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Original Article

The association between nail fold capillaroscopic findings and lupus nephritis in patients with systemic lupus erythematosus

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Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease with common vascular involvement. Nailfold capillaroscopic changes have been described in SLE.

Objectives. To detect the peripheral microvascular abnormalities in SLE patients by NFC and explore the relation between these abnormalities and lupus nephritis.

Methods. Fifty SLE patients with lupus nephritis (LN) fulfilling the 2019 EULAR/ACR classification criteria were included in our study. A thorough history taking, clinical, and rheumatological evaluation was conducted on each patient. The patient underwent SLEDAI calculation, and kidney biopsy were done as needed. Nailfold videocapillaroscopy was used to evaluate the capillary circulation.

Results. According to the capillaroscopic changes in SLE patients with and without LN, significant differences were observed regarding elongated and dilated capillaries. The comparison of the activity index and capillaroscopic **changes in SLE patients revealed** higher activity indices in patients with elongated capillaries. Elongated capillaries were associated with a greater chronicity index. Using Multivariate logistic regression analysis, it demonstrates that (Capillary length and venous limb) were predictors for LN in SLE.

Conclusion: Nailfold capillaroscopic changes, such as dilated or elongated capillaries, are more prevalentin SLE patients with LN compared to those without LN. Elongated capillaries are associated with elevated activity and chronicity indices in patients. Furthermore, venous limb and capillary length might serve as indicators of LN in individuals with SLE.

Keywords: Systemic lupus erythematosus, renal biopsy, dilated capillaries

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Introduction

Systemic lupus erythematosus (SLE) is considered a multi-factorial autoimmune disease, characterized by the production of a variety of autoantibodies and thus causes a series of complement cascade activation reaction. Some of the symptoms that can be seen in a patient with SLE include Raynaud's phenomenon (RP), skin problems, arthritis, heart problems, neurological problems, blood vessel problems, periungual sores, and kidney problems. Vascular inflammation and endothelial cell injury caused by autoantibodies and circulating immune complexes can result in various organ dysfunctions. [1]

Inflammatory mediators associated with SLE harm vascular endothelial cells, leading to their demise and subsequent neovascularization. Finally, after several studies, a new model of microcirculation in SLE patients was found using nailfold capillaroscopy (NFC. [2]

Mortality and morbidity in SLE patients are largely caused by vascular involvement, which is also the most devastating symptom of the disease. Vasculopathy, which are non-inflammatory vascular lesions, and vasculitis, which are inflammatory vascular lesions characterized by fibrinoid necrosis of the vascular walls, can affect any artery type. Microvascular complications manifest as pulmonary and intestinal vasculitis, pulmonary hypertension, lupus nephritis, livedo reticularis, and cutaneous vasculitis. [3]

Lupus nephritis (LN) is a severe and prevalent form of SLE. In individuals with LN, the renal histological lesions are linked to various clinical traits, treatment reactions, and results. [4], and can present as glomerular, tubulo-interstitial, and micro-vascular lesions. A characteristic of LN, renal microvascular abnormalities are becoming more and more recognized. In addition to glomerulonephritis, growing evidence suggests that renal vascular lesions might impact long-term renal outcomes negatively and may be a key factor in therapeutic strategy selection. [5]

NFC is a highly effective, low-cost, and simple imaging method used for detecting the morphological analysis of capillaries in the nailfold [6], with the added benefit of detecting micro-vascular changes early in some inflammatory CTDs. While NFC has been widely utilized for diagnosing systemic sclerosis and scleroderma-like diseases [7] , there is a growing body of evidence suggesting its potential utility in detecting early microangiopathic changes in SLE. [8] There has been new evidence linking microcapillary pathological abnormalities to SLE clinical course. [8]

Lupus nephritis and capillaroscopic alterations have found commonalities, which may indicate that they can be helpful in determining the severity of the disease. Enhanced treatment options and safeguards against systemic organ failure might result from additional research into the function of microvascular alterations in the etiology of SLE. [9] Despite the prevalence of SLE, our literature search found very little research on the correlation between capillaroscopic alterations and LN. Thus, this study set out to evaluate the alterations in nailfold capillaries in SLE patients and the relationship between these changes and LN.

PATIENTS AND METHODS

This cross-sectional study was conducted at the Department of Rheumatology, Rehabilitation and Physical Medicine at Sohag University Hospital, after taking approval from the Scientific Ethical Committee of Sohag University Hospital. Our study included 50 SLE patients divided into two groups, 30 patients with LN, and 20 patients without LN. The participants met the 2019 EULAR/ACR classification criteria. [10]

The patients were subjected to full history taking, Clinical and rheumatological examination. Investigations in the form of:

A) Laboratory tests were conducted, including a complete blood count (CBC), an erythrocyte sedimentation rate (ESR), a full urine analysis, P/C ratio, tests for kidney and liver function, immunofluroscence for antinuclear antibodies (ANA), immunoblotting for ANA profile, and quantitative determination of serum complement levels (C3, C4).

B) Renal biopsy was done if any of the following was present proteinuria >500 mg/dl in 24 hrs urinary protein collection, urinary RBCs casts or urinary RBCs >5/high power field. It was categorized using the criteria set out by the International Society of Nephrology/Renal Pathology Society (ISN/RPS). Additionally, activity and chronicity indices were calculated [11, 12].

C) Disease activity assessment by (SLEDAI). [13]

D) The nailfold videocapillaroscopy was used to evaluate the capillary circulation. Non-invasive

"in vivo" monitoring of peripheral microcirculation is now possible with NFC. Microcirculation describes vasculature in vessels smaller than 300 μm in diameter. The NVC procedure was carried out with the use of DINOCAPTURE 2.0 version 1.5.29.B, a digital videocapillaroscopy system that had a 200×n magnification.

Before a capillaroscopy, be sure to wash your hands well, refrain from drinking coffee or smoking for at least six hours, and do not remove your nails' cuticles. [14-15] The capillaroscopy procedure was performed on the middle two fingers (excluding the thumbs) of each hand of the subjects. A computer connected to the system captured and analyzed NVC images with the help of DINOCAPTURE 2.0, a program licensed to AnMo Electronics Corporation. To depict 3 mm of the nail bed, the images were cropped to the same size but in different positions. After taking pictures of all four nailfolds, the evaluation of a single patient took about 8 to 12 minutes.

Statistical analysis

Data were analyzed using Statistics Package for Social Sciences (SPSS) version 25, 2017. Qualitative data were expressed as frequency and percentage. Continuous quantitative data were expressed as mean ± standard deviation (Mean ±SD). Kolmogorov–Smirnov test was used to determine the distribution of different variable. Independent sample t test was used when comparing between two groups (for normally distributed data). Fisher exact test or Chi-square test was used when comparing between non-parametric categorical data. Logistic regression analysis was used to examine the association of (categorical or continuous) independent variable(s) with an event occurring. When the data was not normally distributed Mann-Whitney test was used to compare two groups. Graphs were produced by using Excel or STATA program.

Results

The demographic, clinical, and laboratory data of SLE patients

Our study included 50 patients with SLE-. Among the 50 patients there were 30 female patients (60%) and 20 male patients (40%). The age range of our patients was between 19-55 years. The mean age was 33.32±9.79. The range of the disease duration was between 1 to 21 years. The mean disease duration was 5.32± 4.59. Clinical data of our patients, the mucocutaneous manifestations were the most common (100%), followed by the constitutional manifestations (98%). The musculoskeletal manifestations were (82%). The pulmonary manifestations were (62%). LN patients were (60%) and the neurological manifestations were (32%). The cardiac manifestations were about (30%). The GIT manifestations were the least among our patients (28%). SLEDAI of our patients ranged from 10 to 23 points, with a mean of 15.5±3.3. The mean activity index was 2.9 ± 2.8 while the mean chronicity index was 1.3± 1.4.

An analysis of ANA IF and antidsDNA revealed that all patients tested positive, although 12% tested positive for both RO and La antibodies. The percentage of patients who tested positive for anti-Smith and anti-Ribosomal antibodies, respectively, were 8% and 6%. An antibody against histones was present in 4% (table 1). Out of all the abnormal laboratory findings in SLE patients, 58 percent had leukopenia, 28 percent had thrombocytopenia, 86 percent were anaemic, and 16 percent has lymphopenia. Proteinuria was found in (60%), hematuria was found in (12%) while, Pyuria, was found in (10%) and cellular casts were found in (34%) as shown in figure (1a).

The relation between lupus nephritis and capillaroscopic changes in SLE patients

This illustrates the capillaroscopic changes in SLE patients with and without LN, significant differences were observed regarding elongated and dilated capillaries, which was higher in patients with LN group than those without LN (p=0.02 and p=0.03, respectively), as shown in table (2) & figure (1b). The comparison of the activity index and capillaroscopic changes in SLE patients revealed higher activity indices in patients with elongated capillaries (p=0.03). No significant differences were found regarding avascular areas, hemorrhages, or dilated capillaries), as shown in table (3) & figure (1c). Regarding the chronicity index and capillaroscopic changes in SLE patients, significant differences were noted regarding the presence of elongated capillaries, with higher chronicity indices in patients with elongated capillaries (p=0.04). No significant differences were found regarding avascular areas, hemorrhages, or dilated capillaries as shown in table .[4] Using Multivariate logistic regression analysis,

this table demonstrates that (Capillary length and venous limb) were predictors for LN in SLE group as shown in table. [5]

Table (1) Demographic, clinical, and laboratory data of SLE patients

Variables		Mean ±SD, n (%)	Variables	Mean ±SD, n (%)
Age/year		33.32±9.79	ESR (mm/hr)	66.5 ± 37.9 (10-122)
Gender	**Female**	30 (60%)	HB	10.3 ± 1.3 (6.8-12.8)
	Male	20 (40%)	WBCs	4.5 ± 2 (1.9-11.2)
Disease Duration (years)		5.32±4.59	PLTs(cells/mcl)	206.9 ± 87.4 (40-367)
SBP (mm Hg)		118.8 ± 14.1	ALT(U/L)	17.9 ± 16.2 (10-88)
DBP (mm Hg)		76.4 ± 10.2	AST(U/L)	14.9 ± 15.9 (11-77)
Constitutional manifestations		49 (98%)	creatinine (mg/dl)	1 ±0.6 (0.4-2.7)
Mucocutaneous manifestation		50 (100%)	urea (mg/dl)	25.4 ± 9.9 (12-48)
Pulmonary manifestations		31 (62%)	P/C ratio	1.2 ± 1.6 (0.1-7.6)
Cardiac manifestations		15 (30%)	C3(mg/dl)	84.7 ± 12.7 (55.1-100)
GIT manifestations		14 (28%)	C4(mg/dl)	22.7 ± 10.5 (6.1-45.2)
Neurological manifestations		16 (32%)	ANA IF	50 (100%)
Musculoskeletal manifestations		41 (82%)	Anti-dsDNA	50 (100%)
LN		30 (60%)	Anti-smith	4 (8%)
Activity index		2.9 ± 2.8	Anti-RO	6 (12%)
Chronicity index		1.3± 1.4	Anti-La	6 (12%)
SLEDAI		15.5±3.3	Anti-Ribosomal	3 (6%)
			Anti-histone	2 (4%)
			ANA IF	50 (100%)
			Anti-dsDNA	50 (100%)
			Anti-smith	4 (8%)

SBP: Systolic blood pressure, DBP :Diastolic blood pressure, LN: Lupus nephritis, SLEDAI : Systemic lupus erythematosus disease activity index

Table (2) .Comparison between SLE patients with lupus nephritis and those without lupus nephritis regarding capillaroscopic changes

Variables	No lupus nephritis N=20	Lupus nephritis N=30	P value
Avascular area	**2 (10%)**	**2 (6.67%)**	**1.00**
Hemorrhages	**1 (5 %)**	**2 (6.67%)**	**0.24**
Elongated capillaries	**5 (25%)**	**18 (60%)**	**0.02**
Dilated capillaries	**7 (35%)**	**20 (66.67%)**	**0.03**
Giant capillaries	**0**	**3 (10%)**	**0.27**
Bushy capillaries	**4 (20%)**	**6 (20%)**	**1.00**
Meandering capillaries	**3 (15%)**	**6 (20%)**	**0.72**
Ramified capillaries	**1 (5%)**	**2 (6.67%)**	**1.00**

P value is considered significant if< 0.05

Table (3). Comparison between activity index and capillaroscopic changes in SLE patients

Variables	Activity index Mean ± SD, Median (range)	P value
Avascular area	2.25±2.62, 2 (0:5)	0.67
Hemorrhages	7.0±2.83, 7 (5:9)	0.10
Elongated capillaries	3.91±2.87, 4 (0:9)	0.03
Dilated capillaries	3.18±3.08, 4 (0:9)	0.53
Giant capillaries	5.33±1.53, 5 (4:7)	0.10
Bushy capillaries	3.3±3.13, 4.5 (0:9)	0.55
Meandering capillaries	3.67±3.08, 5 (0:9)	0.31
Ramified capillaries	3.0±2.64, 4 (0:5)	0.88

P value is considered significant if< 0.05

Table (4) .Comparison between chronicity index and capillaroscopic changes in SLE patients

Variables	Chronicity index Mean ± SD, Median (range)	P
Avascular area	0.75±0.96, 0.5 (0:2)	0.41
Hemorrhages	3.0±1.41, 3 (2:4)	0.18
Elongated capillaries	1.78±1.51, 2 (0:5)	0.04
Dilated capillaries	1.48±1.60, 1 (0:5)	0.72
Giant capillaries	1.67±0.58, 2 (1:2)	0.45
Bushy capillaries	1.4±1.43, 1.5 (0:4)	0.84
Meandering capillaries	1.56±1.42, 2 (0:4)	0.54
Ramified capillaries	1.0±1.0, 1 (0:2)	0.76

P value is considered significant if< 0.05

Table (5): Multivariate logistic regression analysis of capillaroscopic data as a predictor for lupus nephritis in SLE group

	B	SE	p-value	Odds	95% CI	
Elongated capillaries	1.116	0.611	0.068	3.05	1.116	0.611
Avascular Areas	-0.442	1.045	0.672	0.64	-0.442	1.045
Capillary density	0.197	0.209	0.346	1.22	0.197	0.209
Capillary length(µm)	0.011	0.005	0.022	1.01	0.011	0.005
Capillary width(µm)	0.027	0.023	0.244	1.03	0.027	0.023
Arterial limb(µm)	0.059	0.058	0.310	1.06	0.059	0.058
Venous limb(µm)	0.116	0.049	0.017	1.12	0.116	0.049
Apical width(µm)	0.054	0.029	0.065	1.06	0.054	0.029
Dilated capillaries	-0.067	0.580	0.908	0.94	-0.067	0.580
Giant capillaries	20.903	23205	0.999	1196648032	20.9	23205
Bushy	0.000	0.722	1.000	1.00	0.000	0.722
Meandering	0.348	0.775	0.653	1.42	0.348	0.775
Ramified	0.305	1.260	0.809	1.36	0.305	1.260
Microhemorrhages	0.305	1.260	0.809	1.36	0.115	16.05
PVPS	0.442	1.045	0.672	1.56	0.201	12.05
Inter-Capillary distance(µm)	-0.463	0.873	0.596	0.63	0.114	3.486
Skin transparency	-0.342	0.651	0.599	0.71	0.198	2.546
Capillary disorganization	0.496	0.990	0.616	1.64	0.236	11.44

PVPS: Subpapillary venous plexus visibility P value is considered significant if< 0.05

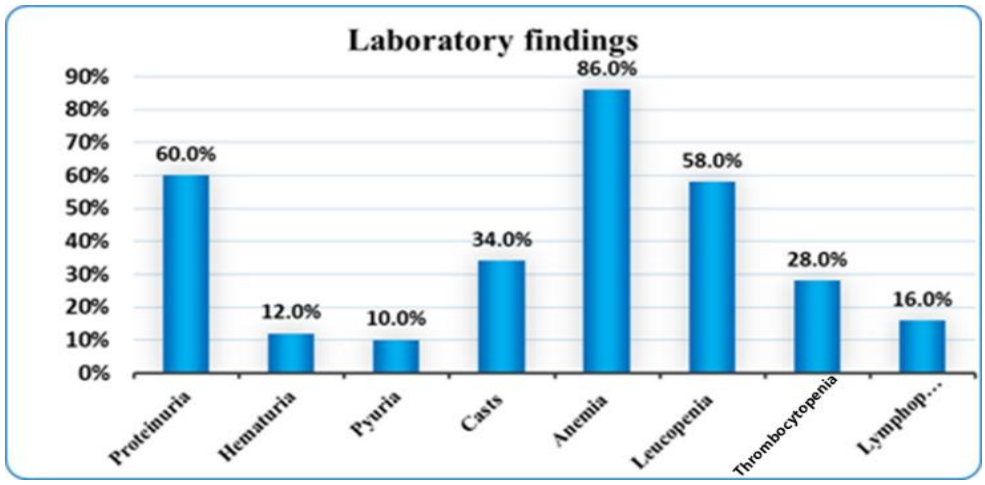
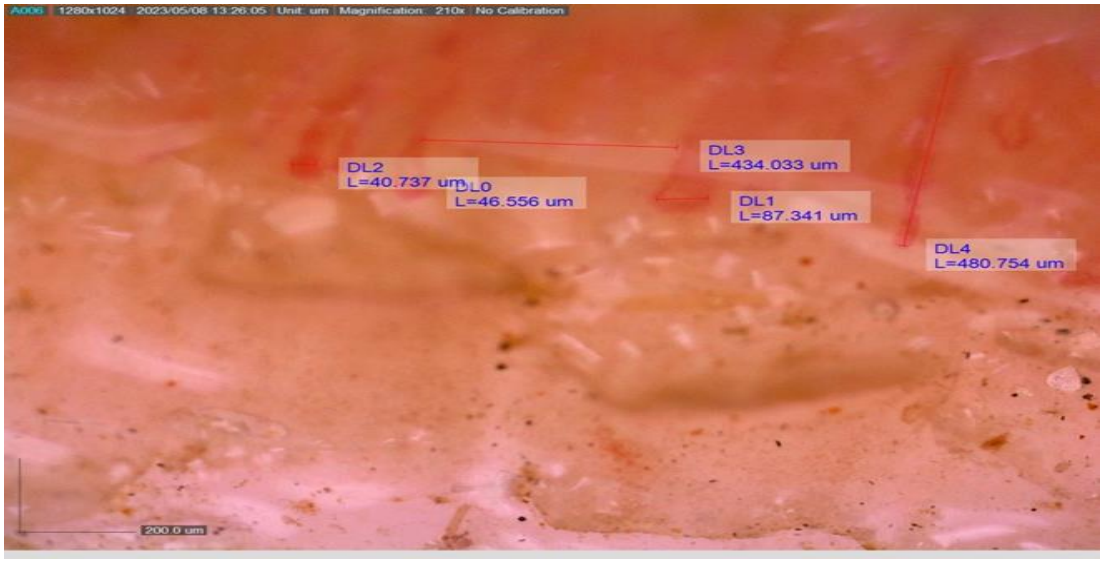
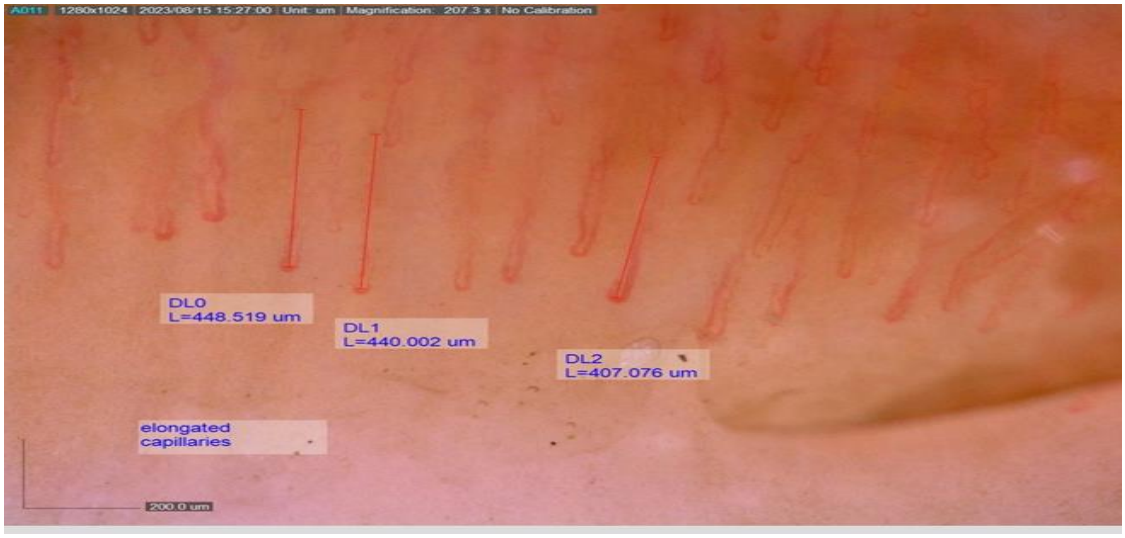


Figure (1a): Abnormal laboratory findings in SLE group



Figure(1b) Nailfold capillaroscopy image showing multiple dilated & elongated capillaries



Figure(1c) Nailfold capillaroscopy image showing multiple elongated capillaries

Discussion

The most severe symptom of systemic lupus erythematosus (SLE) is the involvement of blood vessels, which is a major cause of mortality and disability among people with SLE. Any kind of the blood vessels can be affected by inflammatory vascular lesions that include fibrinoid necrosis of the vascular walls and leukocytic infiltration, and any kind of vessel can be affected by non-inflammatory vascular lesions. LN, pulmonary and intestinal vasculitis, pulmonary hypertension, and livedo reticularis are some of the microvascular manifestations. [3] Endothelial cells lining blood vessels are vulnerable to SLE inflammatory mediators, which can lead to their death and the development of new blood vessels. A novel NFC model of microcirculation in SLE patients was eventually identified after a number of studies [2]. The vascular involvement of SLE, widely believed to be the most severe symptom, is one of the main reasons of increase mortality and morbidity of the disease. Both inflammatory and non-inflammatory vascular lesions can impact any kind of blood vessel; the former also causes fibrinoid necrosis of the vascular walls and leukocytic infiltration.

Elongated and dilated capillaries were more common in the SLE patients with LN group compared to the SLE patients without LN, suggesting a statistically significant difference in capillaroscopic alterations between the two groups. In agreement with our results, Shenavandeh and Habibi.[17] found a relationship between the presence of elongated capillary loops and renal involvement in SLE patients. Also, Samar Medhat et al.[18] reported a relationship between renal biopsy results and NFC findings in SLE patients. While, Schonenberg-Meinema et al. [19] showed LN was linked to "large pathological haemorrhages per mm" in SLE patients. In disagreement with us, Sakit Mahmud et al. [20] noted that 10 out of 27 SLE patients (37.04%) with renal disease also had meandering capillaries. In agreement with our results regarding the capillary width, Ali et al. [21] noticed that the group with nephritis exhibited noticeably greater capillary breadth and haemorrhage than the group without nephritis..

On comparing the activity index and capillaroscopic changes in SLE patients we found higher activity indices in patients with elongated capillaries. This is in line with us, Nasser et al. [22] who found that the patients with SLE in Egypt who exhibited anomalies in their NFCs also exhibited elevated activity indices. A systematic review by Cutolo et al. [15] revealed that seven researchs found a correlation between activity indices and NFC scores, along with an increased prevalence of aberrant morphology (i.e. "meandering") and haemorrhages.

In SLE patients, there were notable variations in the chronicity index and capillaroscopic alterations; those with elongated capillaries had higher indices of chronicity. Kabasakal et al. [23] discovered the prevalence of vascular lesions in LN, which may significantly impact the overall activity, longevity, and severity of the syndrome.

Using Multivariate logistic regression analysis, our results demonstrate that (Capillary length and venous limb) were predictive risk factors for LN in SLE group. In agreement, Shenavandeh et al. [17] found elongated capillary loops in (66.7%) of SLE patients which was significantly more common in patients with renal involvement than those without. In line with us, Hend Adel et al.[24], found that LN patients had microbleeding, wide capillaries, and big diameters. Similarly, Ragab et al. [25] determined that there was a favorable and statistically significant relationship between meandering capillaries and 24-hour urinary proteins.

Conclusion:

Nailfold capillaroscopic abnormalities in the form of elongated and dilated capillaries are more common in SLE patients with LN than those without LN, with higher activity and chronicity indices in patients with elongated capillaries. In addition, capillary length and venous limb may be predictors for LN in SLE patients.

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