

Microvascular alterations and disease features in Behçet's disease: Insights from nailfold capillaroscopy

Behçet hastalığında mikrovasküler değişiklikler ve hastalık özellikleri: Tırnak dibi kapillaroskopisinden elde edilen bulgular

Recep Yılmaz^{1,2}, Müçteba Enes Yayla¹, Murat Torgutalp^{1,3}, Aşkın Ateş¹, Tahsin Murat Turgay¹, Gülay Kınıklı¹

¹Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye

²University of Health Sciences Türkiye, Sincan Training and Research Hospital, Department of Rheumatology, Ankara, Türkiye

³Department of Gastroenterology, Infectious Diseases and Rheumatology (including Nutrition Medicine), Charité-Universitätsmedizin Berlin, Berlin, Germany

Abstract

Objective: The objective of this study was to compare nailfold capillaroscopy findings in patients with Behçet's disease (BD) with those in healthy individuals, and to assess the relationship between these findings and BD subtypes, disease activity, and other characteristics.

Methods: This cross-sectional study included 165 healthy individuals and 153 patients with BD. Demographic and clinical data were collected. Capillaroscopic findings from eight fingers (excluding thumbs) were evaluated in patients with BD and in healthy controls. Capillaroscopic patterns for each participant were assessed using both qualitative and quantitative methods.

Results: Of the included patients, 41.2% were male, with a mean ($\pm$ standard deviation) age of 41.2 (11.4) years and a mean disease duration of 12.1 (9.2) years. Bushy capillaries (24.2%), dilated capillaries (32%), and microhemorrhages (39.2%) were significantly more prevalent in the patient group than in the healthy control group ($p < 0.001$). Quantitative assessment revealed that scores for dilated capillaries, microhemorrhages, capillary losses, and capillary irregularities were significantly higher in patients than in healthy individuals ($p < 0.001$). No statistically significant relationship was found between the presence of clinical signs and capillaroscopy scores, except for erythema nodosum.

Conclusion: Capillaroscopic abnormalities were more frequent in BD patients than in healthy controls. However, except for erythema nodosum, no significant correlations were found between total capillaroscopy scores and clinical features of BD.

Keywords: Behçet's syndrome, microcirculation, capillaroscopy, vasculitis, rheumatic diseases

Özet

Amaç: Bu çalışmanın amacı, Behçet hastalığı (BH) olan hastalarda tırnak dibi kapillaroskopi bulgularını sağlıklı bireylerle karşılaştırmak ve bu bulguların BH alt tipleri, hastalık aktivitesi ve diğer özelliklerle ilişkisini ortaya koymaktır.

Yöntem: Bu kesitsel çalışmaya 165 sağlıklı birey ve 153 Behçet hastası dahil edilmiştir. Demografik ve klinik veriler toplanmıştır. BH hastaları ve sağlıklı kontrollerde başparmaklar hariç sekiz parmağın elde edilen kapillaroskopik bulgular değerlendirilmiştir. Her katılımcının kapillaroskopik paternleri hem nitel hem de nicel yöntemlerle analiz edilmiştir.

Bulgular: Dahil edilen hastaların %41,2'si erkek olup, yaş ortalaması $41,2 \pm 11,4$ yıl ve hastalık süresi ortalaması $12,1 \pm 9,2$ yıl olarak bulunmuştur. Çalı kapillerler (%24,2), dilate kapillerler (%32) ve mikrohemoraji (%39,2) hasta grubunda, sağlıklı kontrollere göre anlamlı olarak daha sık saptanmıştır ($p < 0,001$). Nicel değerlendirmede dilate kapillerler, mikrohemoraji, kapiller kayıp ve kapiller düzensizlik skorlarının hasta grubunda, sağlıklı bireylere göre anlamlı olarak daha yüksek olduğu gösterilmiştir ($p < 0,001$). Klinik bulgular ile kapillaroskopi skorları arasında, eritema nodosum dışında istatistiksel olarak anlamlı bir ilişki bulunmamıştır.

Sonuç: Kapillaroskopik anormallikler Behçet hastalarında sağlıklı kontrollere göre daha sık görülmektedir. Ancak eritema nodosum dışında, toplam kapillaroskopi skorları ile klinik özellikler arasında anlamlı bir ilişki saptanmamıştır.

Anahtar Kelimeler: Behçet sendromu, mikrosirkülasyon, kapillaroskopi, vaskülit, romatizmal hastalıklar

Correspondence / İletişim: Recep Yılmaz MD,

Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology; University of Health Sciences Türkiye, Sincan Training and Research Hospital, Department of Rheumatology, Ankara, Türkiye

E-mail: recep.yilmaz0621@gmail.com ORCID ID: orcid.org/0000-0001-8806-8621

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Introduction

Behçet's disease (BD) is a systemic vasculitis with a chronic, relapsing-remitting course. It has a wide range of clinical manifestations including recurrent mucocutaneous lesions, ocular involvement, central nervous system involvement, and vascular involvement.^[1] Genetic, environmental, and immunologic mechanisms contribute to the pathogenesis of BD.^[2] Most manifestations of BD are associated with an underlying vasculitic process. Vascular involvement can affect vessels of different sizes, with venous involvement being more common than arterial involvement.^[3] However, there is insufficient information regarding the extent of microvascular structural damage and its impact on the clinical manifestations of the disease.

Nailfold capillaroscopy has become an established tool for the assessment of peripheral microvascular abnormalities, particularly in systemic sclerosis (SSc), where it plays an important role in the evaluation of microvascular changes and may provide information regarding disease progression and organ involvement.^[4] In SSc, capillaroscopic abnormalities may also contribute to early disease recognition, including in patients without Raynaud's phenomenon.^[5] Furthermore, nailfold capillaroscopy is increasingly used in other connective tissue diseases, including systemic lupus erythematosus, dermatomyositis, and mixed connective tissue disease. Although the capillaroscopic patterns observed in these diseases are generally less disease-specific than those in SSc, they may provide valuable information regarding microvascular involvement and disease severity.^[4,6]

Early studies investigating nailfold capillaroscopy in BD reported the presence of microvascular abnormalities, suggesting that peripheral microvascular involvement may be a feature of the disease.^[7,8] Despite these initial observations, the clinical significance of capillaroscopic findings and their relationship with disease characteristics remain insufficiently understood.

The present study aimed to evaluate nailfold capillaroscopic abnormalities in patients with BD compared with healthy controls using both qualitative and quantitative assessment methods, with blinded image evaluation. Furthermore, we investigated the associations between capillaroscopic findings and disease activity indices, clinical characteristics, and laboratory parameters.

Materials and Methods

Participants

This cross-sectional study was conducted at the Department of Rheumatology, Ankara University Faculty of Medicine, from March 2017 to February 2018. This study included 153 unselected

consecutive patients from our specialized BD outpatient clinic. Eligible participants were aged ≥ 18 years and fulfilled the International Study Group for Behçet Disease classification criteria.^[9] We randomly included 165 age- and gender-matched healthy individuals as the control group. Patients with concomitant rheumatic diseases, hyperthyroidism, diabetes mellitus, hypertension, chronic kidney disease, pregnancy, malignancy, or Raynaud syndrome were excluded from this study. The study was approved by the Ankara University Faculty of Medicine Clinical Research Ethics Committee (approval no: 05-235-17, date: 13.03.2017) and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent before participation.

Variables and Data Collection

The clinical activity of patients with BD was evaluated using both the Behçet disease current activity form (BDCAF)^[10] and the Behçet syndrome activity score (BSAS).^[11] Age, sex, comorbidities, body mass index (BMI), smoking history, and disease characteristics were noted. Patients with BD were categorized into subgroups according to their predominant organ involvement: mucocutaneous, ocular, vascular, neurological, and enteric. Capillaroscopy scores in patients with BD were assessed according to clinical subtype and disease activity over the preceding month. Capillaroscopic findings in patients with BD were compared with those in a healthy control group to assess their statistical significance. BDCAF, BSAS, and routine laboratory tests, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were used to assess whether there was a significant association between disease activity and capillaroscopic findings.

Capillaroscopic Assessment

Capillaroscopy was conducted in a sitting position at room temperature. Peanut oil was applied to the nailfold, and imaging was performed with a Dino-Lite Capillaroscope Pro 200 (MEDL4N Pro) at 200 $\times$ magnification. For each participant, the following parameters were recorded: capillary density, capillary visibility, aneurysms, tortuosity, bushy capillaries, avascular areas, capillary count, dilated and giant capillaries, microhemorrhages, capillary branching, and disorganization of capillary architecture. A dilated capillary is defined as having a diameter greater than 20 μm , while a giant capillary has a diameter exceeding 50 μm . Capillary loss is identified when there are fewer than 9 capillaries per 1 mm linear segment, and an avascular area is defined as a gap larger than 500 μm between two capillaries. A microhemorrhage was defined as the presence of hemosiderin deposits outside the veins or hemorrhagic areas. Other morphological abnormalities were assessed based on appearance, including tortuous and bushy capillaries.

During capillaroscopy, two images were captured at every 1 mm interval along each finger of every participant, excluding the thumbs, resulting in 16 images per finger. Two experts (M.E.Y., M.T.) evaluated the images acquired during the examination in a double-blind manner. The capillaroscopic findings were assessed using both qualitative and quantitative grading methods.^[12] A semi-quantitative analysis was performed to assess capillary abnormalities, including capillary loss, dilated capillaries, giant capillaries, microhemorrhages, capillary branching, and capillary irregularities. Capillaroscopic findings were evaluated on a 0-3 scale: 0 indicated no changes, 1 indicated involvement or loss of fewer than 33% of capillaries, 2 indicated involvement or loss of 33-66% of capillaries, and 3 indicated involvement or loss of more than 66% of capillaries. The score for the capillaroscopic finding was determined by calculating the arithmetic mean of the scores from the two images. For each capillaroscopic finding that was quantitatively scored, the scores for the four fingers on both hands were summed, the arithmetic mean was calculated, and the total score for that finding was determined. For each parameter, the main score was determined by computing the arithmetic mean of the assessments provided by the two specialists. A composite capillaroscopy score was calculated for each participant by averaging the final scores of capillaroscopic abnormalities evaluated semi-quantitatively. This score was used to summarize the overall burden of capillaroscopic abnormalities based on established semi-quantitative capillaroscopic assessment methods.^[4,12]

Statistical Analysis

Data were analyzed using SPSS version 21 (SPSS, Chicago, USA). Normality was assessed using histograms, probability plots, and Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed variables are presented as mean $\pm$ standard deviation, and non-normal variables as median (range). Continuous variables were compared using Student's t-test or Mann-Whitney U test, and categorical variables were compared using chi-squared test or Fisher's exact test. Spearman's

correlation was used to assess relationships between variables. Because the analyses were exploratory, no formal adjustment for multiple comparisons was performed. Statistical significance was defined as $p < 0.05$.

Results

Demographic and Clinical Characteristics of the Participants

The study included 153 patients and 165 healthy controls. Baseline characteristics of patients with BD and healthy controls are shown in Table 1. Clinical characteristics and disease manifestations of patients with BD are shown in Table 2.

Capillaroscopic Assessment: Qualitative and Quantitative Results

Capillaroscopic findings in the patient and healthy groups were evaluated using both qualitative and quantitative methods. A qualitative assessment of capillary density, capillary visibility, aneurysms, tortuous and giant capillaries, and avascular areas did not reveal significant differences between the two groups. Bushy capillaries, dilated capillaries, and microhemorrhages were significantly more frequent (24.2%, 32%, and 39.2%, $p < 0.001$, respectively) than in healthy controls (Figure 1). Additionally, quantitative scoring of nailfold capillaroscopic findings revealed that patients with BD had significantly higher scores for dilated capillaries, microhemorrhages, reduced capillary numbers, and capillary irregularities than those of healthy controls ($p < 0.001$). The median (range) total capillaroscopy score was 0.16 (0-1.75) in patients versus 0 (0-0.50) in controls ($p < 0.001$). Scores for giant capillaries and capillary branching did not differ significantly between groups.

Does Capillaroscopy Scoring Correlate with the Disease Features?

The relationship between clinical involvement and total capillaroscopy scores in BD patients was assessed. No significant

Table 1. Baseline characteristics of patients with Behçet's disease and healthy controls

Characteristic	Patient group (n=153)	Healthy group (n=165)	p-value
Age, years, mean (SD)	41.2 (11.4)	39.7 (8.2)	0.189
Male, n (%)	63 (41.2)	63 (38.2)	0.585
Body mass index, kg/m ² , mean (SD)	25.9 (5.1)	25.5 (4.3)	0.407
Smoker, n (%)	67 (43.8)	71 (43)	0.891
Age at diagnosis, years, mean (SD)	29 (8.8)	-	-
Disease duration, years, mean (SD)	12.1 (9.2)	-	-
BDCAF ^a score, mean (SD)	2.8 (1.5)	-	-
BSAS ^b score, mean (SD)	20.7 (14.1)	-	-
Colchicine use, n (%)	150 (98)	-	-
Immunosuppressive therapy, n (%)	56 (36.6)	-	-

^a: Behçet's disease current activity form, ^b: Behçet's syndrome activity score, SD: Standard deviation

Table 2. Clinical characteristics and disease manifestations of patients with Behçet's disease		
Characteristic	Throughout the disease course n (%)	Within the preceding 4 weeks n (%)
Oral ulcer	153 (100)	98 (64.1)
Papulopustular lesion	119 (77.8)	64 (41.8)
Erythema nodosum	99 (64.7)	31 (20.3)
Genital ulcer	131 (85.6)	15 (9.8)
Arthralgia	119 (77.8)	93 (60.8)
Arthritis	25 (16.3)	9 (5.9)
Pathergy positivity ^a	71 (56.3)	-
Ocular involvement	64 (41.8)	14 (9.2)
Vascular involvement	54 (35.3)	1 (0.6)
Gastrointestinal involvement	4 (2.6)	-
Neurological involvement	12 (7.8)	-

^a: The pathergy test was performed in 126 patients

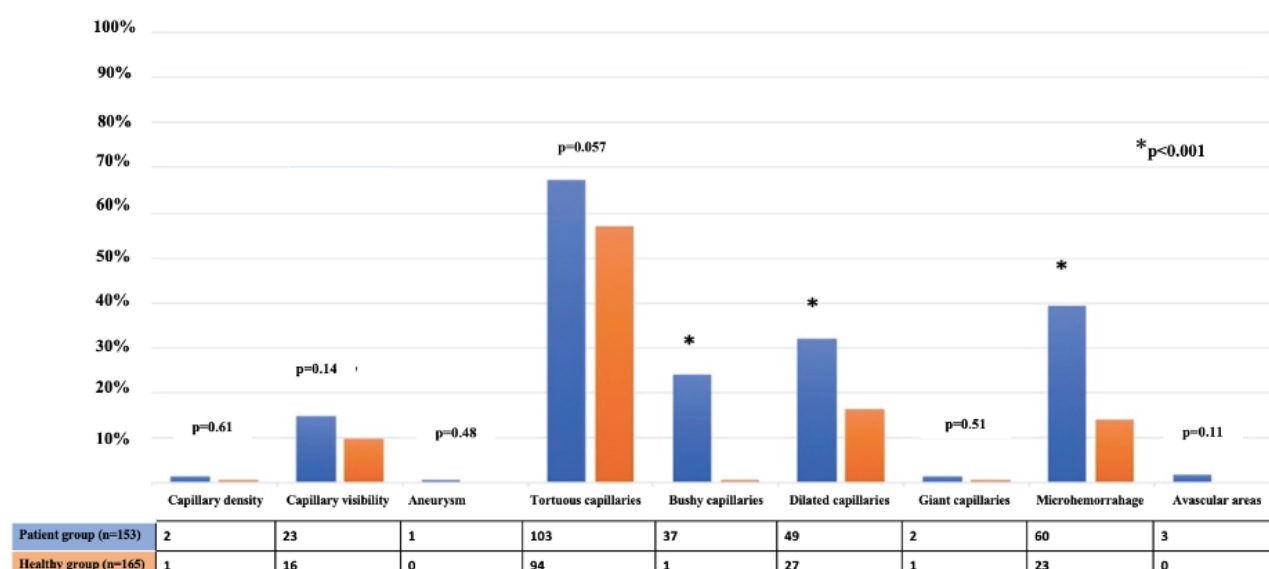


Figure 1. Qualitative evaluation of the capillaroscopic findings of the patient and healthy groups

associations were found, except for erythema nodosum. Total capillaroscopy scores were evaluated in relation to oral ulcers, erythema nodosum, papulopustular lesions, genital ulcers, and ocular involvement over the past four weeks, but no correlation with disease activity was observed (Table 3). Capillaroscopy scores were also not associated with age, sex, disease duration, ESR, CRP, BDCAF, or BSAS; however, a weak correlation with BMI was noted ($r=0.142$, $p<0.05$).

Discussion

In this study, we evaluated nailfold capillaroscopic findings in patients with BD and in healthy controls using both qualitative and quantitative methods. Our results demonstrated that dilated capillaries, bushy capillaries, and microhemorrhages were significantly more frequent in the BD group than in healthy

controls. These abnormalities were consistently observed across both qualitative and quantitative assessments, suggesting that microvascular involvement is a prominent feature of BD.

Microvascular alterations in BD have been reported with varying prevalence and patterns. Early investigations by Wechsler et al.^[7] documented nailfold capillaroscopic abnormalities in approximately 43% of patients with BD, whereas Vaiopoulos et al.^[8] subsequently reported a markedly higher prevalence of 75%. Subsequent studies have produced conflicting findings regarding specific capillary morphologies. For example, Alan et al.^[13] observed increased tortuosity and irregular shapes in BD but found no significant differences in microhemorrhages or giant capillaries compared with controls. In contrast, other reports noted a marked increase in capillary dilatation and microhemorrhages, although no significant avascular areas

Table 3. Total capillaroscopy scores of patients with Behçet disease according to their clinical involvements and activity			
Clinical involvement (n=present/absent)	Total capillaroscopy score		p
	Present	Absent	
Vascular involvement, median (range) (n=54/99)	0.19 (0-1.48)	0.13 (0-1.75)	0.814
Mean (SD)	0.28 (0.34)	0.3 (0.35)	-
Ocular involvement, median (range) (n=64/89)	0.19 (0-1.48)	0.13 (0-1.75)	0.358
Mean (SD)	0.32 (0.36)	0.27 (0.33)	-
Neurological involvement, median (range) (n=12/141)	0.19 (0-1.48)	0.13 (0-1.75)	0.222
Mean (SD)	0.38 (0.43)	0.28 (0.34)	-
Genital ulcer, median (range) (n=131/22)	0.19 (0-1.75)	0.13 (0-1.48)	0.121
Mean (SD)	0.31 (0.36)	0.16 (0.19)	-
Erythema nodosum, median (range) (n=99/54)	0.13 (0-1.75)	0.19 (0-1.48)	0.026
Mean (SD)	0.25 (0.32)	0.37 (0.38)	-
Papulopustular lesions, median (range) (n=119/34)	0.19 (0-1.75)	0.13 (0-1.2)	0.238
Mean (SD)	0.30 (0.35)	0.24 (0.33)	-
Active oral ulcers, median (range) (n=98/55)	0.16 (0-1.75)	0.16 (0-1.48)	0.620
Mean (SD)	0.28 (0.35)	0.30 (0.34)	-
Active erythema nodosum, median (range) (31/122)	0.13 (0-1.44)	0.19 (0-1.75)	0.096
Mean (SD)	0.21 (0.32)	0.31 (0.35)	-
Active papulopustular lesions, median (range) (n=64/89)	0.16 (0-1.44)	0.16 (0-1.75)	0.978
Mean (SD)	0.26 (0.29)	0.31 (0.38)	-
Active genital ulcers, median (range) (n=15/138)	0.31 (0-0.88)	0.14 (0-1.75)	0.602
Mean (SD)	0.30 (0.30)	0.29 (0.35)	-
Active ocular involvement, median (range) (n=14/139)	0.16 (0-0.69)	0.16 (0-1.75)	0.659
Mean (SD)	0.21 (0.21)	0.30 (0.36)	-
SD: Standard deviation			

were detected.^[14,15] Our results are consistent with the latter and demonstrate significantly higher frequencies of dilated capillaries, bushy capillaries, and microhemorrhages in the BD. We observed no significant differences regarding avascular areas, giant capillaries, tortuosity, or aneurysms. In our study, the microhemorrhage rate was 39.2%, slightly higher than the previously reported range (4.9-36%), while the rate of dilated capillaries was 32%, within the reported range (26-56%).^[13,14,16] Differences among studies likely reflect variations in sample size, magnification, scoring methods, and observer interpretation. Overall, dilated capillaries and microhemorrhages are prominent capillaroscopic findings in BD and may reflect disease-associated microvascular damage.

While qualitative descriptions of capillaroscopic findings in BD exist, objective, quantitative data are lacking in the literature. In this study, quantitative analysis demonstrated that the frequencies of dilated capillaries, microhemorrhages, capillary loss, capillary irregularity, as well as the total capillaroscopy score, were significantly higher in patients with BD than in healthy controls. Moreover, dilated capillaries and microhemorrhages, which have been reported to be more prevalent in qualitative assessments of patients with BD, were also found to be significantly increased when assessed quantitatively.

Several studies have investigated the potential relationship between capillaroscopic abnormalities and clinical features of BD. Vaiopoulos et al.^[8] demonstrated an association between capillaroscopic findings and skin lesions, arthritis, arthralgia, and pathergy test positivity. Movasat et al.^[16] found that the presence of dilated capillaries was significantly associated with hypertension, pathergy test negativity, superficial phlebitis, and younger age at disease onset. Microhemorrhages have been linked to joint symptoms in some cohorts^[16], while other data suggest that the presence of microhemorrhages and “crossing” capillaries are specifically associated with uveitis.^[17] Furthermore, patients presenting with two or more qualitative abnormalities appear more predisposed to major vascular involvement.^[18] In contrast to the aforementioned studies, other research has failed to establish a clear link between capillaroscopic patterns and the clinical phenotype of the disease.^[15] In our study, capillaroscopy scores were not significantly associated with clinical signs, except for erythema nodosum. This finding may be associated with a localized microvascular pattern linked to cutaneous neutrophilic vasculitis.

Another important question is whether disease activity influences capillaroscopic changes. In our study, we investigated this association using two distinct measures of disease activity.

The patients' mean BDCAF score was 2.8 ± 1.5 , and their mean BSAS score was 20.7 ± 14.1 . No significant correlation was found between the total capillaroscopy score and either of the disease activity indices. This is in line with the study by Akman et al.^[14], which also reported no relationship between capillaroscopic findings and disease activity.

One of the notable findings of our study is that although capillaroscopic abnormalities were significantly more frequent in patients with BD, the total capillaroscopy score was not associated with disease activity indices or with most clinical features, except erythema nodosum. These findings suggest that nailfold capillaroscopic abnormalities may reflect underlying microvascular changes rather than short-term fluctuations in disease activity. Persistent endothelial dysfunction, repeated vascular inflammatory processes, and structural vascular alterations may contribute to persistent capillaroscopic abnormalities even in the absence of active clinical inflammation.

Study Limitations

The study has several limitations. First, its cross-sectional design precluded the assessment of the prognostic value of nailfold capillaroscopic abnormalities. Second, treatment exposure was not evaluated and may have influenced the findings. Third, occupational factors such as repetitive hand trauma or vibration exposure were not systematically recorded. Fourth, interobserver reliability was not formally assessed. Finally, no correction for multiple comparisons was applied because the analyses were exploratory. Despite these limitations, the study has notable strengths. The number of participants in both the patient and healthy control groups was substantially higher than that in previous studies, and capillaroscopic findings were analyzed using qualitative and quantitative approaches.

Conclusion

In conclusion, our findings suggest that nailfold capillaroscopy can detect microvascular abnormalities in patients with BD, even in the absence of clear associations with current disease activity or most clinical manifestations. These observations support the concept that capillaroscopic abnormalities may reflect chronic microvascular remodeling rather than active inflammation. Prospective longitudinal studies are needed to determine their prognostic significance and potential role in clinical practice.

Ethics

Ethics Committee Approval: The study was approved by the Ankara University Faculty of Medicine Clinical Research Ethics Committee (approval no: 05-235-17, date: 13.03.2017) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: All participants gave written informed consent before participation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.Y., M.E.Y., M.T., A.A., T.M.T., G.K., Concept: R.Y., M.E.Y., M.T., A.A., T.M.T., G.K., Design: R.Y., M.E.Y., M.T., A.A., T.M.T., G.K., Data Collection and Processing: R.Y., M.E.Y., M.T., Analysis or Interpretation: R.Y., M.E.Y., M.T., A.A., T.M.T., G.K., Literature Search: R.Y., M.E.Y., M.T., Writing: R.Y.

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