

Effects of Lymphadenopathy on Pulmonary Function Tests in Sarcoidosis

Sarkoidoz'lu Hastalarda Lenfadenopatinin Solunum Fonksiyon Testi Üzerine Etkisi

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Abstract

Özet

OBJECTIVE: The pulmonary function test (PFT) is an important quantification test in the follow-up of sarcoidosis patients. We aimed to investigate the effect of lymphadenopathy (LAP) after controlling pulmonary parenchymal involvement on pulmonary function tests (PFTs) in the context of sarcoidosis.

MATERIAL AND METHODS: A total of 63 sarcoidosis patients were enrolled retrospectively in the study. Respiratory functions were evaluated via PFTs. Radiological evaluations of the patients were made with chest x-ray and high-resolution computerized to-mography (HRCT). Bronchoscopic investigations were performed on all patients. Possible factors that affect PFTs were evaluated.

RESULTS: There was a statistically significant correlation between the bronchoscopic findings and PFTs parameters (p<0.01). Forced vital capacity (FVC) was affected more in the presence of LAP in the adjacent bronchi and, it was similar the same for forced expiratory volume in the first second (FEV₁). Considering the grade of HRCT findings, the presence of hilar LAP, intrahilar LAP and lobar LAP had a statistically significant effect on FVC and FEV₁ (p=0.001).

CONCLUSION: We revealed that in addition to parenchymal involvement of the disease, the special localization of lymph node involvement also has an important effect on the PFTs parameters of sarcoidosis patients.

AMAÇ: Sarkoidoz hastalarının takibinde Solunum Fonksiyon Testi (SFT) önemli bir parametredir. Biz, sarkoidozlu hastalarda parankim tutulumunu göz önünde bulundurarak lenfadenopati (LAP) varlığının solunum fonksiyon testi üzerine etkisini araştırmayı amaçladık.

GEREÇ VE YÖNTEMLER: Çalışmamıza sarkoidoz tanısı konmuş, 63 hasta retrospektif olarak alındı. Hastalara SFT yapıldı. PA akciğer grafisi ve yüksek çözünürlüklü bilgisayarlı tomografi'leri (YÇBT) çekildi. Tüm hastaların bronkoskopik incelemeleri ve SFT'yi etkileyen olası faktörler değerlendirildi.

BULGULAR: Bronkoskopik bulgular ile SFT parametreleri arasında istatiksel olarak anlamlı ilişki vardı (p<0,01). Zorlu vital kapasitenin (FVC) ve 1. saniye zorlu ekspiratuvar volümün (FEV₁) bronşlara komşuluğu olan LAP'dan daha çok etkilendiği tespit edildi. YÇBT'de parankim tutulumu derecesi göz önüne alındığında FVC ve FEV₁'in hiler, intrahiler ve lober LAP varlığında istatiksel olarak daha fazla etkilendiği gözlendi (p=0,001).

SONUÇ: Sarkoidoz hastalarında, hastalığın parankim tutulumu yanında, özel yerleşimli lenf nodu tutulumunun da SFT parametreleri üzerinde önemli bir etkiye sahip olduğunu tespit ettik.

ANAHTAR SÖZCÜKLER: Sarkoidoz, lenfadenopati, Solunum Fonksiyon Testi, YÇBT

KEY WORDS: Sarcoidosis, lymphadenopathy, Pulmonary Function Tests, HRCT

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INTRODUCTION

Sarcoidosis is a multi-systemic disease characterized by noncaseating inflammatory histopathologic findings. It commonly affects lung and mediastinal lymph nodes. Although patients commonly present with pulmonary signs, sarcoidosis may present with all types of organ involvement.

Clinical evaluation, chest x-ray, pulmonary function test (PFTs), and high-resolution computerized tomography (HRCT) are important tools in the diagnosis of the disease [1-3]. PFTs and HRCT are also important for the followup of the progression and activation of the disease [3-5]. In addition to restrictive respiratory dysfunction, obstructive dysfunction can also be observed in sarcoidosis. There is a correlation between PFTs and the stage and prognosis of the disease [2]. Lymph node involvement is present in stages I and II; lung parenchyma involvement of the disease is present in all stages, except stages 0 and I of the disease [6]. There are some studies in the literature showing a relationship between the presence of radiologic findings and PFTs, however, there is no previous study, according to our knowledge, investigating separately the parenchymal involvement and individual lymph node involvement effect on PFTs [2,5].



In this study, we aimed to investigate the effect of lymphadenopathy (LAP) alone or after controlling pulmonary parenchymal involvement on PFTs in the context of sarcoidosis. We also aimed to determine the relationship between various radiological and bronchoscopic appearances of sarcoidosis and PFTs.

MATERIAL AND METHODS

A total of 63 sarcoidosis patients, who had a histopathologically verified diagnosis, between January 2006 and December 2011 were included in the study. Their demographic data, clinical history and chest x-ray, HRCT and bronchoscopic findings were obtained from the records of the Atatürk University Research Hospital and were evaluated retrospectively. None of the patients had been previously treated for sarcoidosis. Inclusion criteria were the presence of all data including chest x-ray, HRCT and bronchoscopy and histopathological verification of sarcoidosis. Patients with a previous history of chronic obstructive pulmonary disease, asthma, or cigarette smoking for more than 10 pack/years were not included in the study (n=17).

Chest X-Rays

All patients in the study had chest x-rays, which were classified as follows: stage 0 Normal radiograph; stage I Lymphadenopathy only; stage II Lymphadenopathy associated with pulmonary infiltrates; stage III Pulmonary infiltrates without lymphadenopathy; stage VI Extensive fibrocystic changes and scarring [6].

Pulmonary Function Tests

The pulmonary function tests were performed within one week of the CT examination in 63 patients. All PFTs were performed according to the American Thoracic Society guidelines [7]. The pulmonary function tests were carried out using a computerized spirometer (Vmax22; Sensor Medics Corp, Yorba Linda, CA, USA). Forced expiratory volume in one second (FEV₁), forced vital capacity (FVC) and FEV₁/FVC ratio, and forced expiratory flow during the middle half of the FVC (FEF₂₅₋₇₅) were recorded. FEV₁ and FVC values were also expressed as a percentage of the predicted value for age, sex, and height [8].

CT Examination

A CT examination was performed with either a Spiral CT (X-Vision, Tokyo, Japan) (n=23) or 16-detector-row CT system (Aquillon, Toshiba Medical Systems, Tokyo, Japan) (n=40). All CT examinations were obtained at maximal inspiration in the supine position with 1.5 mm collimationat 20 mm intervals. The volume of the examination extended from the lung apices to the lung bases. The images were photographed with a window level of -600 HU and a window width of 1.300 HU (i.e., lung windows) and a window level of 10 HU and a window width of 300 HU (i.e., mediastinal windows). Additionally, thin-section CT images were reconstructed with a high-spatial frequency (bone) algorithm and photographed with relatively wide window settings to allow evaluation of both pleura and parenchyma (window center -550 HU, window width 1.500 HU).

The CT was reviewed independently by two radiologists who were unaware of the clinical and radiographic data. The final decision was made by consensus of the two radiologists. The reviewers evaluated the images with lung windows for the presence and distribution of fissure displacement, bronchial distortion, masses, nodules, micro-nodule, reticular opacity, traction bronchiectasis, ground-glass opacity, septal lines, intralobular septal lines, cysts, emphysema, subpleural lines, consolidation, bronchovascular thickening or irregularity of the bronchovascular bundles, aspergilloma, atelectasis, air trapping, cavity, and honeycombing. The images with relatively wide windows were evaluated for the presence and severity of pleural thickening, calcification, and effusion and with a mediastinal window for the presence of lymphade-nopathy with or without calcification. Lymph node enlargements with a short axis of 1 cm or more were considered pathologic [9]. The lymph node evaluation was done according to the International Association for the Study of Lung Cancer Staging Committee staging system [10].

Each lung was craniocaudally divided into upper (apex to carina), middle (carina to inferior pulmonary vein), and lower (inferior pulmonary vein to lung base) zones. After the evaluation of the grades (0 to 4) for each of the six lung zones (three zones of each lung) in the craniocaudal axis, the percentages of grade 0 (no involvement), grade 1 (1-25% of the lobe involved) and grade 2 (26-50% of the lobe involved) and the percentages of grade 3 (51-75% of the lobe involved) and grade 4 (76-100% of the lobe involved) were summed separately to show none, mild, moderate, severe and very severe, respectively [11].

Bronchoscopy

Afiberopticbronchoscopy (FOB) (OlympusVideobronchoskopy BF type 1 T240[®]) under local anesthesia was used in the diagnostic evaluation of all patients. Bronchial stenosis, defined as the presence of endobronchial involvement, mural thickening and external compression of the tracheobronchial tree, were recorded during FOB. All bronchoscopic findings were recorded without considering local or diffuse involvement. Local and diffuse involvement were defined as either the presence of only one lobe or more than one lobe involvement, respectively.

All patients were informed about the study and provided consent to participate. The study was planned according to the ethics guidelines of the Helsinki Declaration and study protocol approved by the Atatürk University School of Medicine local ethical committee (B.30.2.ATA.0.01.00/14).

Statistical Analysis

The data were analyzed using the SPSS version 18 statistical software (SPSS Inc., Chicago, IL). The effect of all LAP and HRCT findings on PFT was evaluated via a Student's T test due to normal distribution. The Spearman's rank correlation test was used to assess the following: relation of PFT and age; smoking and chest x-ray; correlation with PFT parameters and localization of LAP and degree of involvement in HRCT; relationship of bronchoscopic findings with PFT. The degree of involvement in HRCT relationship between PFT and LAP was determined by multivariate analysis. P<0.05 was considered statistically significant.

RESULTS

Sixty-three patients were enrolled in the study. The patients consisted of 17 males and 46 females. The average age of the patients was 41 ± 13 years and the range was 21-66; 49 of the patients were non-smokers and the remaining 14 had a history of smoking between 1 and 10 pack/years (mean 6.2 ± 3.2 pack/years).

quency of co-inhabitant?

Table 1. Involvement of lymph node stations and fre-

Number of Regional Nodal Stations	Number of patients	%
1	9	14.3
2	3	4.8
3	8	12.7
4	2	3.2
5	8	12.7
6	11	17.4
7	6	9.5
8	2	3.2
9	4	6.3
10	3	4.8
11	1	1.6
0	6	9.5



Figure 1. The frequency of lymph nodes involvement

Disease stages of the patients according to chest x-ray were as follows: 18 patients (28.6%) were stage I; 39 patients (61.9%) were stage II; 5 patients (7.9%) were stage III; one patient (1.6%) was stage IV. The bronchoscopy findings of the patients were as follows: external compression in 30 (47.6%) patients; mural thickening in 3 (4.7%) patients; and presence of endobronchial involvement in 3 (4.7%). In the remaining patients, the bronchoscopy was normal.

Involvement of lymph node stations and frequency of coinhabitants are shown in Table 1. The frequency of lymph node involvement from the most frequent to the least was as follows: bilateral hilar LAP (BHL) (n=51, 81%); right upper paratracheal LAP and aortopulmonary LAP (n=37, 58.7%); right lower paratracheal LAP (n=34, 54%); left upper and lower paratracheal LAP (n=32, 50.8%); subcarinal LAP (n=28, 44.4%); prevascular LAP (n=20, 31.7%); retrotracheal LAP (n=16, 25.4%); intrahilar LAP (n=14, 22.2%); paraesophageal LAP (n=8, 12.7%); pulmonary ligamentum LAP (n=6, 9.5%); and lobar LAP (n=4, 6.3%) (Figure 1).

The relation of particular site LAP to PFTs was investigated (Table 2). There is a statistically significant relation between PFTs parameters (mean FVC and mean FEV₁) and BHL, and intrahilar LAP and lobar LAP (p=0.005 and p=0.001). The relation between mean FEV₁/FVC and right upper paratracheal LAP, prevascular LAP and left lower paratracheal LAP were statistically significant (p=0.001, p=0.004 and p=0.001). The relation between mean FEF₂₅₋₇₅ (% pred) and subcarinal LAP, paraesophagus LAP and pulmonary ligamentum LAP were statistically significant (p=0.004, p=0.001 and p=0.001). We detected that FVC is more affected by lymphadenopathy which is adjacent or proximal to neighboring bronchi, and this is similar to the results for FEV₁.

	FVC +/-	FEV ₁ +/-	FEV ₁ /FVC +/-	FEF ₂₅₋₇₅ +/-
Right upper paratracheal (n=37)	98/97	93/98	79/84 [†]	71/93†
Left upper paratracheal (n=32)	97/99	93/96	80/81	72/81 ^Y
Pre vascular (n=20)	93/103 [†]	90/98 [†]	79/82 ^Y	72/77
Retrotracheal (n=16)	97/98	92/95	80/80	73/76
Right lower paratracheal (n=34)	99/95	94/92	80/81	74/78
Left lower paratracheal (n=32)	98/97	93/95	81/80 [†]	80/79 [°]
Aortopulmonary (n=37)	97/101	93/96	80/81	75/75
Subcarinal (n=28)	94/100 [°]	90/96 ^Y	80/81	70/77 ^Y
Paraesophagus (n=8)	100/97	92/100 [†]	80/84 [†]	71/80†
Pulmonary ligamentum (n=6)	99/98	98/93	84/79 [†]	72/90†
Bilateral Hilar (n=51)	84/99†	86/94*	79/87 [†]	74/77
İntrahilar (n=14)	93/106 [†]	89/101 ⁺	79/81 [†]	74/75
Lober (n=4)	95/102 [†]	91/103 [†]	78/80	74/75

Table 2. Comparison of pulmonary function tests in the patients with or without particular site lymphadenopathy

FVC (% pred): force vital capacity, FEV₁ (%pred): forced expiratory volume in 1 sec, FEV₁/FVC: forced expiratory volume in 1 sec-forced vital capacity ratio, FEF₂₅₋₇₅ (% pred): forced expiratory flow at 25-75% of vital capacity.

+: pulmonary function test results with lymphadenopathy

-: pulmonary function test results without particular site lymphadenopathy

*: p< 0.05, ^Y: p<0.01, [†]: p<0.001

	FVC (% pred) +/-	FEV ₁ (% pred) +/-	FEV ₁ /FVC +/-+/-	FEF ₂₅₋₇₅ (% pred)
Fissure displacement (n=8)	86/99†	79/96 [†]	80/80 ^Y	59/77 ^Ŷ
Bronchial distortion (n=15)	95/99	90/95	81/81	76/75
Masses (n=1)	91/98	94/94	72/80	65/75
Nodules (n=29)	98/98	93/95	79/83†	74/77
Micronodules (n=17)	94/99*	86/97†	77/82†	61/80 [†]
Reticular opacities (n=17)	96/101*	97/93	80/81	77/74
Traction bronchiectasis (n=10)	96/98	92/94	78/81 ^Y	71/76
Ground-glass opacity (n=12)	88/100 [†]	83/96†	79/81	67/77 ^Ŷ
Septal lines (n=15)	95/99	88/95	79/81†	70/76
Septal thickening (n=15)	97/98	92/95 ^γ	78/81†	72/76
Air cysts (n=2)	85/98	76/94	77/81	49/75
Emphysema (n=7)	83/99†	77/96†	79/81	53/77†
Subpleural lines (n=18)	97/99	90/95	78/81†	70/76
Consolidation (n=4)	99/98	93/94	77/80	72/75
Bronchovascular thickening (n=9)	97/105	92/103*	82/80 ^Y	73/89 ^Y
Atelectasis (n=9)	96/98	95/94	83/80 ^Y	84/73*
Air Trapping (n=9)	81/100 [†]	74/97†	77/81 [°]	55/78 [†]
Cavity (n=2)	93/96	84/91	83/80	72/106
Honeycombing (n=3)	62/98	64/94	85/80	84/74
Pulmonary fibrosis (n=9)	73/95†	65/83†	78/81†	75/77 ^Y
Pleural pathology (n=12)	100/97	97/92	79/81 [°]	77/74

Table 3. Comparison of pulmonary function tests in the patients with or without radiological involvement

FVC (% pred.): force vital capacity, FEV₁ (% pred.): forced expiratory volume in 1 sec, FEV₁/FVC: forced expiratory volume in 1 sec-forced vital capacity ratio, FEF_{25.75} (% pred.): forced expiratory flow at 25-75% of vital capacity.

+: pulmonary function test results with radiological involvement

-: pulmonary function test results without radiological involvement

*: p<0.05, ^Y: p<0.01, [†]: p<0.001

With regard to the relation of PFTs parameters to findings on HRCT, we detected a statistically significant relation between the presence of micronodules in HRCT and all parameters of PFTs (Table 3). FVC (% pred.) and FEV₁ (% pred.) have a significant relation with the findings on HRCT, including fissure displacement, emphysema, air trapping, ground-glass opacity, pulmonary fibrosis, and honey-combing (p=0.001). There is also a strong correlation between FEF₂₅₋₇₅ (% pred) and presence of ground-glass opacity, emphysema, and air trapping in HRCT results of the patients (p=0.001).

Considering the degree of involvement in HRCT, the relation between PFTs parameters and LAP localization are indicated in Table 4. The relation was still present between LAP (hilar, intrahilar and lobar) and PFTs (FVC and FEV₁). Also, FEV₁/FVC has a relation with left lower paratracheal LAP, paraesophagus LAP, pulmonary ligamentum LAP, prevascular, and hilar LAP. FEF₂₅₋₇₅ has a relation with subcarinal and paraesophagus LAP.

We detected a statistically significant correlation between PFTs and bronchoscopic findings (Table 5). When we looked for a correlation between PFTs and age, smoking, and stage of disease on the chest x-ray, we found a statistically significant negative correlation between age and FEV₁/FVC (p=0.002) and FEF₂₅₋₇₅ (p=0.04). There is no statistically significant cor-

relation between PFTs and smoking. There is a statistically significant negative correlation between the radiological stage of sarcoidosis and FVC (p=0.01) and FEV₁ (p=0.01).

DISCUSSION

In the management and follow-up of the patients with sarcoidosis, PFTs and HRCT play important roles. In our study, we revealed that, in addition to the parenchymal involvement of the disease, special localization of lymph node involvement also has an important effect on the PFT parameters of sarcoidosis patients. It is possible that decrease in PFTs resulted from the presence of BHL and intrahilar LAP because of compression on the adjacent bronchi.

Although sarcoidosis primarily affects small airways, large airways can be involved in the disease process, albeit less frequently. Mural thickening, endobronchial involvement, extrinsic compression from enlarged lymph nodes, and architectural distortion of the airway can all lead to bronchial stenosis. Bronchoscopy is a useful tool identifying tracheobronchial stenosis [12,13]. In the present study, bronchial stenosis was found in 57.2% (n=36) of our patients. Bronchostenosis has been described in 2%, 8% and 26% of sarcoidosis patients undergoing bronchoscopy [14-16]. The increased rate of patients with stenosis in our study may result from recording of the stenosis regardless of its degree and extent.

	FVC	FEV ₁	FEV ₁ /FVC	FEF ₂₅₋₇₅
Right upper paratracheal	NS	0.001	NS	0.001
Left upper paratracheal	0.009	0.04	0.009	0.046
Pre vascular	NS	NS	0.001	0.001
Retrotracheal	NS	NS	0.006	NS
Right lower paratracheal	0.001	0.001	0.019	NS
Left lower paratracheal	0.002	0.005	0.001	NS
Aortopulmonary	NS	0.027	0.017	0.018
Subcarinal	NS	NS	NS	0.002
Paraesophagus	0.001	NS	0.001	0.001
Pulmonary ligamentum	0.001	0.050	0.001	NS
Bilateral Hilar	0.001	0.001	0.001	NS
İntrahilar	0.001	0.001	NS	NS
Lobar	0.001	0.001	NS	0.050

Table 4. Relation between presence of lymph node involvement and PFTs according to HRCT parenchymal involvement

FVC (% pred.): force vital capacity, FEV₁ (% pred.): forced expiratory volume in 1 sec, FEV₁/FVC: forced expiratory volume in 1 sec-forced vital capacity ratio, FEF_{25.75} (% pred.): forced expiratory flow at 25-75% of vital capacity. (p value taken from multivariate analysis) NS: non statistically significant

Table 5. Correlation between PFTs and bronchoscopic findings

	FVC (r/p)	FEV ₁ (r/p)	FEV ₁ /FVC (r/p)	FEF ₂₅₋₇₅ (r/p)
Endobronchial involvement	0.02/0.733	0.173/0.003	0.074/0.209	0.136/0.02
External compression	0.205/0.008	0.131/0.02	0.149/0.01	0.139/0.02
Mural thickening	-0.215/0.001	-0.215/0.001	-0.155/0.008	-0.180/0.002

p: Statistical significance r: correlation coefficient

Pulmonary function tests may be affected by bronchial stenosis. Granulomas lying in a perilymphatic distribution along the bronchovascular bundles may compress both small and large airways, producing an obstructive function deficit [17,18]. In the present study, FEV₁/FVC <70 was found in four (11.1%) of the patients who had stenosis; external compression of bronchi due to LAP was present in all four patients. Udwadia et al. [19] reported that all patients (n=12) with bronchostenosis showed an obstructive pattern in their study. Chambellan et al. [20] reported that FEV₁/FVC <70 in 12 (66.7%) of 18 patients who had endobronchial stenosis, external compression due to LAP was present in two (11%) of these patients. It is highly possible that the difference between our results and previous studies resulted from the criteria that we used for bronchial stenosis.

Lymphadenopathy is one cause of bronchial stenosis. When we evaluated the relation of PFTs and presence of LAP, we found a decrease in PFTs parameters in most of the patients who had LAP. We also found that FVC further decreases if there are neighboring LAP to bronchi, which is similar to FEV₁ and FEV₁/FVC is further affected by neighboring LAP to the trachea. Handa et al. [21] found no relation between FEV₁/FVC and mediastinal or hilar LAP. Incontrast, Drent et al. [22] found a slight depressive effect of LAP on PFTs parameters. In our study, the relationship of PFTs and LAP was investigated in more detail, and we determined that the presence of LAP at lower levels and neighboring LAP to bronchi further affect PFTs parameters. PFTs [21,22]. The effect of radiological involvement on PFTs is commonly via a restrictive pathologic mechanism. Also, obstructive impairment is as common as restrictive impairment, particularly in advanced fibrocystic disease or endobronchial disease [23]. Hansell et al. [11] concluded that reticular pattern, pulmonary fibrosis has the most profound effect on obstructive lung impairment in sarcoidosis. We detected nodules, micronodules, reticular pattern and pulmonary fibrosis has the most profound effect on restrictive lung impairment in sarcoidosis. We also observed that the presence of micronodules particularly affects all parameters of PFTs in favor of restriction. We interpret that the smaller amount of obstructive effect in our study is due to a lower number of patients with endobronchial involvement.

There is a correlation between radiological involvement and

In our study, when we looked for a correlation between PFTs parameters and age, smoking, and stage according to chest x-ray, there was a negative correlation between age and FEV₁/FVC and FEF₂₅₋₇₅. We did not detect a significant correlation between smoking and PFTs. There was a negative correlation between the stage according to chest x-ray and FVC, FEV₁ and FEV₁/FVC. Handa et al. [21] detected an independent significant correlation between FEV₁/FVC and age, smoking, and the stages on chest x-ray in their study. Because we excluded the cases with a smoking history of more than 10 pack-year, it was not reasonable to expect to find such a correlation among our cases.

In conclusion, our study results suggest that, in addition to parenchymal involvement of the disease, special localization of lymph node involvement may also have an important effect on the PFTs parameters among patients with sarcoidosis.

Conflict of Interest

No conflict of interest was declared by the authors.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Atatürk University School of Medicine (B.30.2.ATA.0.01.00/14).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions

Conception - M.A., Ö.A.; Design - E.Y.U., F.A.; Supervision - Y.A., Y.B.; Fundings - M.M.; Data Collection and/or Processing - Y.A.; Analysis and/or Interpretation - M.A., Ö.A.; Writer - Ö.A.; Critical Review - M.G.

Çıkar Çatışması

Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

Hakem değerlendirmesi: Dış bağımsız.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Yazar Katkıları

Fikir - M.A., Ö.A.; Tasarım - E.Y.U., F.A.; Denetleme - Y.A., Y.B.; Kaynaklar - M.M.; Veri toplanması ve/ veya işlemesi - Y.A.; Analiz ve/ veya yorum - M.A., Ö.A.; Yazı yazan -Ö.A.; Eleştirel İnceleme - M.G.

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