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Serum Interleukin-34 in Psoriatic arthritis patients and its correlation with disease 1 activity, and subclinical atherosclerosis

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Abstract

Background Psoriatic arthritis (PsA) is a chronic multi-domains autoimmune inflammatory disorder. Patients with PsA have a significant prevalence of cardiovascular affection. Upregulated Interleukin-34 (IL-34) has been seen in many autoimmune disorders, and also in atherosclerotic plaques. The aim of this observational case–control study was to evaluate the serum levels of il-34 in PsA patients and correlate between its level and disease activity, and subclinical cardiovascular affection.

Results In this study, there were 70 PsA patients and 70 healthy volunteers, 43 patients were on Methotrexate, 6 on sulfasalazine, while 40 patients were on biological therapy either monotherapy or in combination with DMARDs. There were significant differences between PsA patients and controls in ESR, high sensitivity-CRP, total lipid profile, and IL-34 levels ($p < 0.05$) while there were no significant differences regarding Echo and ECG results. Also, we found that there was significant elevation in DAPSA score, hs-CRP, IL-34, and cIMT in the active patients when we compared them with inactive patients. IL-34 had significant positive correlations with DAPSA score, hs-CRP, and cIMT ($r = 0.654$, 0.579, and 0.658 respectively).

Conclusion Serum interleukin-34 is an important marker in PsA as its levels were elevated in PsA patients and were correlated with disease activity and subclinical cardiovascular affection.

Keywords Psoriatic arthritis, IL-34, Disease activity, cIMT, Atherosclerosis, DAPSA score

Background

Psoriatic arthritis (PsA) is a form of inflammatory arthritis which is commonly associated with psoriasis. PsA affects nearly thirty to 40% of psoriatic patients [1, 2].

Patients with immune-mediated disorders like psoriasis, PsA, and rheumatoid arthritis have an increased risk of early mortality due to atherosclerotic vascular disease [3, 4]. Although it is well established that individuals with psoriasis or PsA, particularly those who also have metabolic syndrome, have significantly higher rates of cardiovascular (CV) risk factors, this does not entirely explain the higher rates of CV mortality and morbidity in these patients [5, 6].

High-resolution carotid ultrasonography is used to measure the intima and media thickness of the carotid arteries. Atherosclerosis in arterial beds has been linked to increased intima-media thickness (IMT) of the common carotid artery [7, 8].

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In asymptomatic individuals, IMT behaves as a risk factor for myocardial infarction and stroke independent of known cardiovascular risk factors [9]. Based on this, assessing carotid IMT with ultrasound techniques provides useful information on atherosclerosis in susceptible individuals in the early stages of the disease [10].

Interleukin-34 (IL-34) is a hematopoietic cytokine that has a role in the differentiation of macrophages and osteoclastogenesis. IL-34 overexpression has been linked to rheumatic autoimmune diseases as rheumatoid arthritis and PsA [11]. Upregulated IL-34 has also been seen in human atherosclerotic plaques, especially in unstable plaques, suggesting that IL-34 has proinflammatory actions which may increase susceptibility to the incidence of acute coronary syndrome and death [12].

Our aim in this work was to evaluate the serum level of IL-34 in PsA patients and correlate its level and disease activity, and subclinical atherosclerosis.

Patients and methods

This is a single-center case–control study.

Setting

Patients were selected from the outpatient clinic of Rheumatology and Rehabilitation Department, Tanta University Hospitals. Supplement 1 shows the consort flow diagram of this study.

Patients

Seventy patients meeting CASPAR criteria for PsA [13] and 70 healthy volunteers matched for age and sex were included in this study. Patients with other dermatological or rheumatic disorders, obese (BMI > 30), cardiac patients, patients with hypertension, diabetics, acute illness, pregnant women, and patients receiving medications affecting lipid metabolism (as lipid-lowering agents, corticosteroids > 10 mg/day, B-blockers, oral contraceptive pills, thyroxin, and vitamin E) were excluded.

Ethics approval and consent to participate

This study is in agreement with the ethical guidelines of the Declaration of Helsinki and it follows the ethical standards of Tanta Faculty of Medicine, with the institution's ethics board approval number 35413/4/22. Informed written consent from all patients was obtained in accordance with the local ethical committee. Privacy of all patients' data was granted as there was a code number for every patient file that included all investigations.

I. Clinical assessment

Demographic data and detailed medication history were taken. PSA activity using Disease Activity Index for Psoriatic Arthritis (DAPSA) score [14] was measured using tender and swollen joint counts, patient pain and patient global assessments, and acute phase reactants.

II. Laboratory assessment:

Routine laboratory investigations

High sensitivity C reactive protein (hs CRP) concentrations were measured using the Diamed Eurogen CRP ELISA kit. ESR (mm/h) was determined by Westergren method. Total lipid profile [total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL)] also were measured on KONILAB Prime 60i Thermo Scientific-Finland autoanalyzer.

Specific laboratory investigations

By using quantitative enzyme-linked immunosorbent assay (ELISA); Serum IL-34 level was measured using (kits: WH-1752, Wkea Med Supplies Corp., Changchun, Jilin, China). Two milliliters of venous blood was collected and kept at – 70 °C until analyzed, using sandwich enzyme immunoassay technique. A monoclonal antibody specific for IL-34 has been pre-coated onto a microplate. Standards and samples were pipetted into the wells and any IL-34 present was bound by the immobilized antibody. An enzyme-linked polyclonal antibody specific for Il-34 was added to the wells after washing away any unbound substances. Then, a substrate solution was added to the wells and color develops in proportion to the amount of IL-34 bound in the initial step. The intensity of the color was measured after the color development was stopped under 450 nm wavelength.

III. Cardiovascular assessment:

1. Echocardiographic examination

All patients had a complete transthoracic echocardiography examination with a GE Vivid 7 Dimension echo machine with S4 transducer, which included two-dimensional, color, and Doppler (continuous and pulsed wave) as well as tissue Doppler. The images were obtained from apical and left parasternal windows, with patients lying in the lateral left decubitus position.

The following measurements were taken in accordance with the American Society of Echocardiography's recommendations [15]. Left atrial end-systolic diameter (LAESD), left ventricular end-diastolic diameter (LVEDD), right ventricular end-diastolic diameter (RVEDD), left ventricular posterior wall end-diastolic thickness (LVPWEDT), interventricular septum end-diastolic thickness (IVSEDT), ejection fraction (EF), fractional shortening (FS), and aortic root diameter (AO) were measured.

LV diastolic function was assessed by measuring the mitral flow velocity recorded in the apical four-chamber view by trans-mitral pulsed-wave Doppler sampling. The parameters included peak early diastolic velocity (E wave; m/s) and late diastolic velocity (A wave; m/s), E to A ratio (E/A), E wave deceleration time (DT; ms), isovolumetric relaxation time (IVRT; ms), pulsed-wave (pw), moreover, tissue Doppler imaging of the mitral annulus velocities (TDI): early diastolic (É) and late diastolic (Á) velocity and É/Á ratios were measured.

Diastolic dysfunction was defined by the presence of one of the following patterns:

1) Impaired relaxation pattern if E/A ratio was < 1.1, DT > 240 ms, IVRT > 90 ms, and A-pw < 25 cm/s.
2) Pseudonormalized pattern if E/A ratio was between 1.1 to 1.5, DT between 160 and 240 ms, IVRT between 60 and 90 ms, and A-pw > 25 cm/s.
3) Restrictive pattern was considered to be present if E/A ratio was > 1.5, DT < 160 ms, IVRT < 60 ms, and A-pw > 25 cm/s [16].

2. Electrocardiography (ECG)

In the supine position, a resting standard 12-lead ECG was recorded at 25 mm/s chart speed and 1 mm/mv calibration. The following ECG characteristics were assessed: abnormalities consistent with myocardial ischemia, PR interval, QT interval, QRS duration, electrical axis, and presence of rhythm disorders; premature beats, low voltage, atrioventricular conduction disorders, and intraventricular conduction disturbances [17].

3. Carotid intima-media wall thickness (cIMT) assessment

SAMSUNG MEDISON (UGEO H60) with a linear transducer (midfrequency 10 MHz) was used to evaluate the common carotid arteries. cIMT was defined as the distance from the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface of the far wall. cIMT of the common carotid artery was measured between 1 and 3 cm proximal to the bifurcation of the carotid artery on the left and right sides. cIMT was measured at the distal wall of the carotid artery on a 10-mm segment [18]. Increased cIMT was defined as ≥ 0.9 mm. Carotid plaque.was defined as cIMT ≥ 1.2 mm [19]. The recorded scans of patients and controls were independently analyzed by two ultrasound operator.

Study outcomes

Primary outcome

Assessment of the serum levels of il-34 in PSA patients.

Secondary outcome

Correlates between il-34 level and disease activity, and subclinical cardiovascular affection.

Statistical analysis

Data were statistically analyzed using SPSS version 20, described in terms of mean ± standard deviation (SD). Student's *t* test for independent samples when variables were normally distributed. For comparing categorical data, Chi-square test was performed. Correlation between variables was examined using Pearson's correlation coefficient. Multiple regression analysis was used to identify variables that may correlate independently with IL-34. *P* values less than 0.05 were considered statistically significant [20].

Results

Seventy PSA patients and seventy controls were enrolled in this study. Age, sex, BMI, smoking, and blood pressure measurements did not significantly differ between patients and controls. The mean duration of psoriasis was 7.25 ± 3.75 years, while the mean duration of PSA was 3.74 ± 1.63 years. Forty-nine patients were on csDMARDS [43 methotrexate (MTX), 6 sulfasalazine (SSZ)], and 40 were on bDMARDs (14 anti-TNF, 26 anti-IL17). Twenty-one patients on bDMARDs receiving monotherapy, while 19 receiving combined therapy with csDMARDs (13 with MTX and 6 with SSZ). The DAPSA score indicated that eight patients were in remission, and the mean DAPSA score was 11.65 ± 6.82. The clinical and demographic data for both patients and controls were displayed in (Table 1).

There were significant differences between PsA patients and controls; ESR, hs-CRP, total lipid profile, and serum levels of IL-34 were elevated in PsA patients compared to controls. Also, there was a significant difference between PsA patients and controls in measuring cIMT, while there were no significant differences regarding Echo and ECG results. Laboratory and cardiac assessments were summarized in (Table 2). Figure 1 showed cIMT findings in PsA patient.

When we compared active patients with patients who were in remission or mild activity we found that there were significant elevation in DAPSA score, hs-CRP, IL-34, and cIMT in the active patients, while there was no significant difference regarding age, BMI, duration

Table 1 Demographic and clinical data of patients and controls

	PSA patients (70)	Controls (70)	*P* value
Age (years)	40.85 ± 6.85	38.94 ± 7.17	0.1
Gender: (male/female)	33/37	34/36	0.8
BMI	27.91 ± 2.74	27.54 ± 2.27	0.38
Smokers: (Y/N)	18/52	16/54	0.15
Duration of PSO (years)	7.25 ± 3.75	NA	
Duration of PSA (years)	3.74 ± 1.63	NA	
Treatment received:			
Methotrexate	43	NA	
Sulphasalazine	6		
Anti-TNF	14		
IL-17 inhibitor	26		
Systolic blood pressure (mmHg)	125.38 ± 10.5	128.03 ± 11.06	0.14
Diastolic blood pressure (mmHg)	72.53 ± 9.06	70.71 ± 7.85	0.2
DAPSA score	11.65 ± 6.82		
Remission (*n*)	8	NA	
Low disease activity (*n*)	40		
Moderate disease activity (*n*)	20		
Severe disease activity (*n*)	2		

PSA psoriatic arthritis, *Anti-TNF* anti-tumor necrosis factor, *IL-17* interleukin-17, *DAPSA* Disease Activity index for Psoriatic Arthritis, *BMI* body mass index

Significant value*: $P < 0.05$

Table 2 Laboratory, radiological, and cardiac assessment

	PSA patients (70)	Controls (70)	*P* value
ESR (mm/h)	28.22 ± 11.78	18.33 ± 5.18	0.0001*
hs-CRP (mg/dL)	9.17 ± 3.08	4.8 ± 2.23	0.0001*
TC (mg/dl)	208.13 ± 24.65	163.16 ± 36.68	0.0001*
TG (mg/dl)	169.23 ± 41.53	121.37 ± 39.86	0.0001*
LDL-C (mg/dl)	161.68 ± 30.33	132.76 ± 26.48	0.0001*
HDL-C(mg/dl)	45.76 ± 12.12	50.95 + 14.75	0.02*
TC/HDL-C	4.62 ± 1.74	3.2 ± 0.73	0.0001*
LDL-C/HDL-C	3.76 ± 0.65	2.6 ± 0.89	0.0001*
Serum IL-34 (ng/L)	1861 ± 791	426.86 ± 111.86	0.0001*
cIMT (mm)	0.79 ± 0.34	0.67 ± 0.25	0.013*
Abnormal echo (*n*)%	(8) 11.4	(6) 8.58	0.57
Abnormal ECG (*n*)%	(5) 7.14	(4) 5.7	0.73

PSA psoriatic arthritis, *ESR* erythrocyte sedimentation rate, *hsCRP* highly sensitive C-reactive protein, *TC* total cholesterol, *TG* triglycerides, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *IL-34* interleukin-34, *cIMT* carotid intima media thickness, *ECG* electrocardiogram

Significant value*: $P < 0.05$

of PSA, and ESR. These findings were summarized in (Table 3).

We found that IL-34 had significant positive correlations with DAPSA score, hs-CRP, and cIMT ($r = 0.654$, 0.579, and 0.658 respectively). The correlation between serum IL-34 and different clinical, laboratory and radiological findings were summarized in (Table 4).

Multiple regression analysis was used to identify variables that may correlate independently with IL-34, so; IL-34 was the dependent variable and DAPSA, hsCRP, and cIMT were the independent variables we found that all the variables evaluated had strong associations with IL-34. The odds ratio OR (95% CI) were 4.185 (0.338–51.771), 2.346 (0.286–18.749), and 2.814 (0.488–15.858) respectively.

Also, multivariable linear regression analysis [with 95% confidence interval (CI)] demonstrated that cIMT was associated only with IL-34, and DAPSA score, these relations were summarized in (Table 5).

Discussion

In our study, we discovered that PsA patients' serum IL-34 levels were substantially greater than those of normal controls and IL-34 level was significantly higher in active PsA than patients in remission or low disease activity. This was consistent with earlier studies that found that PsA patients' serum levels of IL-34 were higher than those of people without arthritis and normal controls [21, 22].

Tian et al. [23] found that serum levels of IL-34 had a significant relation with disease activity in RA patients.

A non-redundant role in skin homeostasis is played by IL-34, a hematopoietic proinflammatory cytokine. Autoimmune disorders are connected with IL-34 over-expression [12].

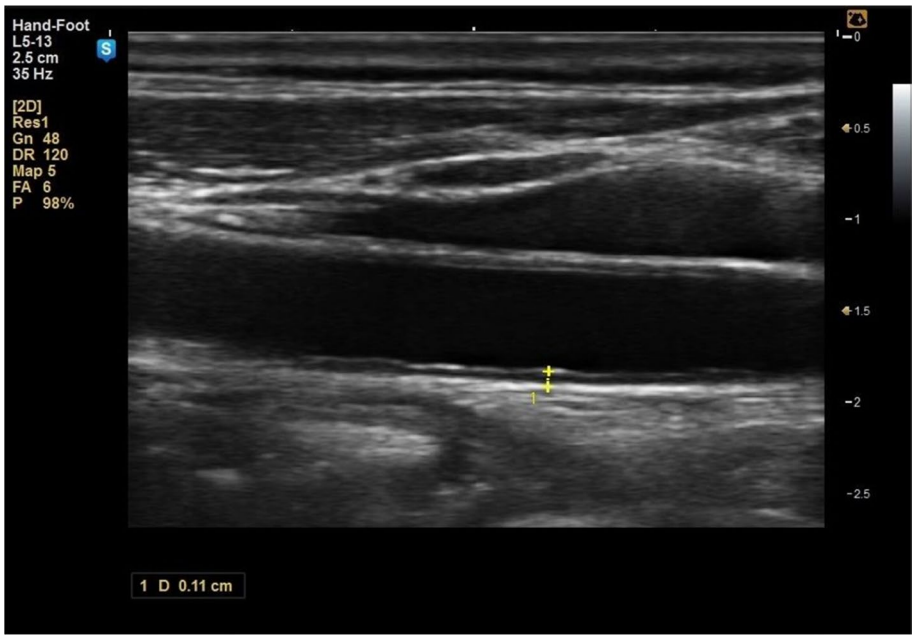

Fig. 1 Carotid IMT in PsA patient

Table 3 Comparison between active patients with patients in remission or mild activity

	Active patients (22)	Patients in remission or mild activity (48)	*P* value
Age (years)	41.7 ± 4.9	40.2 ± 5.8	0.29
BMI	28.2 ± 2.1	27.6 ± 2.1	0.27
Duration of PSA (years)	3.77 ± 1.5	3.71 ± 1.4	0.87
DAPSA score	13.5 ± 4.7	9.7 ± 4.6	0.002*
ESR (mm/h)	27.9 ± 8.7	28.5 ± 11.3	0.82
hs-CRP (mg/dL)	9.6 ± 3.2	8.2 ± 2.4	0.04*
Serum IL-34 (ng/L)	2031.7 ± 540.7	1693.8 ± 658.5	0.04*
cIMT (mm)	0.92 ± 0.31	0.66 ± 0.29	0.001*

PSA psoriatic arthritis, *ESR* erythrocyte sedimentation rate, *hsCRP* highly sensitive C-reactive, *cIMT* carotid intima media thickness, *DAPSA* Disease Activity index for Psoriatic Arthritis, *BMI* body mass index

Significant value*: $P < 0.05$

Table 4 Correlation between serum IL-34 and different clinical, laboratory, and radiological findings

Variables	*r* value	(*p*)
Duration of PSA	0.143	0.24
Systolic blood pressure (mmHg)	0.123	0.31
Diastolic blood pressure (mmHg)	0.103	0.39
DAPSA score	0.654	0.0001*
ESR (mm/h)	0.097	0.42
hs-CRP (mg/dL)	0.579	0.0001*
TC (mg/dl)	0.07	0.56
TG (mg/dl)	0.097	0.42
LDL-C (mg /dl)	0.065	0.59
HDL-C(mg/dl)	0.068	0.57
TC/HDL-C	0.043	0.72
LDL-C/HDL-C	0.063	0.6
cIMT, (mm)	0.658	0.0001*

PSA psoriatic arthritis, *ESR* erythrocyte sedimentation rate, *hsCRP* highly sensitive C-reactive protein, *DAPSA* Disease Activity index for Psoriatic Arthritis, *TC* total cholesterol, *TG* triglycerides, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *IL-34* interleukin-34, *PsASon* ultrasound composite scores for the assessment of inflammatory and structural pathologies in psoriatic arthritis, *cIMT* carotid intima media thickness, *ECG* electrocardiogram

Significant value*: $P < 0.05$

In this study, there were significant positive correlations between IL-34 and the DAPSA score and hs-CRP. According to previous studies by Farrag D. et al. [21], the serum IL-34 level correlated significantly with the composite psoriasis disease activity index, BASDAI, peripheral joint score, and dactylitis score in the PsA group. This suggests a link between IL-34 serum levels and psoriatic disease activity, especially arthritis, but no correlation between IL-34 serum levels and radiographic joint damage scores in the hands and feet of PsA patients was detected.

IL-34 displays pleiotropic biological effects in particular tissues and cell types, including myeloid cells, epithelial cells, endothelial cells, fibroblasts, neurons, and cancer cells, from inflammatory to autoimmune disorders, IL-34

Table 5 Multivariate linear regression analysis for cIMT in PsA patients

	cIMT	
	Beta coefficient	***p***
IL-34	0.257	0.021*
DAPSA	0.355	0.006*

IL-34 interleukin-34, *DAPSA* Disease Activity Index for Psoriatic Arthritis, *cIMT* carotid intima media thickness

Significant value*: $P < 0.05$

appears to be connected to a wide range of conditions. It has been demonstrated that IL-34 increases the proliferation of Th17 cells, transcription factor expression, and IL-17 production, all of which are known to be crucial in the pathogenesis of PsA [24].

In this study there was a significant difference between PsA patients and controls in measuring cIMT. CIMT was higher in the active patients, also IL-34 had significant positive correlations with cIMT.

Hodis et al. concluded that the increase of 0.1 mm IMT increases the likelihood of an acute myocardial infarction by 11% [25]. As found by evaluating the carotid intima-media thickness, endothelial functions were found to be compromised in PsA patients, demonstrating a significant association between PsA and subclinical atherosclerosis as cIMT was higher in PsA patients than in healthy controls [26, 27]. In controversy, Apraş Bilgen et al. [2] reportedno significant difference in cIMT between the PsA patients and the controls and this can be attributed to greater use of anti-TNF-alpha treatment (76.7% of PsA patients received anti-TNF-alpha) which was reported to reduce cIMT [28].

However, it had been reported that the increased cIMT was not correlated with parameters of disease activity and there is no difference in cIMT between patients with and without an active joint lesion [2, 18, 29].

The c-IMT was higher in PsA patients on DMARDs than in those on TNF-α blockers. Inflammation reduction may disrupt the series of events that increases vascular risk in PsA patients [30].

The mechanism underlying inflammation-induced atherogenicity is complex. Cardiovascular disease has been linked to elevated CRP levels, which may affect arterial elasticity. Along with established cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, smoking, family history), inflammatory cytokines like IL-1, IL-6, and TNF- have been identified as important factors [31, 32].

IL-34 can increase the production of chemokines and cytokines such as IL-6, IL-8, and C motif chemokine ligand 2 (CCL2). Additionally, TNF and IL-1 can increase the expression of IL-34, denoting that IL-34 may function as a pro-atherogenic agent. IL-34 may encourage angiogenesis through the activation of CD14 bright CD16 + monocytes. IL-34 may have an impact on the process of atherosclerosis and ischemic myocardial damage by regulating monocyte migration and macrophage differentiation [33, 34].

This study has certain limitations because it was single-centered; a multicenter study would have been better, in addition to a relatively small number of participants. Future longitudinal studies are required to evaluate the relationship between IL-34 and disease activity, as well as cardiovascular risks in PsA patients, as our study was cross-sectional.

Conclusion

Serum interleukin-34 is an important marker in PsA as its levels were elevated in PsA patients and correlated with disease activity, and subclinical atherosclerosis.

Abbreviations

CV	Cardiovascular
cIMT	Carotid intima-media thickness
CCL2	C motif chemokine ligand 2
CI	Confidence interval
DAPSA	Disease Activity Index for Psoriatic Arthritis
EF	Ejection fraction
ELISA	Enzyme-linked immunosorbent assay
FS	Fractional shortening
hs CRP	High sensitivity C-reactive protein
HDL	High-density lipoprotein
IL-34	Interleukin-34
IVRT	Isovolumetric relaxation time
IVSEDT	Interventricular septum end-diastolic thickness
LAESD	Left atrial end-systolic diameter
LVEDD	Left ventricular end-diastolic diameter
LVPWEDT	Left ventricular posterior wall end-diastolic thickness
LDL	Low-density lipoprotein
PsA	Psoriatic arthritis
Pw	Pulsed-wave
RVEDD	Right ventricular end-diastolic diameter
TDI	Tissue Doppler imaging
TC	Total cholesterol
TG	Triglyceride

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43166-023-00183-z.

Additional file 1: Supplement 1. Consort flow diagram of this case control study.

Authors' contributions

MHA and SAT conceived the idea for the study and in conjunction with SHE designed the study and wrote the analysis plan. SAT, DM, and RME undertook data analysis and interpretation, supported MHA. The manuscript was written by SAT and MHA, with contribution from SHE. All authors contributed in the study methodology, analysis, and interpretation of the data and outcomes as well as the manuscript writing, reading, and approval of the final version.

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Availability of data and materials
Data will be available when reasonable request.

Declarations

Ethics approval and consent to participate
All steps are performed according to the revised ethical principles of the Declaration of Helsinki in 2000, and local ethical and methodological protocols for approval of the study were followed.
This study is in agreement with the ethical guidelines of the Declaration of Helsinki and it follows the ethical standards of Tanta Faculty of Medicine, with the institution's ethics board approval number 35413/4/22. Informed written consent from all patients was obtained in accordance with the local ethical committee. Privacy of all patients' data was granted as there was a code number for every patient file that included all investigations.

Consent for publication
Not applicable.

Competing interests
M H Abu-Zaid is associate editor in ERAR Journal. The rest of the authors declare that they have no competing interests.

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