)</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>4.4 (3.5-5.9)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>36 (27-55.5)</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>367.5 (284-473.8)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>80.7 (45.8-134)</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>509.4 (277.1-806.6)</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>600 (493.5-683.5)</td>
</tr>
<tr>
<td>D-Dimer (µg/L)</td>
<td>810 (540-1330)</td>
</tr>
<tr>
<td>Troponin T (µg/L)</td>
<td>0.01 (0.007-0.013)</td>
</tr>
</tbody>
</table>

Quartile 1: ≤ 3.5 mg/dl, Quartile 2: 3.6 mg/dl to 6 mg/dl for women and 3.5 mg/dl to 7 mg/dl for men, Quartile 3: ≥ 6 mg/dl for women and ≥ 7 mg/dl for men. Values are presented as median (interquartile range) or number (percent). Kruskal-Wallis analysis with Bonferroni adjustment was used to compare groups. Compared with Quartile 1: significant P value labeled as*, Compared with Quartile 2: significant P value labeled as #.

AST: aspartate aminotransferase; CRP: C-reactive protein; dBP: diastolic blood pressure; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HT: hypertension; LDH: lactate dehydrogenase; sBP: systolic blood pressure.

The median age of the patients was 57 (IQR, 49-65) years and 70.5% of them were male. Sixty-four (43.8%) patients had a history of hypertension and 48 (32.9%) had diabetes mellitus. 47 (32.2%) patients had a mild to moderate, and 99 (67.8%) had a disease classified as severe. The overall median serum uric acid level on admission was 4.4 (IQR, 3.5-5.9) mg/dl. Participants in the highest serum uric acid quartile were significantly more hypertensive, and diabetics and showed significantly lower eGFR and higher troponin T levels compared to patients in the lowest serum uric acid quartile. On the other hand, patients in the lowest serum uric acid quartile were admitted with more severe disease than patients in Quartile 2.

Overall, patients were followed for a median of 7 days (IQR, 5–12). During hospitalization, the lowest serum uric acid values were recorded for 93 patients. The lowest serum uric acid value was 3.7 (IQR, 3.2-4.5) mg/dl, and the time from admission to the lowest level of serum uric acid was 4 (IQR, 1–6) days. At the time of the lowest level of uric acid recorded during hospitalization, 74 (78.7%) of patients were classified as severe.

During follow-up, 19 (13.1%) participants experienced AKI and 15 (10.3%) died. Individuals in the
highest quartile of serum uric acid had the highest proportion of patients developing AKI. There were no significant differences in mechanical ventilation and in-hospital mortality rates among the groups (Table 2).

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>All Cases (n = 146)</th>
<th>Quartile 1 (n = 34)</th>
<th>Quartile 2 (n = 90)</th>
<th>Quartile 3 (n = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury, n (%)</td>
<td>19 (13.1)</td>
<td>4 (11.8)</td>
<td>8 (8.9)</td>
<td>7 (31.8)*</td>
<td>0.023</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>16 (10.9)</td>
<td>3 (8.9)</td>
<td>9 (10)</td>
<td>4 (18.2)</td>
<td>0.441</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>15 (10.3)</td>
<td>3 (8.9)</td>
<td>8 (8.9)</td>
<td>4 (18.2)</td>
<td>0.449</td>
</tr>
</tbody>
</table>

Quartile 1: ≤ 3.5 mg/dl, Quartile 2: 3.6 mg/dl to 6 mg/dl for women and 3.5 mg/dl to 7 mg/dl for men, Quartile 3: ≥ 6 mg/dl for women and ≥ 7 mg/dl for men. Values are presented as median (interquartile range) or number (percent). Kruskal-Wallis analysis with Bonferroni adjustment was used to compare groups.

Compared with Quartile 1: significant P value as*, Compared with Quartile 2: significant P value labeled as #.

There were significantly positive correlations between AKI and age, hypertension, SCr, hyperuricemia, CRP and Troponin T (r=0.263, P=0.001; r=0.192, P=0.02; r=0.182, P=0.028; r=0.235, P=0.004; r=0.219, P=0.008; r=0.236, P=0.004, respectively). A significantly negative correlation was noted between AKI and eGFR (r=-0.189, P=0.023). Multivariate logistic regression analysis of risk factors associated with the development of AKI in patients hospitalized with COVID-19 is shown in Table 3.

### Table 3

Multivariate logistic regression analysis of risk factors associated with the development of AKI in patients with COVID-19 on admission

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.061</td>
<td>0.998-1.129</td>
<td>0.057</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.742</td>
<td>0.534-5.687</td>
<td>0.358</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>1.008</td>
<td>0.965-1.054</td>
<td>0.707</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>4.314</td>
<td>1.190-15.633</td>
<td>0.026</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.009</td>
<td>1.002-1.016</td>
<td>0.009</td>
</tr>
<tr>
<td>Troponin T(µg/L)</td>
<td>0.014</td>
<td>0.000-1.693</td>
<td>0.781</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; eGFR: estimated glomerular filtration rate.

AKI development was independently associated with CRP and hyperuricemia (OR, 1.009; 95% CI, 1.002-1.016, P=0.009 and OR, 4.314; 95% CI, 1.190-15.633, P=0.026).

ROC curve analyses were used to compare the predictive value of admission serum uric acid value for development of AKI. The ROC curve showed that area under the curve (AUC) of the concentration of serum admission uric acid was 0.693 (95% CI 0.537–0.849, P=0.006) and the cutoff value was 5.45 mg/dl (sensitivity: 68.4%; specificity: 75.6%) (Figure 1).

Fig. 1. ROC curve showed the prognostic value of admission uric acid (UA) in predicting AKI.
Discussion. Our study showed that patients in the lowest serum uric acid quartile had a higher risk of developing severe symptoms than patients in Quartile 2 (3.5 mg/dl to 6 mg/dl for women and 3.5 mg/dl to 7 mg/dl for men). The percentage of severe disease increased during hospitalization at the time of the lowest value of serum uric acid recorded. Patients with hyperuricemia were more diabetic and hypertensive and we found that higher admission serum uric acid levels were associated with higher troponin levels and increased risk of AKI. Hyperuricemia and increased CRP were independent risk factors for the development of AKI. Although patients with lower uric acid values developed more severe symptoms on admission, mechanical ventilation, and mortality rates were not found to be significantly different among patients with COVID-19 grouped based on admission serum uric values.

Uric acid is generated in the liver from the catabolism of exogenous and endogenous purine mononucleotides into hypoxanthine and guanine [26]. Hypoxanthine is further oxidized by xanthine dehydrogenase/oxidase to form xanthine, which is further oxidized by the same enzyme to form uric acid. This constitutes the end product of purine nucleotide metabolism in higher primates [27]. In other mammals, uric acid is further degraded by uricase, an enzyme that primes lactic acid production, to become allantoin, which is more water-soluble than uric acid and can be efficiently excreted in urine [28]. In humans, approximately two-thirds of all uric acid is excreted in the urine, and one-third is excreted in the gastrointestinal tract [29]. Uric acid is filtered by the glomeruli and reabsorbed by the proximal tubule with a normal fractional excretion of 10% [26]. URAT1 reabsorbs glomerular-filtrated uric acid and is localized on the luminal side of proximal tubule cells, while GLUT9 allows intracellular uric acid to exit through the basolateral side of the cells [30]. At high concentrations, uric acid is thought to induce cytokine and chemokine production (ie, Tumour necrosis factor-alpha, monocyte chemoattractant protein-1), leading to the activation of the inflammatory process in several tissues and causing endothelial dysfunction and fibrosis. Nonetheless, under physiologic concentrations, urate acts as a potent antioxidant being able to sequester superoxide anion and hydroxyl radicals [13, 31].

SARS-CoV-2 infection is likely to cause uric acid dysregulation, resulting in abnormal serum uric acid concentrations. In our clinical observation, patients with COVID-19 infection had lower serum uric acid levels than the normal range. It is consistent with previous research findings [14-17, 32]. The prevalence of hypouricemia is approximately 0.3% in the general ambulatory population and ranges between 1.2% and 2.5% among hospitalized patients [33, 34]. In our study, 9.7% of the patients developed hypouricemia during hospitalization. In a previous study, the prevalence of low serum uric acid levels increased from 6.6% upon admission to 19.7% during hospitalization among patients with COVID-19 [35].

Low serum uric acid might be the cause or result of the illness. As a primary antioxidant, serum uric acid could be consumed by oxidizing agents to prevent an inflammatory response therefore, the cytokine storm syndrome initiated by SARS-CoV-2 infection was likely to cause an obvious consumption of uric acid and a significant decrease in its serum levels. Although little is known about the effects of cytokines on uric acid transport, it is speculated that some cytokines modulate activities of specific channels or transporters by various mechanisms [36-38], and thus may affect functions of urate transporters including URAT1 and GLUT9 [39-40]. In a previous study, it was shown that SARS-CoV-2 infection caused an early and specific dysfunction of the kidney proximal tubule characterized by low molecular weight proteinuria, defective tubular handling of uric acid and phosphate, and neutral aminoaciduria. Inappropriate uricosuria was found to be associated with disease severity and the need for mechanical ventilation in this study [16].

Low serum levels of uric acid were found to be strongly associated with disease severity and with progression to death and respiratory failure requiring mechanical ventilation [35]. Hu et al showed that serum uric acid levels at admission were lower in patients with COVID-19 than in controls and also the serum uric acid level was lower in severe patients than those in moderate patients, particularly in males [32]. Chen et al reported a U-shaped association between higher and lower baseline serum uric acid levels and increased risk of composite outcomes including intensive care unit admission, mechanical ventilation and death [41]. Liu et al. found that low levels of uric acid on admission were associated with 28-day all-cause mortality in 12,413 patients with COVID-19 [18].

Nevertheless, high uric acid concentrations can have direct pathophysiological effects, including increased oxidative stress, inflammation, endothelial dysfunction, activation of the renin-angiotensin-aldosterone system, and insulin resistance [42]. Hyperuricemia has been found to be associated with various diseases, including coronary heart disease [43], hypertension [44], kidney failure [45], and chronic obstructive pulmonary disease exacerbations [46]. While serum uric acid is likely a biomarker of a catabolic state, it may also have a contributory role in the AKI. A marked rise in serum uric acid can result in high urinary uric acid concentrations that can form crystals and cause tubular injury and inflammation and oliguric or non-oliguric AKI. There is also increasing evidence that uric acid may also contribute to AKI in the absence of crystal deposition, possibly by causing low-grade tubular injury and activation of inflammasomes leading to intrarenal inflammation [47]. In non-COVID-19, hyperuricemia has shown to be associated with a higher risk of AKI, progression of chronic kidney disease (CKD), and mortality [48]. A study conducted in Wuhan hospital with 174 COVID-19 patients showed that serum uric acid was an independent predictor of AKI, with moderate...
accuracy (AUC 0.71) to predict AKI [49]. Chauhan K et al also showed that hyperuricemia was independently associated with AKI and in-hospital mortality as well as associated with higher procalcitonin and troponin I levels in hospitalized COVID-19 patients [50].

This study has several limitations. First, the number of patients included in this study is limited and also the observation design did not permit us to establish causality between serum uric acid concentrations and outcomes. Second, we could not include patients with critically severe diseases because of the study design. Third, an accurate baseline serum creatinine and urine output was not available, which may have led to an under or overestimation of AKI or erroneous associations. In addition, because of the retrospective nature of the study, information about the use of the following drugs, known to interfere with uric acid metabolism such as (allopurinol, febuxostat, fenofibrate, angiotensin receptor blockers and trimethoprim-sulfamethoxazole) could not be recorded.

The present study demonstrated that the severe disease rate on admission was found to be higher in patients with the lowest serum uric acid values compared to patients with serum uric acid values; of 3.6 mg/dl to 6 mg/dl for women and 3.6 mg/dl to 7 mg/dl for men. Hyperuricemia and increased CRP were independent predictors of AKI. Following patients admitted with high uric acid levels closely in terms of renal functions would be helpful for early detection of AKI. The relationship between uric acid and COVID-19 is complicated and further studies are needed to clarify this issue.

Funding: None

Conflicts of interest: The authors declare no conflict of interest.

Data availability statement: The data that support the findings of this study are available from the corresponding author, [M.O.], upon reasonable request.

Authors’s contributions:

Meric Oruc: Conception and design, data acquisition, analysis and interpretation of data, drafting the article, providing intellectual content of critical importance to the work described

Asye Batirel: Conception and design, analysis, providing intellectual content of critical importance to the work described

References:


