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Clinical significance of the lipid profile, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in different rheumatic disease patients

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ABSTRACT

Objectives. To assess the lipid profile, neutrophil-lymphocyte ratio(NLR) and platelet-lymphocyte ratio(PLR) in different rheumatic diseases and to study their relation to disease activity and/or severity.

Patients and methods. 257 patients (47 rheumatoid arthritis (RA), 100 systemic lupus erythematosus (SLE), 49 systemic sclerosis (SSc), 33 axial spondyloarthritis (axSpA) and 28 vasculitis (21with primary vasculitis and 7 with Behçet's disease 'BD') and 70 controls were recruited. The disease activity and/or severity were assessed for each disease. The lipid profile was measured including: total cholesterol (TC), high-density lipoprotein (HDL),triglycerides (TG), low-density lipoprotein (LDL), very-low density lipoprotein (VLDL) and the LDL:HDL was calculated. The NLR and PLR were recorded.

Results. In RA, NLR, PLR and HDL were significantly higher ($p<0.0001$, $p=0.001$, $p=0.01$). The disease activity score (DAS-28) was significantly associated with dyslipidemia ($p=0.02$) and correlated inversely with NLR ($r=-0.3$, $p=0.02$). NLR and PLR correlated significantly with TG ($p=0.02$, $p=0.03$) respectively. In SLE, NLR, PLR and TG were significantly higher ($p<0.0001$, $p<0.0001$, $p<0.001$). The SLE disease activity index (SLEDAI) was significantly related to dyslipidemia ($p=0.01$) and NLR ($p=0.005$).PLR correlated inversely with the damage index ($r=-0.2$, $p=0.01$). SLEDAI correlated significantly with TG, ($r=0.4$, $p<0.0001$) and LDL: HDL ($r=0.4$, $p<0.0001$) and inversely with HDL($r=-0.4$, $p<0.0001$). In SSc, NLR and PLR were significantly higher ($p<0.0001$, $p=0.03$). HDL correlated inversely with modified Rodnan skin score (mRss) ($r=-0.3$, $p=0.04$). In axSpA, NLR, PLR and lipid profile were similar to controls. In vasculitis, HDL was significantly higher ($p=0.02$) and TG correlated inversely with vasculitis damage index (VDI) ($r=-0.5$, $p=0.03$). In BD, PLR correlated significantly with the Arabic BD current activity form (Ar-BDCAF) ($r=0.9$, $p=0.003$). NLR correlated significantly with TC ($r=0.4$,$p=0.03$) and PLR inversely with TG($r=-0.5$, $p=0.04$). NLR, PLR and ESR were valuable predictors of disease activity in RA, SLE, SSc and vasculitis. On comparing the different rheumatic diseases, NLR and TG were significantly higher in SLE ($p<0.0001$, $p=0.002$) and PLR in vasculitis ($p=0.004$).

Conclusion. Dyslipidemia is frequently associated with the rheumatic diseases. NLR and PLR are feasible markers with a promising role in evaluation of their disease activities.

Keywords: rheumatic diseases, dyslipidemia, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR)

List of abbreviations (in alphabetical order):

ACVD	– Atherosclerotic cardiovascular disease	Anti-CCP	– Anti-cyclic citrullinated peptide
ALC	– Absolute lymphocyte count	APC	– Absolute platelet count
ANA	– Antinuclear antibodies	Ar-BDCAF	– Arabic BD current activity form
ANC	– Absolute neutrophil count	AS	– Ankylosing spondylitis
		ATP III	– Adult Treatment Panel III

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AUC – Area under the curve
axSpA – Axial spondyloarthritis
AZA – Azathioprine
BASDAI – Bath AS disease activity index
BD – Behçet's disease
BDI – BD damage index
bDMARDs – biological DMARDs
BMI – Body mass index
BVAS – Birmingham vasculitis activity score
c-ANCA – cytoplasmic ANCA
CBC – Complete blood cell count
CI – Confidence interval
CRP – C reactive protein
csDMARDs – conventional synthetic disease-modifying anti-rheumatic drugs
CVD – Cardiovascular disease
DAS-28 – Disease activity score
DM – Diabetes mellitus
EGPA – Eosinophilic granulomatosis with polyangiitis
ESR – Erythrocyte sedimentation rate
GPA – Granulomatosis with polyangiitis
HCQ – Hydroxychloroquine
HDL – High-density lipoprotein
IL-6 – Interleukin-6
LDL – Low-density lipoprotein
LR – Likelihood ratio
MPA – Microscopic polyangiitis
mRss – modified Rodnan skin score
MMF – Mycophenolate mofetil
NHL – Neutrophil to-hemoglobin and lymphocyte
NLR – Neutrophil-lymphocyte ratio
PAN – Polyarteritis nodosa
PLR – Platelet-to-lymphocyte ratio
PsA – Psoriatic arthritis
PV – Primary vasculitis
RA – Rheumatoid arthritis
RDs – Rheumatic diseases
RDW – Red blood cell distribution width
RF – Rheumatoid factor
ROC – Receiver operator characteristic
SII – Systemic immune inflammation index
SLE – Systemic lupus erythematosus
SLEDAI – Systemic lupus erythematosus disease activity index
SLICC-DI – Systemic Lupus International Collaboration Clinic-damage index
SSc – Systemic sclerosis
TA – Takayasu arteritis
TC – Total cholesterol
TG – Triglycerides
VDI – Vasculitis damage index
VLDL – Very-low density lipoprotein
WC – Waist circumference

INTRODUCTION

Atherosclerotic cardiovascular disease (ACVD) which is a major co-morbidity associated with the rheumatic diseases (RDs) is multi-factorial, moving beyond the traditional cardiovascular risk markers [1]. Inflammation and immune dysregulation which are cardinal features of RDs seem to play a pivotal role in the pathogenesis of atherosclerosis [2]. The traditional risk markers for cardiovascular disease (CVD) including dyslipidemia, hypertension, smoking and diabetes do not fully explain the heightened risk of ACVDs in systemic lupus erythematosus (SLE) [3] and rheumatoid arthritis (RA) patients [4]. It has been revealed that inflammation has a major role in ACVDs [2], which highlights the strong interplay between inflammation, atherogenesis and CVD events.

The inflammatory indices such as interleukin-6 (IL-6) could predict the risk for CVDs [5]. Other hematological parameters such as the neutrophil-lymphocyte ratio (NLR) has been widely emerging as an inflammatory marker, denoting the burden of inflammation in different chronic conditions [6]. A significant relationship is noted between NLR and platelet-lymphocyte ratio (PLR) with CVD risk factors including dyslipidemia [7]. The NLR was significantly increased in RDs including ankylosing spondylitis (AS), Behçet's disease (BD) and RA compared to the controls; and also, the PLR was higher in RA and SLE [8]. In Takayasu arteritis (TA), NLR and PLR were significantly associated with the disease activity [9]. Notably, dyslipidemia has been a matter of interest and widely studied in various RDs; and it has been associated with the disease activity [10], reinforcing the interplay between inflammation and dyslipidemia.

The aim of the current work was to assess and compare the lipid profile, NLR and PLR in different RDs; as well as to determine their association with disease activity and/or severity and to detect their role in discriminating disease activity and/or severity. Assessment of the interrelation between NLR, PLR and lipid profile parameters has been well thought out.

PATIENTS AND METHODS

The study involved 257 adult patients; 47 with RA, 100 with SLE, 49 with systemic sclerosis (SSc), 33 with axial spondyloarthritis (axSpA) and 28 with vasculitis (21 with primary vasculitis and 7 with BD), recruited from the Rheumatology department, Faculty of Medicine, Cairo University Hospitals; and fulfilling the corresponding classification criteria for RA [11], SLE [12], SSc [13] and axSpA [14]. The study included 21 patients with primary vasculitis: 5 Takayasu arteritis (TA), 3 granulomatosis with polyangiitis (GPA), 1 microscopic polyangiitis (MPA), 1 eosinophilic granulomatosis with polyangiitis (EGPA) (Churg Strauss), 2 polyarteritis nodosa (PAN), 2 Cogan syndrome, 1 urticarial vasculitis, 1 cryoglobulinemic vasculitis and 5 undifferentiated vasculitis according to the 2012 Chapel Hill consensus [15]; and 7 BD patients [16]. Patients were excluded if they were known to have hypothyroidism, liver disease, Cushing disease, malignancy or infection; and if they were on medications that alter or reduce lipids over the past 3 months. Age and sex matched apparently healthy volunteers (n=70) were recruited as a control group, with a suitable number of controls matched for each corresponding disease; 50/70 for RA, 50/70 for SLE, 50/70 for SSc, 30/70 for axSpA and 30/70 for vasculitis patients.

All patients underwent history taking, clinical examination including body mass index (BMI), waist circumference (cm) and laboratory investigations including complete blood count (CBC) with differential. Ratio of the absolute neutrophil count (ANC) to absolute lymphocyte count (ALC) was calculated to estimate NLR and absolute platelet count (APC) to ALC to estimate PLR. The serum lipid profile was assessed in all subjects after overnight fasting including total cholesterol (TC), high-density lipoprotein (HDL), triglycerides (TG), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). Dyslipidemia was defined according to the Adult Treatment Panel (ATP III) criteria [17]. The LDL:HDL ratio was also calculated.

The disease activity score (DAS-28) [18] was assessed in RA, SLE disease activity index (SLEDAI) [19] in SLE, Bath AS disease activity index (BASDAI) [20] in axSpA, Birmingham vasculitis activity score (BVAS) [21] in primary vasculitis and the Arabic version of BD Current Activity Form (Ar-BDCAF) [22] in BD. The disease severity was assessed using: the SLICC/ACR damage index [23] in SLE, modified Rodnan Skin Score (mRss) [24] in SSc, the vasculitis damage index (VDI) [25] in primary vasculitis and the BD damage index (BDI) [26] in BD.

STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical package for social science (SPSS) version 22. Data were presented as mean ±standard deviation, median and range, or number and percentages. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of variables was done using Mann Whitney U, Kruskal Wallis or Chi-square χ^2) tests. Exact test was used when the expected frequency was < 5. Spearman's correlation test and multivariate linear regression analysis were considered. Receiver operator characteristic (ROC) analyzed the optimum cut-off value for the studied parameters. The likelihood ratio of a positive test was calculated as sensitivity ÷ (1-specificity), while of a negative test was calculated as (1-sensitivity) ÷ specificity for each determined cut off value. Two-sided p values <0.05 were considered significant.

ETHICS

All participants provided informed consent to participate; and the current work was approved by the Scientific Research and Ethical Committee (SReC) (40-SReC-RCU2021) and in accordance with the guidelines of Helsinki.

RESULTS

Characteristics of the RDs patients are presented in Table 1. The anti-rheumatic drugs were identified in the studied groups of patients: oral glucocorticoids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs: methotrexate, leflunomide, sulfasalazine, hydroxychloroquine (HCQ), azathioprine, cyclophosphamide, mycophenolate mofetil and cyclosporine) and biological DMARDs (bDMARDs: infliximab, adalimumab, etanercept, golimumab and rituximab). None of the patients of the different RDs were receiving IL-6 inhibitors as tocilizumab. All RDs patients and their controls were age and gender matched (p>0.05). Comparison between RA, SLE, SSc, axSpA, vasculitis patients and their corresponding controls regarding NLR and PLR are illustrated in Figure 1. When comparing RA, SLE, SSc, axSpA, vasculitis patients and their controls, the lipid parameters were comparable (p>0.05); apart from HDL in RA (53±17.6; 27-119) versus their controls (45.4±9.6; 27-83) (p=0.01), TG in SLE (167.9±91.6; 54-492) versus their controls (111.96±53.7; 32-256) (p<0.0001) and LDL in vasculitis (52.6±13.9; 30-95) versus their controls (43.6±15.4; 12-78) (p=0.02). The LDL:HDL ratio was comparable in the RDs versus their controls (p>0.05). When comparing RA, SLE, axSpA, vasculitis patients and their corresponding control group, the frequency of dyslipidemia was similar (p=0.06, p=0.49, p=1, p=0.78) respectively. In SSc, the frequency of dyslipidemia was 75.5% versus 54% in their controls (p=0.04).

TABLE 1. Characteristics of the studied rheumatic diseases

Parameter Mean ±SD or n (%)	RA (n=47	SLE (n=100)	SSc (n=49)	axSpA (n=33)	Vasculitis (n=28)		p
					PV (n=21)	BD (n=7)	
Age (years)	44.3±13.7 (21-75)	33.8±10.3 (18-63)	43.3±13.7 (18-79)	40.7±10 (17-62)	40.4±15.8 (19-77)	34.4±6.6 (29-44)	**<0.0001**
Gender:							**<0.0001**
male	4 (8.5)	7(7)	7 (14.3)	24 (72.7)	10 (47.6)	6 (85.7)	
female	43 (91.5)	93(93)	42 (85.7)	9 (27.3)	11 (52.4)	1 (14.3)	
Disease duration	12.3±7.4 (1-27)	8.9±7.02 (1-27)	7.4±5.6 (1-24)	12.4±8.1 (1-35)	6.1±6.1 (1-22)	8±8.4 (1-25)	**<0.0001**
Age at onset	31.9±13.02	24.6±10.9	36.1±12.5	28.2±10.9	34.3±16.2	26.4±3	**<0.0001**
Comorbidities:							
DM	7 (14.9)	11(11)	3 (6.1)	2 (6.1)	3 (14.3)	1 (14.3)	0.68
Hypertension	9 (19.1)	47(47)	8 (16.3)	1 (3)	12 (57.1)	1 (14.3)	**<0.0001**
BMI	29.4±5.6 (19.7-45.2)	27.9±6 (15.1-48.9)	25.8±5.9 (14.6-46)	28±3.3 (23.4-35.9)	28.7±8.1 (15.6-51)	26.5±3.8 (22.7-32.7)	**0.04**
WC (cm)	100.2±16.4 (46-130)	98.9±13.7 (70-137)	96.6±11.6 (70-123)	103.1±11.8 (80-127)	100±14.1 (68-133)	102.8±14 (90-125)	0.36
NLR	3.7±3.9	4.4±3.3	3.2±2.7	1.8±0.97	4.3±3.6	4.4±1.99	**<0.0001**
PLR	217.4±165.3	257.3±186.9	178.8±101.9	138.7±50.2	286.7±484.9	209.5±115.2	**0.004**
TC (mg/dl)	188.5±37.1	204.5±59.3	183.6±34.9	191.7±36	200±48.2	199.6±56.4	0.4
TG (mg/dl)	121.4±54.3	167.9±91.6	125.1±67.5	130.9±72.7	135.5±99.9	122.7±62.3	**0.004**
LDL (mg/dl)	113.8±30.8	124.7±52.3	113.4±30.3	116±26.5	126.9±40.7	132±44.1	0.7
HDL (mg/dl)	53±17.6	48.7±19.4	46.3±11.9	47.4±17.7	52.8±13.9	51.4±15.6	0.3
VLDL (mg/dl)	24.2±10.8	34±18.5	25±13.7	25.7±14.7	26.1±19.9	26.2±13.4	**0.002**
LDL:HDL ratio	2.2±0.7	2.9±1.5	2.6±0.9	2.7±1.2	2.5±1.2	2.6±0.8	0.4
Dyslipidemia	35(74.5)	82(82)	37(75.5)	23(69.7)	16(76.2)	5(71.4)	0.7
Disease activity and/or severity:	**DAS-28** 5.2±2.27 (0-8.5	**SLEDAI** 8.3±5.9 (0-29)		**BASDAI** 4.9±1.8 (2.1-8)	**BVAS** 5±3.9 (0-12)	**BDCAF** 5.14±2.7 (1-10)	–
		SLICC-DI 0.45±0.79 (0-4)	**mRss** 22.9±8.3 (2-43)		**VDI** 1.9±2.3 (0-6)	**BDI** 3.2±2.9 (0-7)	–

Abbreviations: RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, SSc: Systemic sclerosis, axSpA: Axial spondyloarthritis, PV: primary vasculitis, BD: Behçet's disease, DM: Diabetes mellitus, BMI: Body mass index, WC: Waist circumference, NLR: Neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, TC: Total cholesterol. TG: Triglycerides, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very-low density lipoprotein,DAS-28: Disease Activity Score-28, SLEDAI: Systemic lupus erythematosus disease activity index, SLICC-DI: Systemic Lupus International Collaboration Clinic-damage index, mRss: modified Rodnan skin score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BVAS: Birmingham vasculitis activity score, VDI: Vasculitis damage index, BDCAF: BD current activity form, BDI: Behçet damage index. Statistically significant P values are in bold

Comparisons between RA, SLE, SSc and vasculitis patients with and without dyslipidemia are shown in Tables 2 and 3. In SLE, on comparing the clinical manifestations between patients with and without dyslipidemia, no significance was found (p>0.05); except for arthritis which occurred in 62.2% in those with dyslipidemia versus 27.8% in those without (p=0.01). In axSpA patients, BASDAI was similar among patients with and without dyslipidemia (p=0.75); and the NLR and PLR were comparable (p=0.09, p=0.17) respectively. Regarding gender differences, the mean NLR and PLR were similar in all RDs; except SSc: the mean PLR was 350.8±57.8 (159-323) among males and was 168.04±103.2 (38-455) among females (p=0.02).

Correlations of NLR, PLR with the lipid profile parameters and variable disease parameters in RA, SLE, SSc and vasculitis patients are shown in Table 4. On regression in RA, only the NLR remained significantly correlated with the current steroid dose (B=0.5, p≤0.0001). In SLE, TG correlated inversely with the age (r=-0.2, p=0.05). TG, TC, LDL and LDL:HDL ratio correlated significantly with the current steroid dose (r=0.3, p=0.005, r=0.2, p=0.03, r=0.2, p=0.04 and r=0.3, p=0.01 respectively). TG and LDL: HDL correlated significantly with SLEDAI (r=0.4, p<0.0001 and 0.4, p<0.0001 respectively); while HDL correlated inversely (r=-0.4, p<0.0001). TG and LDL:HDL ratio correlated significantly with consumed C3 (0.3, p=0.02 and r=0.3, p=0.02 respectively) and with erythrocyte sedimentation rate (ESR) (r=0.4, p<0.0001 and r=0.4, p<0.0001 respectively); while HDL correlated inversely with ESR (r=-0.4, p<0.0001). TC, TG, LDL and LDL:HDL ratio correlated significantly with serum uric acid (r=0.4, p<0.0001, r=0.3, p=0.001, r= 0.3, p= 0.002 and r=0.2, p=0.02 respectively). On regression in SLE, TC remained significantly correlated with the steroid

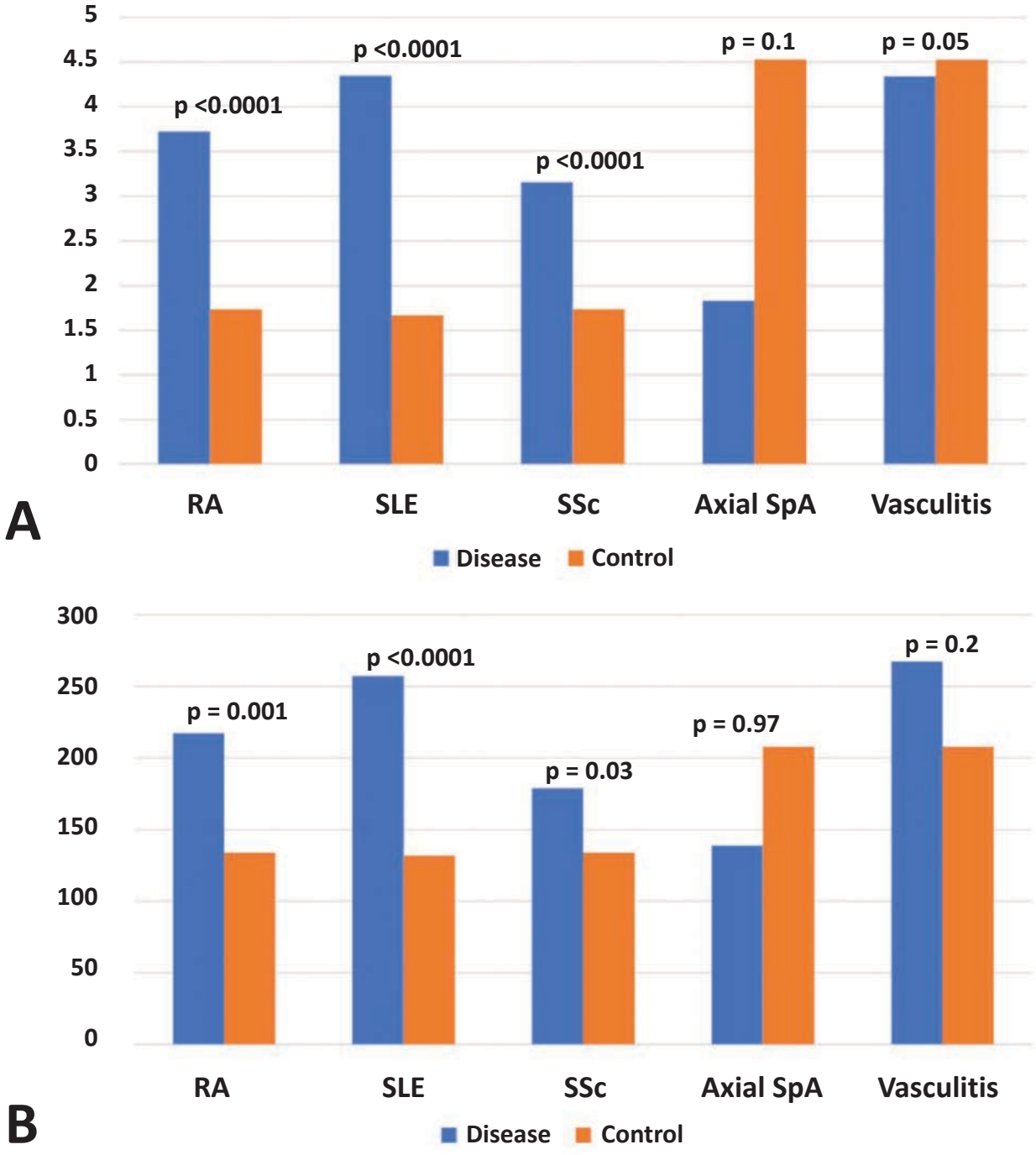

FIGURE 1. Mean neutrophil-lymphocyte ratio (NLR) (A) and platelet-lymphocyte ratio (PLR) (B) among different rheumatic diseases and their corresponding control

dose and serum uric acid (B=1.3, p=0.007 and B=5.97, p=0.01 respectively). The LDL remained significantly correlated with the steroid dose and serum uric acid (B=1.17, p=0.007 ad B=5.62, p=0.009 respectively). The HDL remained significantly correlated with ESR (B=-0.15, p=0.009) and showed a tendency to correlate with SLEDAI (B=-0.7, p=0.05). LDL:HDL ratio remained significantly correlated with SLEDAI (B=0.12, p=0.02). In SSc, HDL correlated inversely with mRss (r=-0.3, p=0.04) and with ESR (r=-0.4, p=0.028). TG correlated significantly with uric acid (r=0.4, p=0.048). On regression in SSc, HDL remained significantly correlated with ESR (B=-0.18, p=0.02). In vasculitis, TC, LDL and HDL correlated inversely with disease duration (r=-0.6, p=0.002, r=-0.6, p=0.002 and r=-0.4, p=0.04 respectively). TG correlated inversely with VDI (r=-0.5, p=0.03) and significantly with the current steroid dose (r=0.4, p=0.004). On regression in vasculitis, NLR remained significantly correlated with TC (B=0.03, p=0.02); and PLR remained significantly correlated with BDCAF (B=29.5, p=0.03). In axSpA patients, TC correlated significantly with the age of the patients (r=0.4, p=0.03). LDL correlated inverse-

TABLE 2. Characteristics of the studied rheumatic diseases

Variable mean± SD or n (%)	Dyslipidemia in RA patients (n= 47)			Dyslipidemia in SSc patients (n= 49)		
	With (n=35)	Without (n= 12)	p	With (n=37)	Without (n= 12)	p
Age (years)	46.1±14.2	38.8±10.8	0.14	44.7±13.5	38.7±13.9	0.2
Gender:						
male	4(11.4)	0(0)	0.56	5(13.5)	2(16.7)	1
female	31(88.6)	12(100)		32(86.5)	10(83.3)	
Disease duration (years)	11.5±7	14.6±8.3	0.28	8.3±5.9	4.4±3.6	0.03
Neutrophils (%)	65±12.6	65.2±15.4	0.79	61.03±10.6	60.8±16.6	0.54
Lymphocytes (%)	25.5±10	23.9±10.9	0.52	28.4±10.2	26±13.9	0.19
NLR	3.8±4.3	3.6±2.4	0.63	3.1±2.8	3.3±2.4	0.3
PLR	216.2±185.7	220.8±95.1	0.38	162.5±93.1	230.8±115.7	0.06
ESR (mm/hour)	46.4±34.2	44.3±18.7	0.92	46±30.7	41.8±32.8	0.55
Uric acid (mg/dl)	3.99±1.14	3.2±1.1	**0.04**	4.6±1.24	3.8±1.5	0.12
Creatinine (mg/dl)	0.7±0.28	0.63±0.15	0.68	0.9±0.92	0.56±0.18	**0.005**
Positive RF	13/18 (72)	5/6 (83.3)	1	-	-	-
Positive anti-CCP	9/11 (81.1)	2/2 (100)	1	-	-	-
Positive ANA	-	-	-	28/32(87.5)	8/9(88.9)	1
DAS-28	5.2±2.3	5.19±2.3	1			
Active (≥2.6)	25 (73.5)	10 (83.3)		-	-	-
Remission (<2.6)	9 (26.5)	2 (16.7)	0.7			
High disease activity	17 (68)	4 (40)				
Moderate disease activity	7 (28)	2 (20)	**0.02**	-	-	-
Low disease activity	1 (4)	4 (40)				
mRss	-	-	-	24.03±6.5	19.4±12.1	0.29
Current steroid dose	7.4±4.9 (0-20)	6.3±2.9 (0-10)	0.55	6.04±7.6 (0-30)	11.04±11.7 (0-40)	0.17
Leflunomide	13 (38.2)	8 (66.7)	0.11	1(2.7)	2(16.7)	0.14
Biologics	12 (34.3)	4 (33.3)	1	0(0)	1(8.3)	0.25
Methotrexate	12 (34.3)	2 (16.7)	0.302	5(13.5)	2(16.7)	1
Hydroxychloroquine	7 (20)	2 (16.7)	1	1(2.7)	4(33.3)	**0.01**
Sulfasalazine	1 (2.9)	1 (8.3)	0.45	0 (0)	0(0)	-
Cyclophosphamide	1 (2.9)	0(0)	-	7(18.9)	0(0)	-

RA: Rheumatoid arthritis, SSc: Systemic sclerosis, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ESR: Erythrocyte sedimentation rate, RF: Rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide, ANA: Antinuclear antibodies, DAS-28: Disease Activity Score-28, mRss: modified Rodnan skin score. Statistically significant P values are in bold

TABLE 3. Comparison between SLE and vasculitis patients with and without dyslipidemia

Variable Mean ± SD (Range) or n (%)	Dyslipidemia in SLE patients (n= 100)			Dyslipidemia in vasculitis patients (n=28)		
	With (n=82)	Without (n=18)	p	With (n=21)	Without (n=7)	p
Age (years)	32.9±9.99	37.4±11.1	0.14	39.6±13.5	36.7±16.88	0.58
Gender:						
male	6(7.3)	1(5.6)	1	12(57.1)	4(57.1)	1
female	76(92.7)	17(94.4)		9(42.9)	3(42.9)	
Disease duration (years)	8.4±6.9	11.2±7.38	0.2	6.8±7.38	5.7±4.1	0.71
Neutrophils (%)	69.4±12.8	68.5±15.1	0.85	71.8±10.98	61.3±12.1	**0.06**
Lymphocytes (%)	22.2±11.3	21.8±11.9	0.84	19.7±10.7	30.6±12.1	**0.04**
NLR	4.2±2.97	4.9±4.35	0.9	4.96±3.4	2.48±1.5	0.05
PLR	266.9±192.9	214.4±154.9	0.3	195.6±102.4	482.9±833.8	0.8
ESR (mm/1st hour)	70.2±33.3	33.3±30.2	**<0.0001**	46.3±35.5	30.8±31.5	0.37
Uric acid (mg/dl)	6.1±2.5	4.9±2.25	**0.09**	4.9±1.5	5.2±1.7	0.81
Urea (mg/dl)	58.9±44	31.5±22.5	**0.001**	30.7±8.2	24±20.9	**0.22**
Creatinine (mg/dl)	1.4±2.28	0.9±0.86	**0.04**	0.86±0.27	0.81±0.3	0.41

Variable Mean ± SD (Range) or n (%)	Dyslipidemia in SLE patients (n= 100)			Dyslipidemia in vasculitis patients (n=28)		
	With (n=82)	Without (n=18)	p	With (n=21)	Without (n=7)	p
24 hours urinary proteins (gm/dl)	1.9±2.1	1.3±1.59	0.39	-	-	-
Consumed C3	29/44(65.9)	0(0)	-	-	-	-
Consumed C4	14/42(33.3)	1/4(25)	1	-	-	-
Positive ANA	77/79(97.5)	16/16(100)	1	-	-	-
Positive c-ANCA	-	-	-	2/8(25)	0(0)	-
SLEDAI	9.1±5.7	5±5.71	**0.01**	-	-	-
SLICC-DI	0.4±0.75	0.6±0.97	0.57	-	-	-
Primary vasculitis:						
BVAS	–	–	–	4.3±3.1	7.2±5.7	0.28
VDI				1.56±2.09	2.8±2.77	0.41
BD:						
BDCAF	–	–	–	6.2±2.28	2.5±2.1	0.08
BDI				3.5±3.51	2.5±2.12	0.81
Current steroid dose (mg/day)	23.6±11.9 (5-50)	16.3±13.4 (5-50)	**0.02**	26.5±10.77 (0-40)	15.36±11.76 (0-30)	**0.04**
AZA	31(37.8)	7(38.9)	-	3(14.3)	3(42.9)	**0.14**
Hydroxychloroquine	56(68.3)	13(72.2)	1	1(4.8)	0(0)	-
Biologics	2(2.4)	1(5.6)	0.45	1(4.8)	1(14.3)	0.44
MMF	13(15.9)	6(33.3)	0.1	1(4.8)	0(0)	1
Cyclophosphamide	13(15.9)	1(5.6)	0.45	8(38.1)	2(28.6)	1
Methotrexate	2(2.4)	1(5.6)	0.43	1(4.8)	0(0)	-
Leflunomide	1(1.1)	0(0)	-	0(0)	0(0)	-
Cyclosporine	0(0)	0(0)	-	2(9.5)	0(0)	-

SLE: Systemic lupus erythematosus, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ESR: Erythrocyte sedimentation rate, ANA: Antinuclear antibodies, c-ANCA: cytoplasmic ANCA, SLEDAI: Systemic lupus erythematosus disease activity index, SLICC-DI: Systemic Lupus International Collaboration Clinics-damage index, BVAS: Birmingham Vasculitis Activity Score, VDI: Vasculitis damage index, BD: Behcet's disease, BDCAF: Behcet's Disease Current Activity Form, BDI: Behcet's Disease Damage index. AZA: Azathioprine, MMF: Mycophenolate mofetil. Statistically significant P values are in bold

TABLE 4. Correlation of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and lipid profile parameters with each other and with variable disease parameters in RA, SLE, SSc and vasculitis patients.

Parameter r(p)	RA (n= 47)		Parameter r(p)	SSc (n=49)	
	NLR	PLR		NLR	PLR
Age (years)	0.07 (0.6)	0.03 (0.8)	Age (years)	-0.1(0.45)	-0.04(0.7)
Disease duration (years)	-0.06 (0.7)	-0.07 (0.65)	Disease duration	-0.004(0.9)	0.05(0.7)
DAS-28	-0.3 (0.02)	-0.06 (0.7)	mRss	-0.07(0.6)	0.2(0.2)
Steroid dose (mg/day)	0.53 (**<0.0001**)	0.23 (0.1)	Steroid dose (mg/day)	0.2(0.1)	-0.02(0.8)
NLR	-	0.5 (**<0.0001**)	NLR	-	0.5(**<0.0001**)
PLR	0.5 (**<0.0001**)	-	PLR	0.5(**<0.0001**)	-
ESR (mm/1st h)	-0.06 (0.7)	0.27 (0.1)	ESR (mm/1st hour)	-0.03(0.85)	0.09(0.5)
Uric acid (mg/dl)	-0.06 (0.7)	-0.02 (0.9)	Uric acid (mg/dl)	-0.08(0.67)	-0.2(0.2)
Total cholesterol(mg/dl)	-0.09 (0.56)	-0.09 (0.9)	Total cholesterol	0.03(0.8)	-0.2(0.1)
Triglycerides (mg/dl)	0.34 (**0.0**2)	0.32 (**0.04**)	Triglycerides (mg/dl)	-0.1(0.47)	-0.1(0.35)
LDL (mg/dl)	-0.08 (0.6)	-0.08 (0.59)	LDL (mg/dl)	0.2(0.23)	-0.05(0.76)
HDL (mg/dl)	-0.18 (0.25)	-0.17 (0.2)	HDL (mg/dl)	0.08(0.6)	0.03(0.8)
LDL: HDL	0.07 (0.66)	0.08 (0.6)	LDL: HDL ratio	0.17(0.3)	0(0.9)
	SLE patients (n= 100)			Vasculitis (n=28)	
	NLR	PLR		NLR	PLR
Age (years)	-0.08(0.4)	-0.17(0.1)	Age (years)	-0.02(0.9)	-0.05(0.7)
Disease duration (years)	-0.29 (**0.00**3)	-0.3 (**0.001**)	Disease duration	-0.3(0.1)	-0.3(0.2)
SLEDAI	0.3 (**0.005**)	0.2 (0.13)	BVAS	-0.1(0.6)	0.017(0.9)
			VDI	-0.2(0.5)	0.1(0.7)

SLICC-DI	-0.14(0.2)	-0.2 (**0.01**)	BDCAF BDI	0.2(0.6) -0.3(0.5)	0.9(**0.003**) 0.4(0.43)
Steroid dose (mg/day)	0.2(**0.02**)	0.06(0.6)	Steroid dose (mg/day)	0.2(0.24)	-0.008(0.9)
NLR	-	0.5 (**<0.0001**)	NLR	-	0.5(**0.006**)
PLR	0.5 (**≤0.0001**)	-	PLR	0.5(**0.006**)	-
ESR (mm/ 1st hour)	0.05(0.6)	0.2(0.1)	ESR (mm/1st hour)	0.15(0.5)	0.26(0.2)
Uric acid (mg/dl)	0.14(0.2)	-0.07(0.5)	Uric acid (mg/dl)	0.08(0.8)	-0.19(0.4)
Total cholesterol (mg/dl)	0.2(0.1)	0.04(0.7)	Total cholesterol	0.4(0.03)	-0.04(0.8)
Triglycerides (mg/dl)	0.12(0.3)	0.13(0.2)	Triglycerides (mg/dl)	-0.1(0.6)	-0.5(**0.004**)
LDL (mg/dl)	0.08(0.4)	0.08(0.4)	LDL (mg/dl)	0.35(0.09)	-0.03(0.9)
HDL (mg/dl)	0.04(0.7)	-0.14(0.2)	HDL (mg/dl)	0.16(0.5)	0.24(0.3)
LDL: HDL ratio	0.03(0.7)	0.1(0.3)	LDL: HDL ratio	0.25(0.2)	-0.2(0.35)
Consumed C3	0.2(0.3)	0.09(0.5)	-	-	-
Consumed C4	-0.003(0.98)	0.04(0.8)	-	-	-

RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, SSc: Systemic sclerosis, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ESR: Erythrocyte sedimentation rate, DAS-28: Disease Activity Score-28, mRss: modified Rodnan skin score, SLEDAI: Systemic lupus erythematosus disease activity index, SLICC-DI: Systemic Lupus International Collaboration Clinics-damage index, BVAS: Birmingham Vasculitis Activity Score, VDI: Vasculitis damage index, BD: Behcet's disease, BDCAF: Behcet's Disease Current Activity Form, BDI: Behcet's Disease Damage index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein. Statistically significant P values are in bold

TABLE 5. Receiver operating characteristic (ROC) analysis and validity of NLR, PLR and ESR to differentiate between active and inactive RA, SLE, SSc, axSpA and vasculitis patients

Variable	**RA patients (n= 47)**							
	AUC	95% CI	Cut-off	Sensitivity	Specificity	LR (+)ve	LR (-)ve	p
NLR	0.78	(0.68-0.82)	1.52	84.2%	44.2%	1.51	0.36	**<0.0001**
PLR	0.72	(0.6-0.84)	121.9	78.9%	44.2%	1.41	0.48	**0.001**
ESR	0.759	(0.65-0.87)	21	76.3%	32.6%	1.13	0.73	**<0.0001**
	SLE patients (n= 100)							
	AUC	95% CI	Cut-off	Sensitivity	Specificity	LR (+)ve	LR (-)ve	p
NLR	0.856	(0.79-0.92)	1.59	91.9%	38%	1.48	0.21	**<0.0001**
PLR	0.748	(0.67-0.83)	121.6	79.8%	38.8%	1.3	0.52	**<0.0001**
ESR	0.827	(0.75-0.91)	24	82.4%	27%	1.13	0.65	**<0.0001**
	SSc patients (n= 49)							
	AUC	95% CI	Cut-off	Sensitivity	Specificity	LR (+)ve	LR (-)ve	p
NLR	0.75	(0.64-0.85)	1.43	81%	46.5%	1.51	0.41	**<0.0001**
PLR	0.63	(0.51-0.75)	121.5	71.4%	44.2%	1.28	0.65	**0.034**
ESR	0.76	(0.65-0.86)	24	73.8%	27.9%	1.02	0.94	**<0.0001**
	axSpA patients (n= 33)							
	AUC	95% CI	Cut-off	Sensitivity	Specificity	LR (+)ve	LR (-)ve	p
NLR	0.57	(0.44-0.71)	-	-	-	-	-	**0.32**
PLR	0.56	(0.43-0.69)	-	-	-	-	-	**0.38**
ESR	0.58	(0.44-0.72)	-	-	-	-	-	**0.26**
	Vasculitis patients (n= 28)							
	AUC	95% CI	Cut-off	Sensitivity	Specificity	LR (+)ve	LR (-)ve	p
NLR	0.831	(0.72-0.95)	2.25	79.2%	14%	0.92	1.49	**<0.0001**
PLR	0.695	(0.56-0.84)	122.8	75%	44.2%	1.34	0.57	**0.008**
ESR	0.674	(0.52-0.83)	24	66.7%	27.9%	0.93	1.19	**0.02**

AUC: Area under the curve, CI: Confidence interval, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, SSc: Systemic sclerosis, axSpA: Axial spondyloarthritis, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ESR: Erythrocyte sedimentation rate, LR: Likelihood ratio. Statistically significant P values are in bold.

ly with disease duration (r=-0.6, p=0.004). TC and HDL correlated significantly with the current steroid dose (0.4, p=0.04 and r=0.5, p=0.03 respectively). NLR and PLR correlated significantly with each other (r=0.4, p=0.02). Neither NLR nor PLR correlated with BASDAI (r=-0.16, p=0.39, r=0.001, p=0.9 respectively). The receiver operating characteristic (ROC) analysis of the NLR, PLR and ESR to assess their sensitivity and specificity in predicting disease activity of the studied diseases is shown in table 5.

DISCUSSION

Inflammation and dyslipidemia have a significant cause-effect relationship [27]. This integration is considered a hallmark of the atherosclerotic process and subsequent ACVDs; highlighting the necessity to address inflammation as an important risk modifier. In this work, NLR and PLR were significantly higher in RA patients versus the controls. Moreover, NLR, PLR and ESR were found to be significant predictors of disease activity in RA. In line, higher NLR and PLR in RA was reported [28] and NLR was higher in a cohort of Egyptian RA patients [29]. Currently, Only NLR correlated inversely with the DAS-28. However, NLR correlated significantly with the ESR and DAS-28 [29].

Thirty-five (74.5%) RA patients had dyslipidemia. The frequency of dyslipidemia in RA was found to range from 55-65% [30]. In the current study, HDL was significantly higher in RA patients versus the controls. However, it was shown that HDL was significantly lower in active RA patients [31]. Regarding DAS-28 in the present work, it was similar between those with and without dyslipidemia; however, higher disease activity grade was significantly associated with dyslipidemia. As noted, the significantly increased frequency of active RA cases associated with dyslipidemia in the current study is inconsistent with the "lipid paradox" described in active RA patients; which is characterized by low HDL, TC and LDL; and subsequently increased CVD risk [32]. The decrease in HDL, and consequently the increase in TC: HDL and LDL:HDL ratios favor an atherogenic profile in active RA patients [31].

In SLE, NLR and PLR were also significantly higher in the patients versus the controls which is in harmony with a recent meta-analysis [33]; and study on Egyptian SLE patients [34]. The NLR and PLR were inversely associated with the disease duration in this study which goes in hand with the work of others [34]. In the present work, NLR correlated significantly with SLEDAI and the PLR inversely with SLICC-DI. On the contrary in another work, PLR correlated significantly with SLEDAI but not with SLICC-DI [34]. In consistency, NLR correlated significantly with SLEDAI in lupus nephritis patients [35]. In disharmony with the present findings, NLR and PLR did not show significant correlation with SLEDAI or SLICC-DI [36]. NLR and PLR were found to be promising determinants of disease activity in the present SLE patients. In line, both would predict disease activity; however, PLR was more powerful in discrimination [36].

Regarding dyslipidemia, it was present in 82% of SLE patients in the present study. Dyslipidemia is highly prevalent in SLE and is increased to 60% after 3 years of diagnosis [37]. TG was significantly higher in SLE patients versus their controls in the present study. Partially consistent with the current results, significantly higher TG was found in SLE patients; and HDL, LDL and TC were significantly reduced [38]. Significantly higher LDL, TC, TG and significantly lower HDL in an analysis of Egyptian SLE patients versus their controls was also reported [39]. The SLEDAI and ESR were significantly higher in SLE patients with dyslipidemia in the present study; and SLEDAI significantly correlated with TG and LDL: HDL and inversely with the HDL. Similarly, significantly higher TC, TG and LDL and lower HDL were shown active SLE cases [39]; reflecting that lipid abnormality is associated with disease activity.

Regarding the drugs used by SLE patients, the current steroid dose was significantly higher in those with dyslipidemia; and TC, TG, LDL as well as LDL:HDL correlated significantly with the current steroid dose. Moreover, on regression, TC and LDL were significantly related. In line, both TC and TG correlated significantly with the steroid dose [40].

In SSc, NLR and PLR were also significantly higher, but not associated with mRss which was in agreement to previous study [41]. On the other hand, NLR correlated with mRss in SSc patients [42]. Dyslipidemia was present in 75.5% in SSc in this study, which was significantly higher versus the controls. In agreement, dyslipidemia was reported in SSc patients in the form of increased triglycerides in 39% and increased TC in 32% [43]. Additionally, lipid profile characterized by low HDL and high LDL and TG levels in SSc has been revealed [44]. In the current study, HDL showed inverse correlation with mRss and ESR. Moreover, on regression, the HDL was independently associated with ESR. Interestingly and in line with the current findings, the cholesterol efflux capacity correlated inversely with mRss [45], which reflects the anti-atherogenic function of the HDL particle. On the contrary, no significant correlation between mRss and LDL, TC, TG and HDL in SSc was found [45]. In the present study, only HCQ use was significantly increased in SSc patients without dyslipidemia. This is not surprising as HCQ is reported to be associated with the lowering of TC, TG and LDL and increase in HDL [46].

In axSpA, no significant difference was shown for NLR and PLR compared to the controls, which is in line with the work of others [47]. Neither NLR nor PLR correlated with BASDAI in the current study. Dyslipidemia was reported in 69.7% of axSpA patients in the present study; and the lipid parameters were comparable to the control. Dyslipidemia was reported in 47.5% of AS patients and in 71.8% of psoriatic arthritis (PsA) patients [48]. None of the lipid subfractions in the present study correlated with BASDAI.

In vasculitis, the NLR and PLR were both comparable to the controls and neither correlated with the BVAS or VDI. In BD patients, only PLR correlated significantly with the BDCAF; and it was independently associated. It was shown that NLR and PLR were promising predictors of disease activity in the present vasculitis patients. In line, NLR and PLR would predict TA [9]. NLR and PLR correlated significantly with TC and TG respectively in the present vasculitis patients; and NLR was independently associated with TC. Partially consistent with the present findings, NLR correlated significantly with TC and TG in premenopausal women [7]. Dyslipidemia was reported in 75% of vasculitis patients in the current work which was similar to their control. Dyslipidemia was reported in 38.3% of TA patients [49].

The significance of the present study is enhanced by the fact that it was leading to investigate the association of the lipid profile with NLR and PLR in RDs. In the present study, there was no significant association between NLR and PLR with the lipid profile parameters in SLE, SSc and axSpA. However, both correlated significantly with TG in RA. Also, it is among limited number of studies assessing the gender-related differences for the NLR and PLR in different RDs. No significant difference was revealed for the NLR and PLR in male and female patients in RA, SLE, axSpA and vasculitis. However, in SSc, the PLR was significantly higher in males.

This is a leading study to assess dyslipidemia and the hematological indices in axSpA and systemic vasculitis patients; and to compare them among different RDs. It is novel to present the frequency of dyslipidemia and compare the hematological indices and lipid subfractions in different RDs. Chronic inflammation which is a common cardinal feature of different RDs is associated with alterations in the cellular lineages of the hematopoietic system [50]. Owing to the common clinical features of the RDs, the overlapping manifestations, the possibility of evolution from one disease to another and in view of the use of non-disease specific therapies, suggest the possibility that different RDs might share common etiological and pathological factors with various expressions [51]. To our knowledge, few papers investigated and compared the hematological indices amongst several RDs; one study showed that that red blood cell distribution width (RDW) was significantly increased in RA versus AS and osteoarthritis patients [52]. Higher RDW was reported in inflammatory conditions as RA and AS versus osteoarthritis and fibromyalgia [53]. Covering more than one RD at the same time was a key objective of this work as previous studies have investigated the relation for each disease separately without knowing which of the RDs deserves most attention in this respect. Each of RA, SLE, SSc, axSpA and vasculitis is heterogenous and complex, with distinct underlying pathogenic mechanisms; however, the current study would reflect the inflammatory status of the implicated diseases. Additionally, it should be noted that the laboratory tests could not serve solely as diagnostics in RDs [54]; however, constellation of inflammatory indices, clinical history and examination are warranted in the diagnosis of RDs.

The lipid profile is subjected to several fluctuations during the disease course due to the variable degrees of inflammation; and thus, investigating the effect of these fluctuations on CVD risk would be of value. Larger longitudinal studies would be valuable to delineate the impact of anti-rheumatic drugs on the lipid parameters and hematological indices. Additionally, the small sample size is another limitation of the current work; however, hopefully, this work throws light on such an important topic for future larger scale studies to be conducted to confirm the findings and detect small differences more easily.

CONCLUSION

In conclusion, dyslipidemia is frequently associated with different RDs; being significantly increased in SSc patients versus their control group; and could be associated with the disease activity in RA and SLE. NLR and PLR are feasible and cost-effective markers that might have a promising role in assessment of disease activity in RA, SLE, SSc and vasculitis patients. In the evaluation of diagnostic accuracy for the hematological indices, Horta-Baas et al. [53] found poor discriminative performance of RDW in active RA patients; with area under the curve (AUC) 0.62, sensitivity 57% and specificity 67%. In line, AUC for different hematological parameters was reported to be 0.66 for systemic-immune inflammation index (SII), 0.62 for neutrophil to-hemoglobin and lymphocyte (NHL) score and 0.69 for C-reactive protein (CRP) in RA patients [55]. As noted, NLR and PLR in the current study did not achieve substantially elevated AUC; but, to date they might serve as acceptable potential markers for discrimination of disease activity in RDs. On comparing the different RDs, NLR and TG were significantly in-

creased in SLE and PLR in primary vasculitis versus other RDs. Significant association was found between NLR and PLR with the lipid profile in RA and vasculitis; highlighting the implicated role of inflammation in dysregulated lipid metabolism and the strong interplay between inflammation and dyslipidemia in ACVDs in RDs.

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