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Correlation between the severity of lung involvement and nasal mucociliary clearance time and acute phase biomarkers in patients with COVID-19

COVID-19 hastalarında akciğer tutulumunun şiddeti ile nazal mukosiliyer klirens süresi ve akut faz biyobelirteçleri arasındaki korelasyon

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ABSTRACT

Objectives: The aim of this research was to evaluate the correlation between the increased nasal mucociliary clearance time (NMCT) and chest computed tomography severity scores (CT-SS) and acute phase biomarkers in patients diagnosed with coronavirus disease 2019 (COVID-19) pneumonia.

Patients and Methods: A total of 116 hospitalized patients were included in the prospective study between November 2021 and June 2022. For the measurement of the NMCT, all patients underwent the saccharin test. The patients were separated into two groups: Group 1, which included 53 patients (28 females, 25 males; mean age: 50.1±13.2 years; range, 19 to 75 years) with an NMCT of 7-13 min, and Group 2, comprising of 63 patients (32 females, 31 males; mean age: 52.3±12.1 years; range, 30 to 82 years) with an NMCT of 14-21 min. The CT-SS was adapted from a previous method including ground-glass opacity, interstitial opacity, and air entrapment and was used to express the severity and rate of involvement of COVID-19 pneumonia.

Results: The mean CT-SS was 3.8±1.6 in Group 1 and significantly higher in Group 2 with 6.2±2.0 ($p<0.001$). In addition, a strong positive correlation was determined between the NMCT and CT-SS ($r=0.711$). The mean lung lobe involvement was 3.6±1.5 in Group 1 and 4.8±0.5 in Group 2, and the difference was statistically significant ($p<0.001$). The mean ferritin levels showed a statistically significant difference at 244.6±146.9 mg/L in Group 1 and 436.5±449.1 mg/L in Group 2 ($p=0.038$).

Conclusion: The saccharin clearance test is not routinely used in clinical practice but with the lights of our study's results increased NMCT results correlates with pneumonia severity scores in CT and it may be useful in the prediction of prognosis of pneumonia in COVID-19 patients.

Keywords: COVID-19, lung involvement score, computed tomography, nasal mucociliary clearance time, acute phase biomarkers.

ÖZ

Amaç: Bu araştırmanın amacı, koronavirüs hastalığı 2019 (COVID-19) pnömonisi olan hastalarda artmış nazal mukosiliyer klirens süresi (NMCT) ile akciğer bilgisayarlı tomografi şiddet skorları (CT-SS) ve akut faz biyobelirteçleri arasındaki ilişkiyi araştırmaktır.

Hastalar ve Yöntemler: Bu prospektif çalışmaya 116 yatan hasta Kasım 2021 - Haziran 2022 arasında dahil edildi. Nazal mukosiliyer zamanın ölçümü için tüm hastalara sakkarin testi uygulandı. Hastalar iki gruba ayrıldı: NMCT'si 7-13 dk olan 53 hasta (28 kadın, 25 erkek; ort. yaş: 50.1±13.2 yıl; dağılım, 19-75 yıl) içeren Grup 1 ve NMCT'si 14-21 dk olan 63 hastadan (32 kadın, 31 erkek; ort. yaş: 52.3±12.1 yıl; dağılım, 30-82 yıl) oluşan Grup 2. Bilgisayarlı tomografi şiddet skoru; buzlu cam opaklığı, interstisyel opaklık ve hava sıkışmasını içeren önceki bir yöntemden uyarlanmış olup COVID-19 pnömonisinin ciddiyetini ve tutulum oranını ifade etmek için kullanılmıştır.

Bulgular: Ortalama CT-SS Grup 1'de 3.8±1.6 idi ve Grup 2'de 6.2±2.0 ile anlamlı derecede daha yüksekti ($p<0.001$). Ayrıca NMCT ile CT-SS arasında güçlü bir pozitif koreleasyon saptandı ($r=0.711$). Ortalama akciğer lobu tutulumu Grup 1'de ortalama 3.6±1.5 iken Grup 2'de 4.8±0.5 ile istatistiksel olarak anlamlı derecede yüksek bulundu ($p<0.001$). Ortalama ferritin değerleri, Grup 1'de 244.6±146.9 mg/L ve Grup 2'de 436.5±449.1 mg/L ile istatistiksel olarak anlamlı bir fark gösterdi ($p=0.038$).

Sonuç: Sakkarin klirens testi klinik pratikte rutin olarak kullanılmamakla beraber çalışmamızda artan NMCT sonuçları ile BT'de pnömoni şiddet skorları pozitif korele olarak bulunmuştur ve bu bulgunun COVID-19 hastalarında pnömoni prognozunu tahmin etmede faydalı olabileceği düşünülmüştür.

Anahtar sözcükler: COVID-19, akciğer tutulum skoru, bilgisayarlı tomografi, burun mukosiliyer temizleme süresi, akut faz biyobelirteçleri.

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Following the emergence of coronavirus disease 2019 (COVID-19) in Wuhan, China, in December 2019, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, the disease spread rapidly with severe consequences and was declared a global pandemic, the like of which has not been seen since the Spanish flu outbreak of 1917.[1] Symptoms generally emerge following a two to 14 day incubation period, when the person is most contagious.[2] In most cases, transmission to a healthy individual occurs via inhalation of the respiratory droplets scattered through the cough or sneeze of an infected person.[3]

Normal nasal physiology is dependent on the clearance of foreign particles from the nasal mucosa and maintaining mucosa moistness. Ciliary activity and regeneration of airway secretions are necessary for these vital functions, which are referred to as mucociliary activity (clearance). Mucociliary clearance (MCC) has a critical role in the defense mechanism of the nasal epithelium, as this mucus layer captures potentially harmful materials, and the ciliary movements remove it from the nasal cavity.[4,5] Mucociliary clearance can be measured using saccharin, radionuclide substances, and methylene blue coloring agents. In 1974, Andersen et al.[6] first described the saccharine clearance test as an *in vivo* technique that could be used to evaluate nasal MCC, and the method was later modified by Rutland and Cole.[7] As the saccharine clearance test has the advantages of being low cost, easy to apply, and reliable, it has become the most commonly used MCC measurement method. The test can be completed in an average of 7-15 min, and a transport time longer than 30 min is accepted as impairment of nasal MCC. As nasal mucociliary time (NMCT) is known to be prolonged in viral respiratory tract infections and chronic sinusitis, it can be assumed that it may also be prolonged together with an increase in nasal symptoms in cases of COVID-19 infection positivity as this is a viral infection.[8]

The diagnosis of COVID-19 is based on real-time reverse transcription polymerase chain reaction (RT-PCR) or next generation sequencing.[9] The computed tomography (CT) findings of patients with COVID-19 are not exclusive to COVID-19, but lesions are usually more common in peripheral areas and observed as multiple ground-glass opacities with asymmetrical distribution.[10-13]

Many biomarkers may show significant changes in severe COVID-19 patients. The most commonly seen laboratory findings are decreased lymphocytes and elevated results of acute phase inflammatory biomarkers, mainly D-dimer, C-reactive protein (CRP), ferritin, and procalcitonin. Continuing increases in these biomarkers are accepted as an indication of severe disease and poor prognosis.[14]

The aim of this study was to evaluate the correlations between increased NMCT and the chest CT severity score (CT-SS) and acute phase biomarkers in patients with COVID-19 pneumonia.

PATIENTS AND METHODS

The prospective study was conducted in the COVID-19 pandemic wards of the Karaman Education and Training Hospital between November 2021 and June 2022. A total of 116 patients with COVID-19 infection confirmed with RT-PCR positivity comprised the study sample. The patients were separated into two groups: Group 1, which included 53 patients (28 females, 25 males; mean age: 50.1±13.2 years; range, 19 to 75 years) with an NMCT of 7-13 min, and Group 2, comprising of 63 patients (32 females, 31 males; mean age: 52.3±12.1 years; range, 30 to 82 years) with an NMCT of 14-21 min. The exclusion criteria were defined as patients who smoked, used cocaine, or any other drugs that may affect mucociliary activity or had a history of nasal surgery or taste/smell disorders.

For all the patients with positive RT-PCR test results who were then hospitalized in the pandemic wards, the routine laboratory test results were evaluated with the chest CT images taken in the COVID-19 emergency department. The acute phase biochemical markers were noted from the laboratory results. The lung involvement scores were determined on the chest CT images routinely performed at the time of presenting to the emergency department.

Measuring the nasal mucociliary clearance time

All the patients underwent the saccharin (artificial sweetener) test in their rooms on the day after receiving a positive RT-PCR test result. The test was administered using the method described by Greenstone and Cole.[15] After a 30-min rest, the patients were prepared for the test seated upright and were told not to sniff or move their head. Using alligator forceps, a 1 mm saccharine granule was placed on the anterior section of the inferior concha. The subjects were instructed to swallow several times for 1 min and to state as soon as they perceived the taste. The time from starting the test to perceiving the taste was recorded as the saccharine clearance time, with results expressed as NMCT. A normal time for saccharin clearance time has been reported as 7-14 min, and pathological clearance time is indicated by a time longer than 20 min.[15]

Radiological evaluation and CT scoring

Tomography images were taken with a single tomography device (16-section Toshiba Alexion; Toshiba Medical Systems, Tokyo, Japan). The images from the apex to the bottom of the lung were acquired with the patient positioned supine and holding their breath on inspiration. The parameters for the scans were set as follows: tube voltage, 120 kV; smart mAs tube current modulation; pitch, 1 mm; matrix, 256×256; layer thickness, 5 mm. The images were without intravenous contrast agent administration and postcontrast pulmonary arterial phase sections. For each patient, the pattern of involvement, distribution of lesions, number of lesions, and number of lobes involved were evaluated by a single radiologist using a standard clinical picture archiving and diagnostic system workstation. The radiologist had 11 years of radiology experience and was blinded to the patient clinical and laboratory data.

The CT-SS scoring system was developed to more clearly express the severity and rate of involvement of COVID-19 pneumonia. This system was adapted from a method previously used to describe ground-glass and interstitial opacities and air entrapment. Liu et al.[16] created the following semiquantitative scoring system to estimate the degree of involvement of each lung lobe: 0 points, normal chest CT; 1 point, <25% involvement; 2 points, 25-50%; 3 points, 50-75%; 4 points, >75%. A maximum total score of 20 points can be obtained for the five lung lobes.

Statistical analysis

Data obtained in the study were analyzed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Distribution of the data was evaluated using the Shapiro-Wilk test. Quantitative variables were compared between groups using the independent samples t-test or the Mann-Whitney U test according to the distribution. Correlations between numerical variables were examined with Spearman's rho correlation analysis. A value of p<0.05 was accepted as statistically significant.

Table 1
The demographic and clinical data of 116 patients diagnosed with COVID-19 pneumonia

	Group 1 NMCT: 7-13 min (n=53)		Group 2 NMCT: 14-21 min (n=63)		
Variables	n	Mean±SD	n	Mean±SD	*p*
Age (years)		50.1±13.2		52.3±12.1	0.373‡
Sex					0.829‡
Male	25		31		
Female	28		32		
CT severity score		3.8±1.6		6.2±2.0	<0.001‡
Lung lobes involved		3.6±1.5		4.8±0.5	<0.001‡
Central/peripheral lung involvement		1.2±0.4		1.3±0.4	0.093‡
NMCT (min.)		11.1±1.6		15.6±1.8	<0.001‡
Procalcitonin (ng/mL)		0.3±1.3		0.2±0.3	0.228†
Ferritin (ng/mL)		244.6±146.9		436.5±449.1	0.038†
D-Dimer (ng/mL)		795.1±867.9		1342.5±1861.5	0.026†
CRP (mg/L)		54.3±45.1		78.0±57.4	0.027‡
Troponin I (ng/L)		8.2±5.8		18.6±43.6	0.210†
WBC (K/uL)		7.1±4.3		6.8±2.7	0.752†
Neutrophils (K/uL)		5.2±4.1		11.0±46.9	0.356†
Neutrophil percentage		68.6±14.5		72.9±10.3	0.090‡
Lymphocytes (K/uL)		1.3±0.6		1.2±0.5	0.380‡
Lymphocyte percentage		22.9±10.7		20.6±8.7	0.257‡
Eosinophils (K/uL)		0.02±0.04		0.03±0.05	0.291†
Eosinophil percentage		0.9±3.9		0.5±0.8	0.349†

NMCT: Nasal mucociliary time; SD: Standard deviation; CT: Computed tomography; CRP: C-reactive protein; WBC: White blood cell; †: Mann-Whitney U test; ‡: Bağımsız örneklem t testi.

RESULTS

The mean NMCT was measured as 11.1±1.6 min in Group 1 and 15.6±1.8 min in Group 2 (Table 1). The mean CT-SS was 3.8±1.6 in Group 1 and statistically significantly higher in Group 2 with 6.2±2.0 ($p<0.001$, Figure 1). The mean lung lobe involvement was 3.6±1.5 in Group 1 and 4.8±0.5 in Group 2, and the difference was statistically significant ($p<0.001$).

From the laboratory tests, the mean ferritin was measured as 244.6±146.9 ng/mL in Group 1 and 436.5±449.1 ng/mL in Group 2, and the difference was statistically significant ($p=0.038$). The mean procalcitonin was 0.3±1.3 ng/mL in Group 1 and 0.2±0.3 ng/mL in Group 2, with no statistically significant difference between the groups ($p=0.228$). The mean D-dimer was 795.1±867.9 ng/mL in Group 1 and statistically significantly higher in Group 2 with 1342.5±1861.5 ng/mL ($p=0.026$). A statistically significant difference was determined between the groups in the mean CRP value (54.3±45.1 mg/L in Group 1 *vs.* 78.0±57.4 mg/L in Group 2, $p=0.027$).

A strong positive correlation was determined between NMCT and CT-SS ($r=0.711$, Figure 2). A moderate positive correlation was determined between the number of involved lobes and NMCT ($r=0.535$). The NMCT and ferritin results were found to be positively correlated at a weak level with an r value of 0.257, and a weak positive correlation was determined between NMCT and D-dimer with an r value of 0.269. No significant correlations were observed between the other laboratory parameters ($p>0.05$).

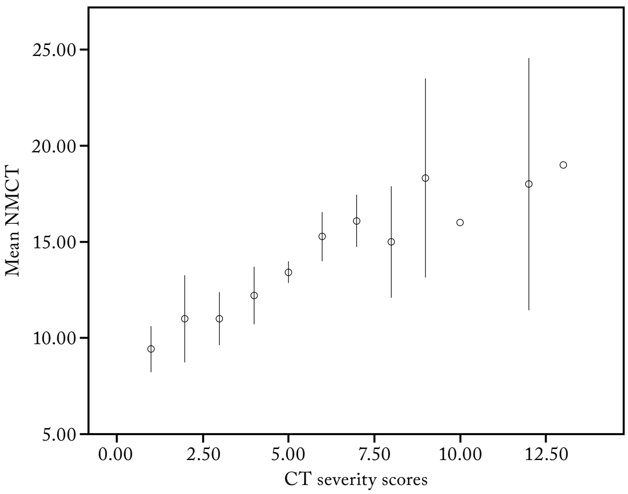

Figure 1. Nasal mucociliary time and CT-SS values.

NMCT: Nasal mucociliary clearance time; CT-SS: Computed tomography severity scores.

DISCUSSION

The outbreak of COVID-19 was declared a global pandemic in March 2020 and has had the most profound destructive effects on life and health throughout the world. The most frequently seen clinical symptoms are cough, fever, dyspnea, and myalgia, and less common symptoms have been reported to be headache, hemoptysis, diarrhea, and loss of taste and smell.[9] The RT-PCR molecular test for the detection of the virus RNA (ribonucleic acid) in respiratory samples has been accepted as the gold standard diagnostic tool for COVID-19 infection. Despite changes in CT findings with disease progression and the fact that these findings are not specific to COVID-19 pneumonia, a meta-analysis by Böger et al.[17] demonstrated that after RT-PCR, CT was the second most sensitive test.

Liu et al.[16] devised a semiquantitative scoring system to evaluate lung involvement. Scoring was made at baseline and then performed again on CT images repeated after progression/exacerbation, and a significant increase was determined in the CT-SS of patients. It was concluded that a poor clinical outcome could be predicted by an increase in the number of involved lobes or a CT score increased from the baseline.[16] In the current study, this CT-SS system was used as it is practical and easy to apply.

In the defense mechanism for the protection of the human upper respiratory tract against pathogens, foreign bodies, and toxins, MCC has an important

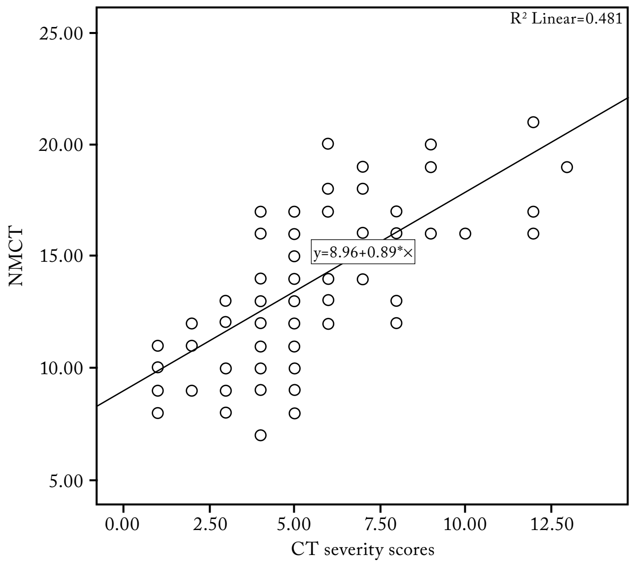

Figure 2. Scatter plot graph indicating a strong positive correlation between NMCT and CT-SS.

NMCT: Nasal mucociliary clearance time; CT-SS: Computed tomography severity scores.

role. Coronavirus disease 2019 is a viral infection causing prolonged MCC through an increase in mucus secretion, impaired ciliary movement, and epithelial damage in the airway. The current study is the first to show a correlation between prolonged NMCT and the severity of the lung involvement using the mentioned novel semiquantitative scoring method. As it is low cost and simple to perform, the saccharin test was used in this study. The patients were separated into two groups according to the NMCT results as the mean duration of clearance varied between 7 and 15 min.[18] These results show that if COVID-19 infection alters the MCC, which is one of the most effective respiratory defense mechanisms, there could be more severe lung involvement.

From a scan of recent similar literature, it was seen that Koparal et al.[19] reported a significant difference in NMCT between COVID-19-positive patients and healthy control subjects. In another study, Kahraman et al.[20] also reported that NMCT was significantly longer in the COVID-19 patient group than in the control group. In contrast, the results of a study by Çeçen et al.[21] showed that the NMCT was not statistically significantly different in the patient and control groups.

In the assessment of the progression and prognosis of the COVID-19 infection, laboratory tests are also used. The most common findings are decreased lymphocytes, increased D-dimer, and increased CRP, ferritin, and procalcitonin. An increase in the levels of lactate dehydrogenase, aspartate transaminase, creatine kinase, troponin I, and urea is often observed in severe cases. Moreover, continued increases in these biomarkers indicate severe disease and a poor prognosis.[16] In a recent meta-analysis that included 16 retrospective studies, Zeng et al.[22] concluded that there was a positive correlation between the severity of COVID-19 and inflammatory markers, particularly CRP, procalcitonin, interleukin-6, and sedimentation rate. The results of the current study showed a statistically significant difference between the groups in terms of the biochemically important acute phase proteins such as ferritin, CRP, and D-dimer. Although at a weak level, a positive correlation was determined between the D-dimer and ferritin results of the patients and the NMCT. These results strongly suggest that prolonged NMCT may weakly predict the severity of the disease.

In this study we only did the saccharin clearence test on the patients hospitalized with the diagnosis of pneumonia. Thus we do not have any assuming about any other group patients like asymptommatic or mild symptomatic patients with COVID-19 positive test results. We evaluated chest CT scans, laboratuary findings and saccharin tests of patients only on the day they applied to the hospital so we can not make a suggestion related to whether there is a change in NMCT as the severity of pneumonia increases.in the following days of the hopitalization.

In conclusion, this study is the first to have evaluated the correlation between the CT-SS and NMCT of hospitalized patients diagnosed with COVID-19 pneumonia. The study results demonstrated a statistically significant difference between the two groups in respect of the CT-SS and number of involved lung lobes, and these variables were also found to be positively correlated. A weak positive correlation was determined between prolonged NMCT and the D-dimer and ferritin results. It is commonly accepted in the literature that these biochemical markers are important parameters that are used to predict prognosis and the severity of COVID-19 pneumonia. Although the saccharin clearance test is not routinely used in clinical practice, it may be useful in the prediction of prognosis and the severity of COVID-19 pneumonia.

Ethics Committee Approval: The study protocol was approved by the Karamanoglu Mehmetbey University Ethics Committee (date: 11.10.2021, no: 07-2021/06). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceptualization: F.Y., Ş.Ş.K.; Data curation: F.Y., F.G.; Formal analysis: F.Y., Ş.Ş.K.; Methodology: F.Y., A.S., F.G.; Writing: A.S., F.Y.; Review and editing: S.K.

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