ORIGINAL RESEARCH

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Quantitative Volumetric CT Analysis of COVID-19 Pneumonia and Correlation with Neutrophil-lymphocyte Ratio

COVID-19 Pnömonisinin Kantitatif Hacimsel BT Analizi ve Nötrofil-lenfosit Oranı ile Korelasyonu

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Abstract

Objective: Although scientific community has various knowledge about coronavirus pandemic, further studies are needed about its nature. The aim of our study is to explore the relationship between the imaging and laboratory findings of Coronavirus disease-2019 (COVID-19).

Method: Our study is a retrospective single-center study on patients with COVID-19. Patients with chest computed tomography and with positive reverse-transcription polymerase chain reaction test results were examined. Total lung volume and lesion volume were calculated semi-automatically by Osirix software. Interclass correlation coefficient was used for testing consistency between the observers. Patients were divided into three groups as mild, moderate, and severe considering the involved lung volume. The relationship between laboratory findings and radiological severity investigated with area under the curve in receiver operating characteristic plot.

Results: One hundred and six patients were included (female: 44, male: 62) in this study and the median age was 55 years. The most common radiologic features were peripheral, multifocal, ground glass opacities with sub-pleural and basal distribution. A positive and moderate correlation was found between the percentage of involvement and the neutrophil to lymphocyte ratio (N/L) (rho=0.635, p<0.001), which was the most correlated laboratory feature with radiological severity. The cut-off value was 1.1195 for N/L ratio (95.5% sensitivity, 85.7% specificity, 0.845 area under the curve, 0.742-0.948 95% confidence interval).

Conclusion: The percentage of involvement can be used as a predictor to decide the severity of the disease in patients, who are thought to have COVID-19 pneumonia.

Keywords: Computed tomography, COVID-19, neutrophil to lymphocyte ratio

Öz

Amaç: Bilim dünyasının koronovirüs pandemisi hakkında çeşitli bilgileri olmasına rağmen, virüsün doğası hakkında daha fazla çalışmaya ihtiyaç duyulmaktadır. Çalışmamızın amacı, Koronavirüs hastalığı-2019'un (COVID-19) görüntüleme ve laboratuvar bulguları arasındaki ilişkiyi araştırmaktır.

Yöntem: Çalışmamız, COVID-19 hastalarının dahil edildiği retrospektif tek merkezli bir çalışmadır. Göğüs bilgisayarlı tomografisi olan ve ters transkripsiyon polimeraz zincir reaksiyonu testi pozitif olan hastalar değerlendirildi. Toplam akciğer hacmi ve lezyon hacmi Osirix yazılımı ile yarı otomatik olarak hesaplandı. Gözlemciler arasındaki tutarlılığı test etmek için sınıf içi korelasyon katsayısı kullanıldı. Hastalar tutulan akciğer hacmine göre hafif, orta ve şiddetli olmak üzere üç gruba ayrıldı. Laboratuvar bulguları ile radyolojik tutulum şiddeti arasındaki ilişki, alıcı işletim karakteristik grafiğinde eğri altındaki alan ile incelendi.

Bulgular: Bu çalışmaya 116 hasta (kadın: 44, erkek: 62) dahil edildi ve ortanca yaş 55 idi. En yaygın radyolojik özellikler periferik, multifokal, subplevral ve bazal dağılımlı buzlu cam opasiteleriydi. Tutulum yüzdesi ve radyolojik şiddet ile en çok ilişkili laboratuvar özelliği olan nötrofil/lenfosit oranı arasında pozitif ve orta düzeyde korelasyon (rho=0,635, p<0,001) bulundu. N/L oranı için cut-off değeri 1,1195 idi (duyarlılık %95,5, özgüllük 85,7, eğri altındaki alan 0,845, %95 güven aralığı 0,742-0,948).

Sonuç: COVID-19 pnömonisi olduğu düşünülen hastalarda hastalığın ciddiyetine karar vermek için tutulum yüzdesi bir öncü gösterge olarak kullanılabilir.

Anahtar kelimeler: Bilgisayarlı tomografi, COVID-19, nötrofil/lenfosit oranı

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Introduction

In December 2019, a novel type of Coronavirus emerged in Wuhan City, China. It quickly spread through China and to other countries with remarkable speed. The infection agent was named by the International Committee on Taxonomy of Viruses acute respiratory distress syndrome-coronavirus-2 (SARS-CoV-2) (1). The World Health Organization (WHO) officially named the clinical features as Coronavirus disease-2019 (COVID-19) on February 11, 2020 (2).

Earlier in the 21st century, Asia suffered from two other Coronavirus outbreaks. The former occurred between 2002 and 2003 in China with SARS-COV as the responsible agent. The latter occurred in Saudi Arabia between 2012 and 2013, with the Middle East respiratory distress syndrome-coronavirus (MERS-CoV) as the responsible agent (3). SARS-COV, SARS-CoV-2 and MERS-CoV belong to the same subtype of Coronavirus family namely Betacoronaviridae. Despite being a zoonotic agent, a high rate of human to human transmission made COVID-19 progress rapidly and on March 11, 2020, the WHO announced it as a pandemic.

SARS-COV-2 is a zoonotic, positive-strand RNA virus, causing different scales of clinical features mostly high fever, coughing and respiratory distress at any level (3,4). The disease course varies from asymptomatic to severe respiratory distress and death. Patients with underlying comorbidities such as diabetes, atherosclerotic vascular diseases, hypertension, immune deficiencies, and other chronic systemic disorders are more vulnerable to COVID-19 infection and often need to be managed in critical care units compared to patients who have no comorbidities (5).

The gold standard test for establishing diagnosis is reverse transcriptase-polymerase chain reaction (RT-PCR). However, a variety of false negative results of RT-PCR complicates the diagnosis and patient management and impacts community health due to the high social transmission rates (6,7). Computed tomography (CT) is an important tool to either support or establish a diagnosis from time to time, especially in patients with a suspended diagnosis. The most prominent alterations in the chest CT for COVID-19 are peripheral, patchy, usually bilateral ground glass opacities in the basal segments of the lungs, which often show progression into consolidation, a crazy paving pattern. Nodules, mediastinal and hilar lymph nodes, and pleural effusion are less likely to be seen (8,9).

The aim of our study is to quantitatively measure the lesion volume in both lungs, to examine the relationship between the blood cell counts, to analyze acute phase reactants for further understanding of blood test changes, to interpret radiological and biochemical features, and to seek predictors for the severity of the disease.

Materials and Methods

Study Design

Between March 10, 2020 and April 25, 2020, we performed a retrospective, single-center study of the SARS-CoV-2 laboratory-confirmed cases, which included 106 patients.

Ethical Committee Approval

This study was approved by the institutional review board and protocol review committee of University of Health Sciences Turkey, Kocaeli Derince Training and Research Hospital (approval number: 2020-66). Due to pandemic, informed written consent was waived by the committee decision.

Patients

One hundred and six patients with COVID 19 were enrolled in this retrospective study from March 10th, 2020 to April 25th, 2020. Patient selection for this study was consecutive. The thorax CT images and laboratory results of all the patients were collected from the hospital database. Patients with cardiac and other systemic disorders effecting pulmonary parenchyma, those suffering from chronical interstitial lung diseases and those with advanced fibrosis and with extensive atelectasis were excluded.

Laboratory Findings

All blood test results were obtained from the hospital information system after image analysis. Neutrophil to lymphocyte (N/L) ratio was also noted. All blood samples were analyzed at the point of admission to the hospital and there were no delays longer than one day. A confirmed case was defined as positive by high throughput sequencing or real-time reverse-transcriptase polymerase-chain-reaction (rRT-PCR) assay of the nasal and pharyngeal swab specimens.

CT Acquisition

Scanning of all patients was performed in the supine position at the end inspiration on a 128 slice multi-detector row CT scanner (GE healthcare, Chicago, Illinois, United States) without using intravenous contrast media. All images were obtained with standard dose protocol, reconstructed at 1 mm slice thickness, with a 1 mm increment, with a matrix of 512 mm x 512 mm. The lung window setting was with a

window level of -500 Hounsfield units (HU) and a window width of 1.400 HU.

Interpretation of Images

All images derived from CT were evaluated independently by two radiologists with 10 and 8 years of experience in imaging (B.K. and B.O), who were blinded to the clinical and laboratory findings, with the food and drug administration approved Osirix 11.0 Dicom viewer. When there was a disagreement between the two radiologists, the final decision was reached by consensus.

For each of the 106 patients, the CT scan was evaluated for the following characteristics: (a) location: Unilateral or bilateral, (b) distribution: Subpleural, peribronchovascular or both (c) involvement pattern: GGO, consolidation and mixed. All GGO, consolidation and linear bands were assessed to calculate the total pathologic volume. GGO was defined as hazy increased lung attenuation with the preservation of the bronchial and vascular margins, and consolidation was defined as opacification with the obscuration of the margins of vessels and airway wall (10).

Image Quantitative Evaluation

Total lung volume of all the patients was analyzed using the threshold method and calculated with Osirix applications automatically (Figure 1). Pathologic densities were drawn using a manual region of interest method, then the total pathologic volumes of these densities were calculated by Osirix software semi-automatically (Figure 2). The percentage of pathologic volume was calculated by dividing the total pathologic volume by the total lung volume for each patient. The percentage of volume was divided into three groups and defined as follows: <25% was mild, ≥25-<50 was moderate, and ≥50 was a severe disease.

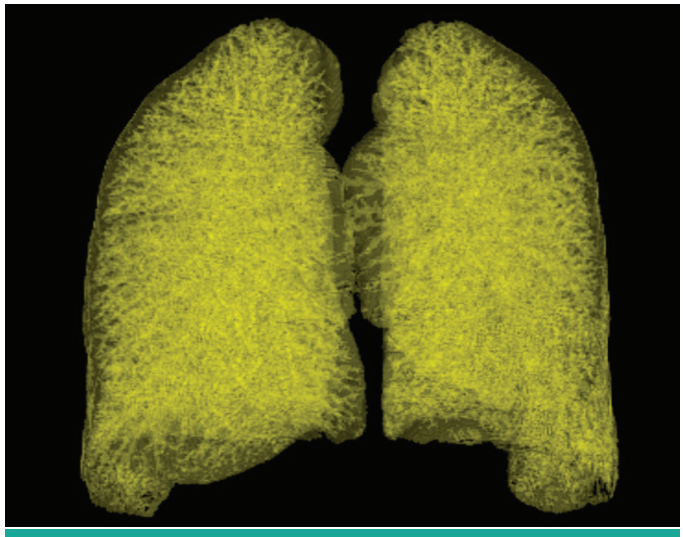

Figure 1. A 47-year-old female patient with COVID-19 pneumonia. FDA approved Osirix (version 11.0) software was used for calculating the total lung volume. The software algorithm calculated lung parenchyma without vessel and airways in 3D volume rendered reconstruction

FDA: Food and drug administration

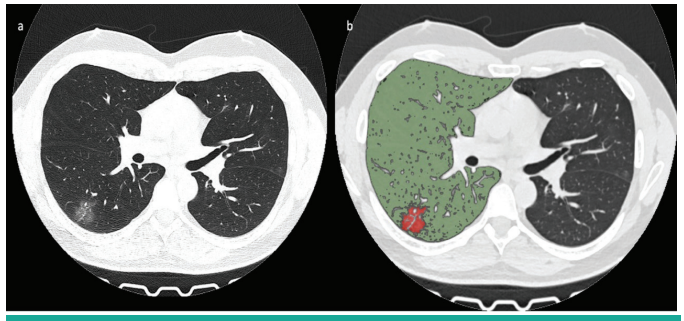

Figure 2. a) Ground glass density area accompanied with vascular enhancement at the lower lobe of the right lung observed on the non-contrast thorax CT of a 34-year-old male patient. b) Total lung volume of lung (green areas, each lung separately) calculated with automatically and pathologic volumes (red areas), calculated using semi-automatic methods

CT: Computed tomography

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS version 25 for macOS) software was used for statistical analysis. Consistency between the raters in the total involvement volume, which was calculated semi-automatically, was tested by intragroup correlation coefficient (ICC). An ICC value bigger than 0.75 was considered as having good repeatability. Whether the numerical data were normally distributed or not was evaluated by the Kolmogorov-Smirnov test. Due to the non-normal distribution of the measured indices, the correlation between the percentage of the pathologic volume and the N/L was performed using the Spearman's rank correlation. Difference between the N/L according to the percentage of pathologic volume was determined by the Kruskal-Wallis H test. The Games-Howell non-parametric method was used for post-hoc analysis and Bonferroni correction was done. The cut-off value, discriminating mild disease from a moderate-severe disease, was determined by receiver operating characteristic (ROC) analysis with the maximum Youden index. The area under the curve (AUC), sensitivity and specificity were calculated for N/L with the exact binominal confidence intervals (95% confidence level). $p<0.05$ was considered as statistically significant.

Results

Inter-observer Consistency

There was a good repeatability with ICC value 0.991 (95% confidence interval 0.987-0.994) between the two observers in evaluating total pathologic lung volume.

Demographic Characteristics

One hundred-six patients were included in the study. Sixty-two patients were male (mean age: 49.76-17.15 years, range: 18-92 years) and 44 patients were female (mean age: 55.16-15.30 years, range: 23-81 years). Considering the percentage of involved volume, the patients were classified as follows: 84 (79.2%) had a mild, 12 (11.3%) had a moderate and 10 (9.4%) had a severe disease. The distribution of age by sex and severity of disease was shown in boxplot graphics (Figure 3).

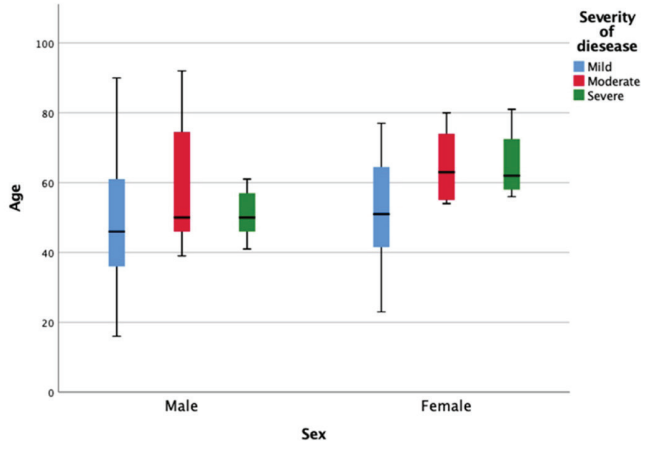

Figure 3. The distribution of ages according to the severity of the disease in males and females

Radiological and Clinical Findings

Eighty-nine (84%) patients had bilateral, 6 (5.6%) patients had right lung, and 11 (10.4%) patients had left lung involvement. Fourty-five (42.5%) cases had peripheral, 2 (1.9%) cases had peribronchovascular, and 59 (55.6%) had diffuse distribution. Seventy-four (69.8%) cases had ground-glass opacities, 2 (1.9%) cases had consolidation, and 30 (28.3) cases had mixed pattern (Table 1).

The total lung volume and the patients' ages showed a normal distribution and the mean total lung volume and SD was 3185.48-1188.08 cm^3. Table 2 presents the median and interquartile range values according to sex, total involvement lung volume, percentage of involvement, neutrophil count, lymphocyte count, N/L ratio, and C-reactive protein (CRP).

Table 1. Side, pattern and distribution of COVID-19

		Number	Percent
Side	Bilateral	89	84%
	Right	6	5.6%
	Left	11	10.4%
Pattern	GGO	74	69.8%
	Consolidation	2	1.9%
	Mixed	30	28.3%
Distribution	Peripheral	45	42.5%
	Peribronchovascular	2	1.9%
	Diffuse	59	55.6%

GGO: Ground glass opacity, COVID-19: Coronavirus disease-2019

Negative and weak correlation was determined between total lung volume and age (rho: -0.330, p<0.001). The percentage of involvement, which was a quantitative parameter, showed a weak dependence on CRP, neutrophil count and lymphocyte count with the Spearman correlation coefficients of 0.352 (p<0.001), 0.307 (p<0.001) and -0.435 (p<0.001), respectively (Table 3). However, a positive and moderate correlation was found between the percentage of involvement and the neutrophil-lymphocyte ratio (rho: 0.635, p<0.001).

The median and interquartile range values were found according to the severity of the disease as follows: Mild was 2.1257 (1.4922-3.5541), moderate was 4.5377 (3.6996-6.1429), and severe was 9.1559 (5.6190-12.5581). Significant differences were found between the groups (p<0.0001). After the Kruskal-Wallis test was performed, statistically significant differences were determined by the post-hoc analysis between a mild and moderate, between a moderate and severe, and between a mild and a severe disease (p=0.044, p=0.039 and p=0.002, respectively, Table 4).

ROC curve analysis (Figure 4) yielded an AUC, which is 0.845 for N/L with a standard error of 0.053 and 95% confidence interval of 0.742-0.948. The cut-off value was found to be 1.1195 for N/L ratio, with a 95.5% sensitivity and an 85.7% specificity.

Eighteen of the 106 (16.98%) patients were hospitalized with dyspnea. The mean hospitalization time was 10.5 (range: 5-19) days. Seventeen of 18 (94.44%) patients who needed hospitalization had both bilateral involvement and diffuse distribution. No patients died during this study.

Table 2. Median and interquartile range values according to sex for non-normally distributed data

	Male			Female		
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75
Total lung volume (cm^3)	3561.5	2728.0	4312.0	2451.5	1885.0	3310.0
Percentage	5.79	1.54	16.53	4.53	1.10	18.43
Neutrophil ($10^3/\mu L$)	3.76	2.79	5.57	3.61	2.48	4.73
Lymphocyte ($10^3/\mu L$)	1.60	1.17	2.01	1.44	0.91	1.87
N/L	2.31	1.53	4.51	2.59	1.70	4.61
CRP (mg/dL)	4.52	1.29	15.52	2.70	0.83	13.19

N: Number of patients, N/L: Neutrophil to lymphocyte ratio, CRP: C-reactive protein

Table 3. Correlation between the percentage of involvement and blood parameters

	rho	p
CRP	0.352	<0.001
Neutrophil	0.307	<0.001
Lymphocyte	-0.435	<0.001
N/L	0.635	<0.001

CRP: C-reactive protein, N/L: Neutrophil to lymphocyte ratio, Spearman's rank correlation was performed

Table 4. Differences between the N/L values according to the disease severity

		p
Mild (2.12)	Moderate (4.54)	0.044
Moderate	Severe (9.16)	0.039
Mild	Severe	0.002

Median value of the N/L was shown in the brackets, Kruskal-Wallis test was used for statistical analysis and post-hoc analysis was performed, N/L: Neutrophil to lymphocyte ratio

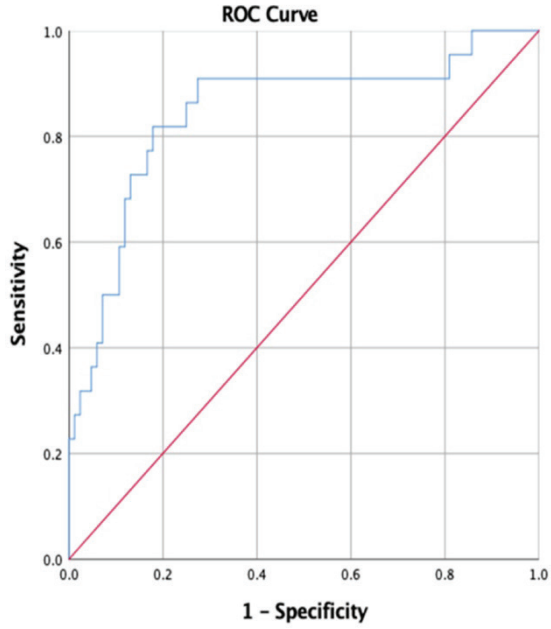

Figure 4. Graphic of receiver operating characteristics for N/L

N/L: Neutrophil to lymphocyte ratio

Discussion

COVID-19 is a serious condition especially in patients with comorbidities. Clinical condition, radiological features and biochemical changes might show inconsistency in some cases. For early detection and prediction of an aggravated clinical condition, radiologic features, biochemical findings and clinical findings should be assessed together. The severity of COVID-19 pneumonia increases with age, acute phase reactants, neutrophil, neutrophil/lymphocyte ratio, and with a decrease of lymphocyte count. Age is the most prominent predictor of the disease severity in COVID-19, as with other viral pneumonias.

The first stage of COVID-19 pneumonia is presented with alveolar edema which is depicted in CT imaging as patchy ground glass opacities. In the first stage of disease, alveoli are not completely filled with exudate. With disease progression, alveolar exudates expand through surrounding alveoli via foraminal paths. At this disease stage, CT reveals crazy paving pattern and patchy consolidations sometimes with "air bronchus sign". In severe cases, extension of these lesions is seen (11).

The most common radiologic features in our study group were peripheral, multifocal, ground glass opacities with subpleural and basal distribution. Consolidation was the second most radiologic feature usually accompanied with more lesion burden compared to patients with only ground glass opacity lesion type. Pleural effusion was extremely rare and no mediastinal lymph node was detected with pathologic appearance.

The findings in our study are consistent with the previous studies and reports (8,11-13). Lymphopenia and increased neutrophil and N/L ratio express the unusual manner of

COVID-19, that is unlikely in other viral infections. On the other hand, radiological features of COVID-19 pneumonia also have some different presentations. Most other viral and atypical bacterial pneumonias show peribronchial nodules, which is not a major manifestation of COVID-19 pneumonia. Underlying mechanisms of these blood changes and unusual radiological features are not well explained yet.

In several previous studies (2,8), radiologic severity degree is obtained by an involved lung lobe and focal lesion count. Contrarily, we classified patients into 3 groups as mild, moderate and severe with a quantitative volumetric approach. In previous studies, the volumetric percentage of lung involvement shows a more specific relationship with clinical changes. Colombi et al. (12) in their study displayed that patients with a lower volume of well aerated lung areas were at high risk of intensive care unit admission and death. Shen et al. (8) in their study depicted that a higher lesion volume was highly related to clinical severity. MuLBSTA score (multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hyper-tension and age) can also be applied to the COVID-19 infection to determine clinical severity and a 90-day survival rate (8,14). With this point of view, we investigated the blood changes of patients with the variable radiological disease severity, to reveal effectivity of commonly used biochemical markers.

Patients managed in intensive care units show more laboratory abnormalities compared to those not requiring intensive care unit management (15,16). In the radiological aspect of severity, the N/L ratio showed the highest correlation with lesion burden. Other biochemical features showing a different level of correlation are lymphopenia, neutrophil increase, and CRP increase. Liu et al. (13) in their study found N/L ratio as the most predictive blood change to display a clinical severity and prognosis and showed more sensitivity and specificity compared to the MuLBSTA score N/L ratio, which is consistent with our findings. They also proposed a new patient management method using N/L ratio and age (13). In our study, we found that the percentage of the involvement was correlated with N/L. In this context, we think that the percentage of involvement can be used as a predictor of the disease severity.

Study Limitations

The major limitation of our study was its retrospective design. Another limitation was that the majority of our subjects' disease course had not finished. Although no patient died during our study, some of the subjects were still active COVID-19 bearers. Hence, certain results for the disease process and the overall results could not be obtained. Our suggestion for researchers planning to study this topic is to assess the clinical condition together with the radiological and biochemical findings. Additionally, blood gas analysis could be included in the biochemical analysis and the interobserver consistency could be tested with less experienced raters. Lastly, automatic segmentation methods could be utilized to work with a broad range of patients.

Conclusion

Biochemical blood changes are highly correlated with radiological features. Age is the most significant reason for clinical and radiological severity. The most correlated hematological change in our study is the N/L, along with an increase of neutrophil, CRP, and a decrease of lymphocyte. So, we have concluded that quantitative volumetric CT analysis is correlated with N/L in COVID-19 pneumonia and can be used as a predictor of the disease severity. Further studies will provide a better understanding of the disease mechanism and the disease course.

Ethics

Ethics Committee Approval: This study was approved by the institutional review board and protocol review committee of University of Health Sciences Turkey, Kocaeli Derince Training and Research Hospital (approval number: 2020-66).

Informed Consent: Due to pandemic, informed written consent was waived by the committee decision.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.K., B.Ö., Design: B.K., B.Ö., Data Collection or Processing: B.K., B.Ö., O.Ö., Analysis or Interpretation: B.K., B.Ö., Drafting Manuscript: B.K., B.Ö., O.Ö., Critical Revision of Manuscript: B.K., Final Approval and Accountability: B.K., B.Ö., O.Ö.

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