

Morphometric Examination of the Trachea and Bronchi in Follow-up Computed Tomography Scans of COVID-19 Patients

Examen Morfométrico de la Tráquea y los Bronquios en Tomografías Computarizadas de Seguimiento de Pacientes con COVID-19

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SUMMARY: The purpose of this study is to evaluate changes in the trachea and bronchi using 3-dimensional reconstruction images obtained from the initial and follow-up computed tomography (CT) scans of COVID-19 patients. A hundred COVID-19 patients over the age of 18 were included in our study. CT images were transferred to Mimics software, and a 3-dimensional reconstruction of the trachea and bronchi was performed. The initial and follow-up CT images of COVID-19 patients were graded as none (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3) according to the total lung severity score. The patients were divided into progression and regression groups according to the grade increase/decrease between the initial and follow-up CTs. Moreover, the patients were divided into groups as 0-2 weeks, 2-4 weeks, 4-12 weeks, and over 12 weeks according to the duration between the initial and follow-up CTs. The mean cross-sectional area, circumference, and diameter measurements of the right upper lobar bronchus, intermediate bronchus, middle lobar bronchus, and left lower lobar bronchus decreased in the follow-up CTs of the progression group. This decrease was not found to be statistically significant. In the follow-up CTs of the regression group, the left upper lobar bronchus and left lower lobar bronchus measurements increased but not statistically significant. Upon comparing the onset of the disease and the follow-up period, statistically significant changes did not occur in the trachea, main bronchus, and lobar bronchus of COVID-19 patients.

KEY WORDS: COVID-19; Follow-up CT; 3-dimensional reconstruction; Trachea; Bronchus.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a highly contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, Hubei Province of China, and quickly spread to other cities and countries other than China (Ye *et al.*, 2020). The epithelial cells that line the respiratory tract are among the first cell types encountered by the virus taken through respiration (Martines *et al.*, 2020). The virus enters the cell by attaching to the angiotensin-converting enzyme 2 (ACE2) receptor located in the ciliary respiratory epithelium. These cells are observed, especially in the lungs, trachea, and distal airways (Ünlü *et al.*, 2021). Bronchiectasis and bronchial wall thickening are observed

among the airway changes in COVID-19 patients. Bronchial wall thickening has been detected in 10-20% of COVID-19 patients (Wu *et al.*, 2020; Ye *et al.*, 2020). Inflammatory damage to the bronchial wall may be the pathogenesis, which results in the destruction of the bronchial wall structure, proliferation of fibrous tissue, fibrosis, and tractional bronchiectasis (Hansell *et al.*, 2008; Ye *et al.*, 2020). Little is known about the effect of COVID-19, the most important health problem of the recent period, on the airways. The purpose of the current research is to assess changes in the trachea and bronchi using 3-dimensional reconstruction images acquired from initial and follow-up CTs of COVID-19 patients.

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MATERIAL AND METHOD

Place and Duration of Study. Lokman Hekim University, Lokman Hekim University Ankara Hospital, Gazi University, Ankara, Turkey, from March 2021 to March 2022.

Study Group. One hundred COVID-19 patients older than 18 years of age with positive RT-PCR test results who presented to the outpatient clinic and emergency department of Lokman Hekim Ankara Hospital between April 2020 and March 2021 with fever, cough, and/or muscle and joint pain were included in the study. Patients with chronic obstructive pulmonary disease, pulmonary fibrosis, interstitial lung disease, mass lesions compressing the trachea and bronchi, and patients with a history of tracheo-bronchial surgery or tracheal intubation were excluded from the study. The initial and follow-up CT images of COVID-19 patients were acquired retrospectively. According to the duration between initial and follow-up CT images, COVID-19 patients were divided into four groups as 0-2 weeks, 2-4 weeks, 4-12 weeks, and over 12 weeks. According to the grade increase/decrease between initial and follow-up CTs, COVID-19 patients were also divided into progression and regression groups.

CT Protocol. The initial and follow-up CT images of COVID-19 patients were taken with a Siemens Somatom Emotion 16 Slice Multidetector CT [110 kV, 134 mAs, rotation time 0.5 sec, pitch 1.0, section thickness 4 mm (1.5 mm in reformat images)] device at Lokman Hekim University Ankara Hospital by telling patients to breathe deeply and hold the breath, with patients in the supine position and arms up.

Evaluation of Lung Involvement on CT. An experienced radiologist, blinded to the patients' information, evaluated lung involvement on the initial and follow-up CT images of all patients. Each of the 5 lung lobes, 3 on the right and 2 on the left, was scored between 0 and 4 depending on the percentage of involvement. Zero points were given if there was no involvement in a lung lobe (0%), 1 point if there was minimal involvement (1-25%), 2 points if there was mild involvement (26-50%), 3 points if there was moderate involvement (51-75%), and 4 points were given if there was severe involvement (76-100%). The total lung severity score was calculated by summing the scores of all lung lobes (0-20). It was classified as grade 0 (no involvement) if the total lung severity score was 0 points, as grade 1 (mild) in case of 1-5 points, as grade 2 (moderate) in case of 6-15 points, and as grade 3 (severe) in terms of 16-20 points (Zhou *et al.*, 2020).

COVID-19 patients with a grade increase in the follow-up CT in comparison with the initial CT were included in the progression group, whereas COVID-19

patients with a grade decrease were included in the regression group. COVID-19 patients with the same grade in the initial and follow-up CTs were excluded from this grouping.

Three-Dimensional Reconstruction of CT Images. Sequential serial CT images in the DICOM format were transferred to Mimics Innovation Suite 24.0 (Leuven-Belgium) software, and a 3-dimensional reconstruction of the trachea and bronchi was performed.

Measurements on a 3-Dimensional Model. Tracheal measurements were performed at three levels, with the first level being the apex of the jugular notch. The second level was at the level of the sternal angle, and the third level was just above the tracheal bifurcation. Measurements were made in the right and left main bronchi at the proximal and distal levels. In the right upper lobar bronchus, intermediate bronchus, middle lobar bronchus, right lower lobar bronchus, left upper lobar bronchus, and left lower lobar bronchus, measurements were performed only at the proximal level. While cross-sectional area, circumference, anteroposterior diameter, and transverse diameter were measured in the trachea and main bronchi, cross-sectional area, circumference, and diameter were measured in the lobar bronchus and intermediate bronchus. (Fig. 1).

Statistical Analysis. Statistical Package for the Social Sciences v23.0 (SPSS Inc, Chicago, IL) was utilized for statistical analysis. The normality distribution of continuous variables was assessed by the Kolmogorov-Smirnov, histogram, and Q-Q plot tests. Categorical variables were given in numbers and percentages, while continuous variables were shown in tables with mean and standard deviation. Pearson's chi-square test was conducted with the objective of comparing categorical variables, and Student's t-test and one-way ANOVA analysis were performed in order to compare normally distributed continuous variables. A $p < 0.05$ value was accepted as statistically significant.

RESULTS

The mean duration between the initial and follow-up CTs of COVID-19 patients was 47.57 ± 72.48 days. Fifty female and fifty male COVID-19 patients were included in the research, and the patients' mean age was 55.06 ± 17.68 . No statistically significant difference was revealed upon comparing patients in the progression and regression groups in terms of demographic characteristics (Table I). The higher proportion of males in the progression group and females in the regression group is a remarkable point here.

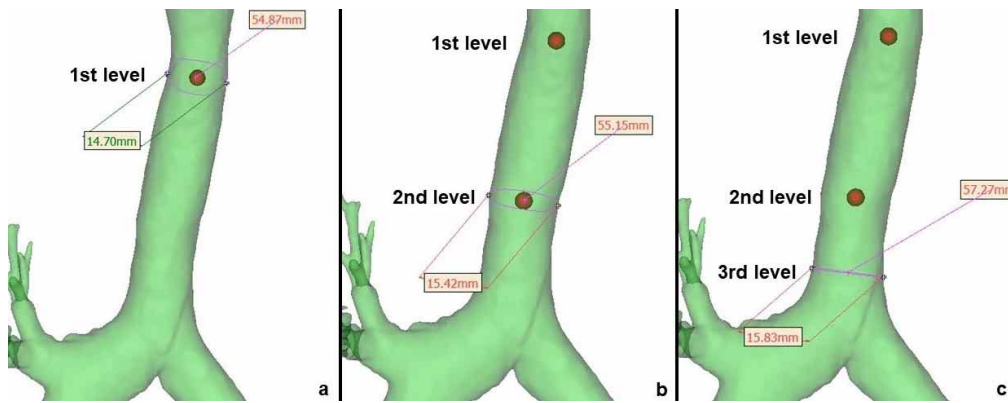


Fig. 1. The circumference and transverse diameter measurements of the trachea at the first (a), second (b), and third (c) levels (front view).

An increase in the proportion of males with an increase in the grade in the follow-up CTs was revealed to be statistically significant ($p=0.045$).

A lower number of lung lobes impacted on follow-up CTs was statistically significant ($p=0.003$). On both the initial and follow-up CTs, the right lower lobe was determined to be involved most frequently (Table II).

Table I. Comparison of demographic characteristics of the patients in the progression and regression groups.

| | Progression (n:29) | Regression (n:29) | p value |
|---------------|--------------------|-------------------|---------|
| Age (Mean±SD) | 56.03±19.15 | 57.17±17.92 | 0.742 |
| Sex n (%) | | | |
| Male | 19 (65.5) | 14 (48.3) | 0.061 |
| Female | 10 (34.5) | 15 (51.7) | |

Table II. Comparison of the patients' lung involvement on the initial and follow-up CTs.

| | Initial CT (n:100) | Follow-up CT (n:100) | p value |
|---|--------------------|----------------------|--------------|
| No. of lobes affected n (%) | | | |
| 0 | 1 (1.0) | 11 (11.0) | 0.003 |
| 1 | 20 (20.0) | 12 (12.0) | |
| 2 | 15 (15.0) | 14 (14.0) | |
| 3 | 13 (13.0) | 9 (9.0) | |
| 4 | 19 (19.0) | 8 (8.0) | |
| 5 | 32 (32.0) | 46 (46.0) | |
| Involved lobes n (%) | | | |
| Right upper lobe | 55 (55.0) | 59 (59.0) | 0.025 |
| Right middle lobe | 47 (47.0) | 59 (59.0) | |
| Right lower lobe | 85 (85.0) | 77 (77.0) | |
| Left upper lobe | 63 (63.0) | 59 (59.0) | |
| Left lower lobe | 74 (74.0) | 75 (75.0) | |
| Involved lung n (%) | (n:99) | (n:89) | |
| Right lung | 16 (16.2) | 10 (11.2) | 0.573 |
| Left lung | 5 (5.1) | 6 (6.7) | |
| Both lung | 78 (78.8) | 73 (82.0) | |
| Total lung severity score | | | |
| (Mean±SD) | 5.41±4.19 | 5.99±4.93 | 0.371 |
| Range of total lung severity score | 0-20 | 0-20 | |
| Severity of lung involment n (%) | | | |
| Grade 0 | 1 (1.0) | 11 (11.0) | 0.008 |
| Grade 1 | 60 (60.0) | 44 (44.0) | |
| Grade 2 | 36 (36.0) | 39 (39.0) | |
| Grade 3 | 3 (3.0) | 6 (6.0) | |

In patients in the progression group, the rates of involvement of each of the involved lung lobes were found to increase on follow-up CTs ($p<0.001$). The opposite was revealed in the regression group, and the rate of involvement of each lung lobe decreased on follow-up CTs ($p<0.001$). The lower lobes of both lungs were extensively involved in the progression and regression groups. (Table III).

The mean cross-sectional area, circumference, and diameter measurements of the right upper lobar bronchus, intermediate bronchus, middle lobar bronchus, and left lower lobar bronchus decreased on the follow-up CTs compared to the initial CTs of the progression group. However, this decrease was not statistically significant. The left upper lobar bronchus and left lower lobar bronchus measurements increased on the follow-up CTs compared to the initial CTs of the regression group. Nevertheless, this increase was not statistically significant.

A decrease, although not statistically significant, was observed in all measurements at first level of the trachea and at the distal level of the left main bronchus on the follow-up CTs compared to the initial CTs of the patient

group with a duration of 0-2 weeks between the initial and follow-up CTs. The measurement values of the right and left upper lobar bronchus, middle lobar bronchus, and right and left lower lobar bronchus of patients with a duration of 0-2 weeks between the initial and follow-up CTs were found to be lower, although not statistically significant, on the follow-up CT compared to the initial CTs. The measurement values of the right and left upper lobar bronchus, middle lobar bronchus, and right and left lower lobar bronchus of patients in the group of 2-4 weeks were revealed to be higher,

although not statistically significant, on the follow-up CT compared to the initial CTs. The measurement values of the left upper lobar bronchus and left lower lobar bronchus of patients with a duration of 4-12 weeks between the initial and follow-up CTs were higher, although not statistically significant, on follow-up CTs compared to the initial CTs. The measurement values of the intermediate bronchus and left lower lobar bronchus in the group with a duration over 12 weeks increased, although not statistically significant on follow-up CTs compared to the initial CTs.

Table III. Comparison of lung involvement of the patients in the progression and regression groups on the initial and follow-up CTs.

| | Progression (n:29) | | | Regression (n:29) | | |
|--|--------------------|--------------|---------|-------------------|---------------|---------|
| | Initial CT | Follow-up CT | p value | Initial CT | Follow-up CT | p value |
| No. of lobes affected n (%) | | | | | | |
| 0 | 0 (0) | 0 (0) | | 0 (0) | 11 (37.9) | |
| 1 | 7 (24.1) | 0 (0) | | 3 (10.3) | 1 (3.4) | |
| 2 | 5 (17.2) | 0 (0) | N/A | 2 (6.9) | 7 (24.1) | N/A |
| 3 | 7 (24.1) | 0 (0) | | 3 (10.3) | 4 (13.8) | |
| 4 | 5 (17.2) | 4 (13.8) | | 7 (24.1) | 1 (3.4) | |
| 5 | 5 (17.2) | 25 (86.2) | | 14 (48.3) | 5 (17.2) | |
| Involved lobes n (%) | | | | | | |
| Right upper lobe | 12 (41.4) | 28 (96.6) | | 21 (72.4) | 8 (27.6) | |
| Right middle lobe | 9 (31.0) | 27 (93.1) | <0.001 | 22 (75.9) | 11 (37.9) | <0.001 |
| Right lower lobe | 26 (89.7) | 29 (100.0) | | 25 (86.2) | 15 (51.7) | |
| Left upper lobe | 16 (55.2) | 28 (96.6) | | 21 (72.4) | 7 (24.1) | |
| Left lower lobe | 20 (69.0) | 29 (100.0) | | 24 (82.8) | 15 (51.7) | |
| Involved lung n (%) | | | | | (n:18) | |
| Right lung | 5 (17.2) | 0 (0) | | 5 (17.2) | 2 (11.1) | |
| Left lung | 2 (6.9) | 0 (0) | N/A | 0 (0) | 0 (0) | N/A |
| Both lung | 22 (75.9) | 29 (100.0) | | 24 (82.8) | 16 (88.9) | |
| Total lung severity score | | | | | | |
| (Mean±SD) | 4.00±3.38 | 10.52±3.97 | <0.001 | 7.55±4.48 | 2.55±3.03 | <0.001 |
| Range of total lung severity score | 1-14 | 6-20 | | 1-20 | 0-13 | |
| Severity of lung involment n(%) | | | | | | |
| Grade 0 | 0 (0) | 0 (0) | | 0 (0) | 11 (37.9) | |
| Grade 1 | 25 (86.2) | 0 (0) | N/A | 8 (27.6) | 16 (55.2) | N/A |
| Grade 2 | 4 (13.8) | 24 (82.8) | | 19 (65.5) | 2 (6.9) | |
| Grade 3 | 0 (0) | 5 (17.2) | | 2 (6.9) | 0 (0) | |

DISCUSSION

Airway changes such as bronchial wall thickening, bronchiectasis, and endobronchial mucus obstruction may be observed in COVID-19 patients. The prevalence of bronchial wall thickening was found to be significantly higher in severe cases in comparison with mild cases (Ufuk & Savas, 2020). Xu *et al.* included 69 COVID-19 patients and 32 individuals as a control group in their study investigating whether airway wall thickening was in the early recovery period in COVID-19 patients. The researchers identified the airway wall thicknesses of COVID-19 patients at the onset and recovery stages of the disease and compared

them with the non-COVID-19 group. The airway wall thicknesses of COVID-19 patients were found to be greater at the onset of the disease than during the early recovery period. Furthermore, the airway wall thicknesses of COVID-19 patients at the onset of the disease were revealed to be greater compared to non-COVID-19 patients. Upon comparing patients without COVID-19 with patients in the early recovery period, the researchers reported a greater airway wall thickness in the early recovery period. These results indicated that airway wall thickening in COVID-19 patients did not completely return to normal in the early

recovery phase (Xu *et al.*, 2021). In our study, the airways were reconstructed, and lumen measurements were performed. The wall structure was not measured. Hence, when there is mucus accumulation or thickening in the airway, it is expected that the cross-sectional area, circumference, and diameter of the airway will narrow. A decrease, although not statistically significant, was identified on the follow-up CTs compared to the initial CTs of the progression group in the mean cross-sectional area, circumference, and diameter measurements of the right upper lobar bronchus, intermediate bronchus, middle lobar bronchus, and left lower lobar bronchus. The measurement values of the left upper lobar bronchus and left lower lobar bronchus increased on the follow-up CTs compared to the initial CTs of the regression group. Nevertheless, this increase was not statistically significant. We think that the fact that we did not obtain statistically significant results originated from our evaluation of the secondary impact of wall thickening and/or mucus accumulation. We wanted to conduct an innovative study due to the presence of previous studies evaluating wall thickness in COVID-19 patients. In the current study, we assessed lumen changes in the trachea and bronchi of COVID-19 patients during the progression and regression periods by employing the 3-dimensional reconstruction method.

Ûnlü *et al.* (2021) included 326 COVID-19 patients in their study evaluating the trachea of COVID-19 patients. Antero-posterior and transverse diameter measurements were performed in the axial section of the CT data. The researchers reported that there was an increase in tracheal diameters in proportion to the severity of pneumonia and severe inflammation might cause edema in the trachea and lead to an increase in tracheal diameters. Measurements in the study were performed in a two-dimensional section, including the wall structure of the trachea. In this study, statistical calculations were made by including the wall thickness. In our study, the lumen opening of the airways was reconstructed, and measurements were carried out. In other words, our study evaluated lumen opening secondary to changes in wall thickness. Our study performed measurements by creating a 3-dimensional model of the tracheobronchial tree with a 3-dimensional structure. We do not find it healthy to measure the trachea, which is not completely vertical, in a 2-dimensional section. However, since we cannot see the impacts of the wall structure directly in the measurements performed by creating a 3-dimensional model, we find it more valuable to evaluate 3-dimensional and 2-dimensional images together.

The measurement values of the right and left upper lobar bronchus, right and left lower lobar bronchus, and middle lobar bronchus of patients with a duration of 0-2

weeks between the initial and follow-up CTs were found to be lower on follow-up CTs compared to the initial CTs, although they did not create a statistically significant difference. The right and left upper lobar bronchus, right and left lower lobar bronchus, and middle lobar bronchus measurement values of patients in the group of 2-4 weeks were higher on follow-up CTs compared to the initial CTs, although they did not create a statistically significant difference. The left upper lobar bronchus and left lower lobar bronchus measurement values were determined to be higher on follow-up CTs compared to the initial CTs, although not statistically significant, in patients with a duration of 4-12 weeks between initial and follow-up CTs. The measurement values of the intermediate bronchus and left lower lobar bronchus were observed to increase on follow-up CTs compared to the initial CTs, although they did not create a statistically significant difference in the group with a duration over 12 weeks. In the literature review we performed, there was no study evaluating the trachea and bronchi of COVID-19 patients both in the short and long term of the disease. Hence, we consider our study innovative.

Guan *et al.* (2020) included 54 patients in their study examining the imaging findings of COVID-19 patients on the initial and follow-up CTs separately in the progression and recovery groups. The mean duration between initial and follow-up CT scans was 7.82 ± 3.74 days, which was considerably less than the mean duration in our study (47.57 ± 72.48). In their study, the researchers revealed the short-term effects of COVID-19 disease on the lung parenchyma. However, our study revealed the short- and long-term effects of COVID-19 disease on the lung parenchyma. In their study, Guan *et al.* reported that the lower lobes of both lungs were extensively involved, similar to our study. In their study, the lung involvement of patients in the progression and recovery groups was compared on initial and follow-up CTs, and no statistically significant results were acquired (Guan *et al.*, 2020). However, our study found that the rates of involvement of each of the involved lung lobes increased on the follow-up CTs of patients in the progression group. In the regression group, the opposite was observed, and the rate of involvement of each lung lobe decreased on the follow-up CT. We consider that these significant results in our study originated from the short-term and long-term impacts.

Xiong *et al.* (2020) included 42 patients in their study in which they analyzed the clinical and CT characteristics of COVID-19 patients. The researchers acquired the initial and follow-up CT images of COVID-19 patients retrospectively, as in our study. They reported that the lower lobes of the lungs were extensively involved, with the left lower lobe being the most vulnerable and most frequently

involved. Our study showed that the lower lobes of the lungs were extensively involved, and the right lower lobe was determined to be the most frequently involved lobe.

Studies have indicated that advanced age and male sex are high-risk factors for worse prognosis in COVID-19 patients (Chen *et al.*, 2020). In our study, the proportion of males increased as the grade increased on follow-up CTs. The proportion of males in the progression group and females in the regression group was higher.

Upon comparing the onset of the disease and the follow-up period, statistically significant changes did not occur in the trachea, main bronchus, and lobar bronchus of COVID-19 patients. In the literature review, we could not encounter any studies evaluating changes in the trachea and bronchi of COVID-19 patients by creating a 3-dimensional model in follow-up CTs. Therefore, we think that our study will contribute to the literature.

ETHICS STATEMENT. Ethics committee approval was granted for our study by the Non-Interventional Clinical Research Ethics Committee of Lokman Hekim University (Decision No. 2021/029 dated: March 10, 2021).

ERKAYA, A.; KUTAY COSKUN, Z.; AKYOL, S.; VEYSEL PEKER, T.; KUÇLU, T.; NUR BARAN AKSAKAL, F. & BEYZA TÛTÛNCÛ, A. Examen morfométrico de la tráquea y los bronquios en tomografías computarizadas de seguimiento de pacientes con COVID-19. *Int. J. Morphol.*, 41(2):349-354, 2023.

RESUMEN: El propósito de este estudio fue evaluar los cambios en la tráquea y los bronquios utilizando imágenes de reconstrucción tridimensionales obtenidas de las tomografías computarizadas (TC) iniciales y de seguimiento de pacientes con COVID-19. En nuestro estudio se incluyeron 100 pacientes con COVID-19 mayores de 18 años. Las imágenes de TC se transfirieron al software Mimics y se realizó una reconstrucción tridimensional de la tráquea y los bronquios. Las imágenes de TC iniciales y de seguimiento de los pacientes con COVID-19 se calificaron como ninguna (grado 0), leve (grado 1), moderada (grado 2) y grave (grado 3) según la puntuación total de gravedad pulmonar. Los pacientes se dividieron en grupos de progresión y regresión según el aumento/disminución del grado entre las TC iniciales y de seguimiento. Además, los pacientes se dividieron en grupos de 0 a 2 semanas, de 2 a 4 semanas, de 4 a 12 semanas y de más de 12 semanas según la duración entre la TC inicial y la de seguimiento. Las mediciones medias del área transversal, la circunferencia y el diámetro del bronquio lobar superior derecho, el bronquio intermedio, el bronquio lobar medio y el bronquio lobar inferior izquierdo disminuyeron en las TC de seguimiento del grupo de progresión. No se encontró que esta disminución fuera estadísticamente significativa. En las TC de seguimiento del grupo de regresión, las mediciones del bronquio lobar superior izquierdo y del bronquio lobar inferior izquierdo aumentaron pero no fueron estadísticamente significativas. Al comparar el inicio de la

enfermedad y el período de seguimiento, no ocurrieron cambios estadísticamente significativos en la tráquea, el bronquio principal y el bronquio lobar de los pacientes con COVID-19.

PALABRAS CLAVE: COVID-19; TC de seguimiento; Reconstrucción tridimensional; Tráquea; Bronquio.

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