Med. J. Cairo Univ., Vol. 89, No. 7, December: 3063-3073, 2021
www.medicaljournalofcairouniversity.net

Systemic Lupus Erythematosus in Egyptian Males: A Study of Clinical Features, Serology, Outcome, and Review of Literature

NORA YOUSRY ELSAID, M.D.; MARWA NIAZY, M.D.; FATEMA TALAAT ELGENGEHY, M.D. and SALLY S. MOHAMED, M.Sc.

The Department of Rheumatology and Rehabilitation, Faculty of Medicine, Cairo University

Abstract

Background: Systemic lupus erythematosus (SLE)is an auto-immune, multi-system disease with female predominance. The difference in clinical manifestations, autoantibody profile and comorbidities between males and females has always been a subject of major debate.

Aim of Study: To study the gender difference in SLE between a uniform group of the same ethnicity in respect to clinical manifestations, comorbidities, disease activity, damage, and mortality.

Material and Methods: A retrospective study was conducted on 559 patients with SLE (58 males and 501 females) following at the Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University Hospitals. The patients' demographic data, clinical manifestations, laboratory investigations, co-morbidities and medications received as well as SLE disease activity index (SLEDAI) at the first, last visit for each patient and accumulated damage according to Systemic Lupus International Collaborative clinics/American College of Rheumatology Damage Index (SLICC/ACR DI), were recorded.

Results: The present study included 559 SLE patients, 58 males (10.4%) and 501 females (89.6%) with mean age of 32.3±9.1 years. Constitutional manifestations, serositis, lupus nephritis, renal failure and Anti-double stranded DNA antibody positivitywere higher in male SLE patients (p-value: 0.04, p-value: 0.045, p-value: 0.023, p-value: 0.002 and p-0.03 respectively), while hematological manifestations were more frequent in females (p-value: 0.04). SLEDAI at last visit SLICC DI and mortality were statistically higher in male SLE group.

Conclusion: Gender differences exist between male and female SLE patients regardless of ethnic, age and duration variabilities with tendency towards more active disease, higher accumulated damage, and higher mortality in males with SLE.

Key Words: *SLE – Male – Disease activity – Damage – Mortality.*

Correspondence to: Dr. Nora Yousry Elsaid, The Department of Rheumatology and Rehabilitation, Faculty of Medicine, Cairo University

Introduction

SYSTEMIC lupus erythematosus (SLE) is an auto-immune, multi-system disease of unknown etiology [1]. It has a female predominance affecting mainly females of childbearing period. Male SLE is rare with a ratio ranging from 4% to 22% of total SLE cases. In reproductive age, female: male ratio is 8-15:1, this gap decreases with age to become 3-8:1 after menopause. Interestingly, the ratio is much lower before puberty ranging from 2 to 6 times female SLE than males [2]. Pregnancy leads to flare in SLE patients. Also, the use of oral contraceptive pills (OCPs), hormonal intrauterine devices (IUDs) and estrogen replacement therapy exacerbates previously quiescent SLE manifestations [3]. Hence, the gender difference and the role of sex hormones in the pathogenesis of SLE were repeatedly studied in both animal and human models. Murine SLE showed a higher female predominance with a worse disease course and an increased mortality [4]. In humans, studies comparing male and female lupus show conflicting results in respect to clinical manifestations, autoantibody profile and comorbidities with a tendency towards a more active disease and a higher mortality in male SLE. As ethnicity, disease duration and age at onset

Abbreviations:

IgG	: Immunoglobulin G.
Anti-dsDNA	: Anti-double stranded DNA.
ESR	: Erythrocyte sedimentation rate.
C3	: Complement.
LAC	: Lupus anti-coagulant.
IgM ACA	: Immunoglobulin M anti-cardiolipin antibody.
Anti-sm	: Anti-smith.
U1RNPn	: U1 ribonucleoprotein.
RP	: Raynaud's phenomenon.
VDRL	: Venereal disease research laboratory.
SLICC/ACR DI	: The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus.
Cr	: Creatinine.
AA	: Africans Americans

affect the clinical characteristics and prognosis of SLE, these factors had always been a hindering obstacle in mapping out the gender difference in SLE [5].

Therefore, our aim was to study the gender difference in SLE between a uniform group of the same ethnicity in respect to clinical manifestations, comorbidities, disease activity and mortality.

Patients and Methods

This is aretrospective cohort study in which we included patients with SLE who attended the Rheumatology and Rehabilitation clinic in Cairo university Hospital in Egypt in the period between January 2003 till January 2019. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Local Ethical Committee in Rheumatology Department.

Medical records of SLE patients were screened. Inclusion criterion included fulfillment of the 1997 American College Rheumatology (ACR) classification criteria for SLE patients [6] and disease duration ranging from 0.5 to 16 years. Lupus nephritis was diagnosed based on the ACR criteria by persistent proteinuria >0.5g/24h, or the presence of cellular casts, persistent hematuria or renal biopsy results consistent with LN [6]. Renal biopsy classification was documented [7]. Estimated glomerular filtration rate (eGFR) was calculated [8], and divided into normal ≥90ml/min/1.73m^2, mildly decreased 60-89ml/min/1.73m^2, moderately decreased 30-59ml/min/1.73m^2, severely decreased 15-29ml/min/1.73m^2 and renal failure <15ml/min /1.73 m^2.

The data of 559 SLE patients were recorded that included demographics (age, age of onset, sex, and disease duration), clinical disease characteristics (constitutional, mucocutaneous, cardiopulmonary, renal, neuropsychiatric, gastrointestinal, musculo skeletal, vascular and Sicca manifestations), laboratory findings, and immunological profile. Past and current medications were collected including cumulative pulse methylprednisolone (by calculating the doses given for each patient during the disease course from medical records).

Assessment of the disease activity was done by calculating the SLE disease activity index (SLEDAI) [9] at baseline and at last visit for each patient. The Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) [10] scores at the last visit were calculated as well. Mortality and cause of death were recorded from the patients' records.

Presence of positive anti-double stranded deoxyribonucleic acid (anti-dsDNA), lupus anticoagulant (LAC), anti-b2 glycoprotein and anticardiolipin antibodies, were determined from the medical records.

Statistical analysis: Data were collected, tabulated, and statistically analyzed using the SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA: IBM Corp.). Quantitative data were expressed as mean ± standard deviation when normally distributed or median, range when otherwise not normally distributed. Qualitative data were expressed as numbers (percentages). The student's *t*-test was used to analyze the difference between two independent groups when data were parametric, while the Mann-Whitney U test was used when the data were nonparametric. Percentages of categorical variables were compared using the Chi square test or Fisher's exact test when appropriate. Regression analysis was used to find factors associated with comorbidities and mortality and the odds ratio was calculated. A two-tailed probability value (p-value) less than 0.05 was considered statistically significant.

Results

This study included 559 SLE patients. They were 58 males (10.4%), and 501 females (89.6%). The age of patients ranged from 14 to 63 years with a mean age of 32.3±9.1 years, and the disease duration range was from 0.5-16 years with a mean of 7.7±4.4 years. Constitutional manifestations and serositis had higher frequencies in male SLE patients' group (p-value: 0.04, p-value: 0.045 respectively). Demographic and clinical data in male patients in comparison to females are presented in (Table 1). Lupus nephritis had a higher frequency in male SLE patients 87.9% (p-value: 0.023). Also other renal affection parameters as 24 hour proteins in urine reported either at first or last visits, creatinine increase for 6 months and renal failure were statistically higher in males group of patients (p-value: 0.019, p-value: 0.005, p-value: 0.001, p-value: 0.002 respectively) as shown in (Table 2). As regards associated comorbidities, diabetes mellitus and avascular necrosis (AVN) tended to occur more in males without statistical significance, while dyslipidemia and thyroid diseases tended to have lower frequencies. None of males had osteoporosis. SLEDAI at last visit and SLICC DI were statistically higher in male SLE group (p-value: 0.007, p-value: 0.025 respectively). Data are listed in (Table 3).

Table (1): Demographic features and clinical characteristics of SLE patients.

Variable N (%)	SLE patients (n=559)		*p*-value
	Males (n=58)	Females (n=501)	
Age (years)	31.6±11.1	32.4±8.9	0.22
Age at onset (in years)	23.8±10.1	24.7±8.5	0.21
Duration (years)	7.7±4.7	7.6±4.4	0.98
Constitutional manifestations	49 (84.5)	359 (71.7)	**0.04**
Mucocutaneous manifestations	47 (81.0)	440 (87.8)	0.14
NPSLE	25 (43.1)	183 (36.5)	0.33
Arthritis	38 (65.5)	346 (69.1)	0.58
Cardiac affection	20 (34.5)	150 (29.9)	0.48
Pulmonary manifestations	35 (60.3)	287 (57.3)	0.66
Pulmonary hypertension	7 (12.1)	57 (11.4)	0.88
Intra-alveolar hemorrhage	3 (5.2)	11 (2.2)	0.17
Serositis	28 (48.3)	175 (34.9)	**0.045**
GIT manifestations	19 (32.8)	110 (22.0)	0.07
Raynaud phenomenon	7 (12.1)	111 (22.2)	0.08
Livedo reticularis	0 (0)	21 (4.2)	0.15
Digital gangrene	3 (5.2)	10 (2.0)	0.14
Secondary vasculitis	18 (31.0)	168 (33.5)	0.7
Thrombosis	11 (19.0)	92 (18.4)	0.91
Sicca manifestations	4 (6.9)	55 (11.0)	0.50
Ocular manifestations	9 (15.5)	62 (12.4)	0.49

SLE : Systemic lupus erythematosus.
NPSLE: Neuropsychiatric systemic lupus erythematosus.
GIT : Gastrointestinal tract.
- Data are presented in the form of mean ± SD or n (%).
Bold values are significant at $p<0.05$.

Table (2): Features of renal disease in males and females lupus patients.

Variable N (%)	SLE patients (n=559)		*p*-value
	Males (n=58)	Females (n=501)	
- Nephritis	51 (87.9)	373 (74.5)	**0.023**
- 24 hour protein in urine (gm/day) at 1st visit	2 (0.7-3.2)	1.3 (0.2-2.5)	**0.019**
- 24 hour protein in urine (gm/day) at last visit	0.8 (0.17-2.45)	0.28 (0.06-1.1)	**0.005**
- Renal biopsy (n=308) (crescentic/class II/III/IV/V/VI/TMA/ GC/II&V/III or IV & V/IV&TMA)	0/1/21/17/1/0/ 0/1/3/0 (0/2.3/47.7/ 38.6/2.3/0/0/ 2.3/6.8/0)	5/30/92/92/ 22/2/1/3/12/5 (1.9/11.4/34.8/ 34.8/8.3/0.8/ 0.4/1.1/4.5/1.9)	0.33
- GFR ml/min/1.73m^2	90.5 (31.5-133)	93(28.75-122)	0.49
- eGFR - Normal/mildly decreased/ moderately decreased/ severely decreased/renal failure (n=553)	29/12/3/9/5 (50/20.7/5.2/ 15.5/8.6)	265/113/47/37/33 (53.5/22.8/9.5/ 7.5/6.7)	0.25
- Creatinine increase for 6 months	18 (31.0)	72 (14.4)	**0.001**
- Renal failure	11 (19.0)	35 (7.0)	**0.002**

TMA : Thrombotic microangiopathy.
GC : Glomerulosclerosis.
e GFR: estimated glomerular filtration rate.
- Data are presented in the form of median (IQR)or n (%).
Bold values are significant at $p<0.05$

Table (3): Comorbidities, disease activity and damage in SLE patients; males and females.

Variable N (%)	SLE patients (n=559)		*p*-value
	Males (n=58)	Females (n=501)	
Systemic hypertension	27 (46.6)	215 (42.9)	0.60
Diabetes mellitus	7 (12.1)	41 (8.2)	0.32
Dyslipidemia (n=476)	21/53 (39.6)	205/423 (48.5)	0.22
Thyroid disease (n=416)	1 /41 (2.4)	33/375 (8.8)	0.23
AVN	8 (13.8)	48 (9.6)	0.31
Osteoporosis:	0 (0.0)	37 (7.4)	**0.024**
SLEDAI at onset (median (IQR))	10 (5-18)	11 (6-17.75)	0.23
SLEDAI at last visit (median (IQR))	4 (0-10.25)	2 (0-8)	**0.007**
SLICC DI (median(IQR))	1 (0.75-3)	1 (0-2)	**0.025**

AVN : Avascular necrosis.
SLEDAI : Systemic lupus erythematosus disease activity index.
SLICC DI: Systemic lupus international collaboration clinic damage index.
- Data are presented in the form of median (IQR) or n (%).
Bold values are significant at $p<0.05$.

Table (4): Laboratory investigations and immunological profile in male and female SLE patients.

Variable N (%)	SLE patients (n=559)	
	Males (n=58)	Females (n=501)
Hematological features	32 (55.2)	343 (68.5)
Anemia	56 (96.6)	475 (94.8)
Leucopenia	22 (37.9)	285 (56.9)
Thrombocytopenia	19 (32.8)	179 (35.7)
Consumed C3 at onset (n=454)	37/47 (78.7)	290/407 (71.3)
Consumed C3 at last (n=406)	21/47 (44.7)	118/359 (32.9)
Consumed C4 at last (n=451)	14/50 (28.0)	77/401 (19.2)
Positive ANA antibody (n=543)	57/57 (100)	481/486 (99.0)
Positive Anti ds DNA antibody (n=477)	45/51 (88.2)	315/423 (74.5)
Positive Aplantibodies (n=398)	17/36 (47.2)	174/362 (48.1)

IQR: Interquartile range.
C: Complement.
ANA: Antinuclear antibody.
Anti ds: DNA: Anti double stranded deoxy ribonucleic acid.
Apl: Antiphospholipid antibodies.
- Data are presented in the form of median (IQR) or n (%).
Bold values are significant at $p<0.05$.

Table 5): Medications received by male and female SLE patients and mortality in both groups.

Variable N (%)	SLE patients (n=559)		*p*-value
	Males (n=58)	Females (n=501)	
Solumedrol pulse intake	49 (84.5)	424 (84.6)	0.98
Cyclophosphamide intake	46 (79.3)	269 (53.7)	**<0.001**
Cyclophosphamide regimen (classic/European/both)	42/2/2 (91.3/4.3/4.3)	237/23/9 (88.1/8.6/3.3)	0.47
Cumulative cyclophosphamide dose (in gram) (median (IQR))	4.3 (3-6)	4 (3-6)	0.22
Number of cyclophosphamide cycles (median (IQR))	6 (4-8.5)	6 (5-9)	0.63
AZA	37 (63.8)	408 (81.4)	0.002
MMF	19 (32.8)	132 (26.3)	0.29
Antimalarial drugs intake	56 (96.6)	471 (94.0)	0.56
Mortality	16 (27.6)	69 (13.8)	0.006

AZA : Azathioprine.
MMF: Mycophenolate mofetil.
- Data are presented in the form of mean ±SD, median (IQR) or n (%). Bold values are significant at $p<0.05$.

Male SLE patients had lower frequency of hematological affection in general and leucopenia in particular compared to females (p-value: 0.04, p-value: 0.006, respectively) as tabulated in (Table 4). Anti-double stranded DNA antibody positivity was higher in males (p-value: 0.03). Cyclophosphamide (CYC) intake was statistically higher in male SLE patients (p-value <0.001), but no difference was elicited on comparing frequencies of CYC regimen (p-value=0.47). On the other hand, azathioprine intake was higher in females' group (p-value=0.002). Mortality rate was higher in males' group (p-value=0.006) (Table 5).

Discussion

In the present paper, we studied the difference between male and female systemic lupus erythematosus patients in an Egyptian cohort. We have addressed the difference in clinical manifestations, comorbidities, disease activity and mortality. Renal affection was significantly higher in male patients which is similar to previous reports **[11-13]**. Not only the prevalence of renal affection, but also the prognosis was worse in the male group as we found that renal failure was significantly higher in the male group. This finding is also consistent with previous studies **[5,14-16]**. Regardless of the ethnicity, male lupus patients showed higher rates of renal affection and a worse prognosis than female lupus. Among the other clinical manifestations, male SLE patients in our cohort showed a higher serositis frequency in comparison to the female group. In agreement with our results, other studies showed the same **[13,16-18]**.

The gender difference in clinical manifestations in SLE patients is still unsettled and previous studies showed conflicting results in this area. Whereas some studies reported a higher incidence of arthritis for example in the male SLE group **[19]**, others found that arthritis has a higher incidence in the female group **[11,17]**. Another example is the prevalence of thrombotic events. We found no statistical difference between males and female SLE patients in the occurrence of thromboses,other studies found a higher incidence in male SLE **[20,21]** and the list goes on.

The variation in the results is mostly due to the difference in ethnicity, disease durations, presentations, and selection of patients. In the current study, we tried to unify these factors as much as we could. The presentcohort was of a uniform ethnicity as well as a matched disease duration, age, and age at presentation between males and females' group.

Although a gender difference in SLE is clearly present, the cause behind it is still obscure. Researchers all over the world postulated different theories. Lu et al., **[22]** proposed a group of theories including the sex hormone theory which may be considered the most appropriate theory, however, it failed to fully explain the difference. The studies involving sex hormones were heavily carried out in murine SLE models **[23]**. Female mice were more susceptible to development of SLE and had more severe disease course which is convincing to a great extent and validating the sex hormone theory. Unfortunately, the problem in human is more complicated. While females are more susceptible to SLE and males seem to be protected, males show a worse prognosis. Lu et al., **[22]** proposed other theories; the sex chromosome theory **[24]** and intrauterine selection theory **[25]**. Nevertheless, they concluded that none of these theories is enough to explain the sex discrepancy in clinical findings and prognosis and it is mostly an interaction of sex hormones, genetic and environmental factors.

Regarding serological findings, there was an increase in anti-ds DNA antibody positivity in male SLE patients. Molina et al., **[26]**, had the same finding in Latin American patients. Since anti-ds DNA antibody positivity correlates with the renal affection in SLE patients **[27]**, it may explain the higher prevalence of renal affection in male SLE. There was no difference between male lupus and female lupus in terms of antiphospholipid (APL) antibodies. Our results are in accordance with reports from Brazil **[28]**, Spain **[17]**, and Turkey **[19]**.

The differences in comorbidities were studied between both groups. While male SLE patients tended to have a higher rate of diabetes and hypertension, females had higher incidence of dyslipidemia. However, in both cases, the difference was not statistically significant. Males tended to have more Avascular necrosis (AVN) than females which may be explained by the higher disease activity and thus requiring more aggressive treatment. This treatment may mean a higher corticosteroid dose and corticosteroids are known to be implicated in the pathogenesis of AVN **[14]**. None of our male SLE patients had osteoporosis (OP). It is worth noting that we do not do a routine dual-energy x-ray absorptiometry (DEXA) scan for our patients, so this result is not really accurate. OP is a silent disease, and a diagnosis could only be made with DEXA results **[29]**. Osteoporosis is a major comorbidity in SLE, it has been extensively studied in female SLE. It is established that male SLE had a higher incidence rate of OP compared to controls of same age **[30]**, yet the gender difference in OP shows conflicting results. Though, a large population study from UK showed that osteoporosis in female SLE has a higher incidence rate than male **[31]**, another study from UK showed a higher relative risk of clinical fracture in male SLE patients than in female SLE patients (adjusted relative risk 1.91 vs. 1.18), although statistical significance was not found **[32]**.

SLEDAI score was compared at baseline and at last visit. It was found that there was no difference in baseline SLEDAI between male and female lupus groups, yet SLEDAI at last visit was higher in male lupus patients than female lupus correspondents.

While the comparison of clinical features between females and males with systemic lupus may be heavily studied in literature, the gender difference in disease activity was sparsely investigated.

Some reports showed a higher disease score in males **[28,33]**, others showed no difference **[14,15]**.

This conflicting result is mostly due to the difference in study designs and the disease activity score measured. While some reports used SLEDAI, others used disease scores as the British Isles Lupus Assessment Group index (BILAG) and Systemic Lupus Activity Measure (SLAM). We used SLEDAI at baseline and at last visit. Other reports used a mean SLEDAI, or a random visit SLEDAI. This point of conflict should be addressed in a more accurate approach.

The use of mean SLEDAI is not appropriate as the mean should not be compared if the corresponding values are not normally distributed. Disease activity should be compared at a determined point in the disease course which should be unified in the two studied groups.

Regarding the damage score, SLICC DI was higher in male SLE patients in our cohort. Several previous studies showed the same result **[5,15,34]**. Many factors influence damage scores in SLE patients **[35]**. Damage consistently progresses with time, moreover, ethnicity and types of organs involved affect damage occurrence and progression **[36]**.

Nevertheless, male gender is considered a predictor of accelerated damage regardless of ethnicity and duration **[37]**.

Mortality in male SLE was higher in our study and several other studies **[34,38,39]**. Taking in consideration that male patients had a more severe disease, higher renal predilection and higher damage indexes, the higher risk of mortality is not much of a surprise given the fact that damage gives a predictive value of mortality **[40]**.

Differences between the current study and other studies demonstrating worldwide male and female lupus differences are shown in (Table 6).

Still, gender difference in SLE clinical presentations, activity and damage need to be more validated in large studies with adjustments in other parameters that may affect results such as disease duration and ethnicity.

The present study is the first study from Egypt addressing the gender difference in males and females with a relatively large number of patients and comparing clinical, serological, disease activity, damage indices and mortality. Limitations include that the nature of the retrospective study forced us to have some missing data especially in serological findings.

Male lupus patients remain an interesting area of study and a mystery which rheumatologists around the world thrive to uncover. After many years of analyzing and debating whether there is a real different entity of lupus in males or only a more severe version, these questions are still unanswered. The cause behind the difference is another story. Further studies are needed to answer the unsettling question why males seem to be protected from lupus but if they are affected, their disease may be worse than females.

Table (6): Literature review of Male/Female lupus studies.

Study	Number of males/ females	Mean age in years in males	Country	Ethnicity	Study design	Clinical manifestations increased in males	Clinical manifestations decreased in males	Immunological profile increased in males	Immunological profile decreased in males
Font et al., (1992)[117]	30/231	34+79 months	Barcelona	Spanish	Cohort	Discoid lesions, subacute cutaneous lupus, serositis	Malar rash, arthritis		
Specker et al., (1994)[121]	21/82		Germany	White	Cross-sectional	Cardiac involvement, renal involvement, endstage renal disease, thromboembolic complications,		Elevated IgG-anti-cardiolipin antibodies	
Molina et al., (1996)[126]	107/1209	26 (at diagnosis)	Mexico	Colombians Mexicans	Cross sectional	Renal involvement, nephrotic syndrome, vascular thrombosis	Raynaud's	anti-dsDNA	
Mok et al., (1999[114]	51/201	31(at onset)	China	Chinese	Cross sectional	Renal impairment, cardiovascular damage	Alopecia, Raynaud's, Renal impairment		anti-Ro
Keskin et al., (2000)[119]	30/100	36.9	Turkey	Turkish	Cross sectional	Arthritis, hepatomegaly, pericarditis	Alopecia, photosensitivity, skin lesions, Raynaud's		
Prete et al., (2001)[141]	2188/426	55.5		White, AA, Hispanic	Retrospective	Older age at onset	Thyroid disease		
Aranow et al., (2002)[120]	18/36	37.3	New York, America	White AA	Case-control	Cerebritis, deep venous thrombosis,		Positive anticardiolipin antibodies	
Voulgari et al., (2002)[113]	68/421	43.1	Greece	Greek	Cohort	Serositis, discoid lesions, renal involvement	Malar rash, Raynaud's, Photosensitivity, muscosal ulcers, involvement anemia, leukopenia, thrombocytopenia		Increased ESR, positive anti-Ro and anti-La
Chang et al. (1998)[142]	72/0	34±16	Taiwan	Chinese	Cohort retrospective	Renal disease, photosenstivity, malar rash	Arthritis, lymphadenopathy		

Table (6): Cont.

Study	Number of males/ females	Mean age in years in males	Country	Ethnicity	Study design	Clinical manifestations increased in males	Clinical manifestations decreased in males	Immunological profile increased in males	Immunological profile decreased in males
Garcia et al., (2005)[115]	123/1091	29.2 (at diagnosis)	Latin America	White, AA, Mestizo	Prospective cohort	Fever, weight loss, hypertension, renal disease, hemolytic anemia		IgG anticardiolipin, low C3	
Andrade et al., (2007)[111]	63/555	37±14.9	United states of America	White, AA, Hispanic	Cohort	Lupus nephritis	Arthritis	LAC	
Mongkoltanatus et al., (2008) 143]	37/72	34.6	Thailand	Thai	Case-control	Renal insufficiency, Thrombocytopenia	Alopecia, arthralgia,Raynaud's, psychosis		
Stefanidou et al., (2011)[112]	59/535	34 (median age at diagnosis)	Greece	Greek	Cohort	Thromboses,nephropathy, strokes, gastrointestinal tract symptoms, antiphospholipid syndrome, tendonitis, myositis, infections	Photosensitivity, Raynaud's, arthralgia, hair loss,		
de Carvalho et al., (2010)[128]	11/70	35.1±11.9	Brazil	Hispanic, Black	Retrospective case-control study	Higher level of serum Cr Increased frequency of high Cr, hematuria, Higher activity index of lupus nephritis	Cutaneous involvement Hematologic involvement		
Soto et al., (2004) 144]	33/158	31	Mexico	Mestizo	Retrospective case-control study	Renal disease, renal failure Discoid lupus, pericarditis, psychosis Lymphopenia, thrombocytopenis	Alopecia, Raynaud's, malar rash	Anti-Sm, Anti-U1RNPn, hypocomplementemia (CHSO% hemolytic test)	False positive VDRL test
Hwang et al., (2015)[15]	53/150	32.9±13.6 (at diagnosis)	Korea	Korean	Retrospective case-control study	Renal disease, dialysis Higher damage score indicated by SLICC/ACR DI Higher mean dose of glucocorticoid	Discoid rash, alopecia, Leukopenia		

Table (6): Cont.

Study	Number of males/ females	Mean age in years in males	Country	Ethnicity	Study design	Clinical manifestations increased in males	Clinical manifestations decreased in males	Immunological profile increased in males	Immunological profile decreased in males
Tan et al., (2012)**[134]**	157/1822	47.3±13.7	United states of America	White, AA	Cohort	Lymphopenia, thrombocytopenia, renal involvement, thrombotic events, and hypertension, higher disability, older age of onset	Malar rash, photosensitivity, oral ulcer, alopecia, RP, and arthralgias	Positive anti-Sm, direct Coombs test, LAC, low C3, and anti-dsDNA.	
Cerevera et al., (2013)**[145]**	39/373	32.6±13.0 (at diagnosis)	France, Germany, Italy, Spain and the UK	Black African, Caucasian	Retrospective cohort	Renal involvement, disease damage, pulmonary damage			
Cooper et al., (2002)**[146]**	25/240	46.2 (14.5) (at diagnosis)	Eastern and central North Carolina and South Carolina.	AA, White, native Americans, Asians, and Hispanics	Case-control study	Proteinuria and hematologic disorders (leukopenia, lymphopenia and thrombocytopenia) w			
Yan et al., (2012)**[147]**	58/458	27.2 (at onset)	China	Chinese	Retrospective cohort study	Rash, higher disease activity	Arthritis	Anti-Sm, anti-Ro, anticardiolipin antibody, and decreased C3 levels	
Jacobsen et al. (1998)**[148]**	59/454		Denmark	Danish	Multicenter series	Nephropathy, end stage kidney disease, serositis	Photosensitivity		
Feng et al. (2010)**[149]**	176/1,614		China	Chinese	Retrospective	Serositis, pleuritis and discoid rash	Malar rash, alopeciaand oral ulcers		Anti-SSA and anti-SSB antibodies
Renau and Isenberg (2012)**[150]**	45/439	30.9 years ±15.6	United Kingdom	Caucasian, Afro Caribbean, South Asian, Chinese andmixed ethnicities	Retrospective		Oral ulcers		Ig M ACA
Crosslin and Wiginton (2011)**[151]**	1412 /13,417		Texas			Greater disease severity, cardiovascular and renal comorbidities			

Table (6): Cont.

Study	Number of males/ females	Mean age in years in males	Country	Ethnicity	Study design	Clinical manifestations increased in males	Clinical manifestations decreased in males	Immunological profile increased in males	Immunological profile decreased in males
RiverosFrutos et al. (2017) **[39]**	353/ 3298	38.7 years ±17.2	Spain	Caucasoid, Mestizosand Afro-Americans	Cross-sectional	Early diagnosis, cardiovascular co-morbidities, loss of weight, lymphadenopathies and splenomegaly, pleural fibrosis, pulmonary embolism, lupus nephritis, deep venous thrombosis, seizures	Inflammatory rash, alopecia, and arthritis, Raynaud's		Anti-Ro
Shaharir et al. (2019) **[52]**	59/418		Malaysia	Malay, Chinese, Indian and Others	Cross sectional	Nephritis	Musculoskeletal manifestations, organ damage, cardiovascular damage, renal damage		Anti-Ro
The current study	58/501	40.3±14.4	Egypt	Africans	Retros-pective	Serositis, constitutional manifestations, hematological manifestations lupus nephritis, renal failure, disease activity, disease damage	Osteoporosis	Anti-DNA	

Conclusion: Gender differences exist between male and female SLE patients regardless of ethnic, age and duration variabilities with tendency towards more active disease, higher accumulated damage, and higher mortality in males with SLE.

Conflict of interest: None.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References

1- GHEITA T.A., NOOR R.A., ABUALFADL E., ABOUSEHLY O.S., EL-GAZZAR I.I., EL SHEREEF R.R., et al.: Adult systemic lupus erythematosus in Egypt: The nation-wide spectrum of 3661 patients and world-wide standpoint. Lupus, Aug. 30 (9): 1526-35, 2021.

2- TEDESCHI S.K., BERMAS B. and COSTENBADER K.H.: Sexual disparities in the incidence and course of SLE and RA. Clin. Immunol., 149 (2): 211-8, 2013.

3- MOKBEL A., GEILAN A.M. and ABOELGHEIT S.: Could women with systemic lupus erythematosus (SLE) have successful pregnancy outcomes? Prospective observational study. Egypt Rheumatol., 35 (3): 133-9, 2013.

4- ZANDMAN-GODDARD G., PEEVA E. and SHOENFELD Y.: Gender and autoimmunity. Autoimmun Rev., 66: 366-72, 2007.

5- HWANG J., LEE J., AHN J.K., PARK E.J., CHA H.S. and KOH E.M.: Clinical characteristics of male and female korean patients with systemic lupus erythematosus: A comparative study. Korean J. Intern. Med., 30 (2): 242-9, 2015.

6- HOCHBERG M.C.: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Vol. 40, Arthritis and rheumatism. United States, p. 1725, 1997.

7- WEENING J.J., D\TEXTQUOTERIGHT AGATI V.D., SCHWARTZ M.M., SESHAN S.V., ALPERS C.E., APPEL G.B., et al.: The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited. J. Am. Soc. Nephrol., 15 (2): 241-50, 2004.

8- TARWATER K.: Estimated glomerular filtration rate explained. Mo. Med., 108 (1): 29-32, 2011.

9- BOMBARDIER C., GLADMAN D.D., UROWITZ M.B., CARON D., CHANG C.H., AUSTIN A., et al.: Derivation of the SLEDAI. A disease activity index for lupus patients. Arthritis Rheum Off J. Am. Coll. Rheumatol., 35 (6): 630-40, 1992.

10- GLADMAN D., GINZLER E., GOLDSMITH C., FORTIN P., LIANG M., SANCHEZ-GUERRERO J., et al.: The development and initial validation of the systemic lupus international collaborating clinics/American college of rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum., Mar. 1; 39 (3): 363-9, 1996.

11- ANDRADE R.M., ALARCÓN G.S., FERNÁNDEZ M., APTE M., VILÁ L.M. and REVEILLE J.D.: Accelerated

damage accrual among men with systemic lupus erythematosus XLIV. Results from a multiethnic US cohort. Arthritis Rheum., 56 (2): 622-30, 2007.

12- STEFANIDOU S., BENOS A., GALANOPOULOU V., CHATZIYANNIS I., KANAKOUDI F., ASLANIDIS S., et al.: Clinical expression and morbidity of systemic lupus erythematosus during a post-diagnostic 5-year follow-up: A male: female comparison. Lupus, 20 (10): 1090-4, 2011.

13- VOULGARI P.V., KATSIMBRI P., ALAMANOS Y. and DROSOS A.A.: Gender and age differences in systemic lupus erythematosus. A study of 489 greek patients with a review of the literature. Lupus, 11 (11): 722-9, 2002.

14- MOK C.C., LAU C.S., CHAN T.M. and WONG R.W.S.: Clinical characteristics and outcome of southern Chinese males with systemic lupus erythematosus. Lupus, 8 (3): 188-96, 1999.

15- GARCIA M.A., MARCOS J.C., MARCOS A.I., PONS-ESTEL B.A., WOJDYLA D., ARTURI A., et al.: Male systemic lupus erythematosus in a Latin-American inception cohort of 1214 patients. Lupus, 14 (12): 938-46, 2005.

16- GAMAL S.M. and ABDEL-LATIF M.I.A.: Sex differences in the immune profile and its relation to clinical manifestations in systemic lupus erythematosus patients. J. Egypt Women's Dermatologic Soc., 11 (2), 2014.

17- FONT J., CERVERA R., NAVARRO M., PALLARES L., LOPEZ-SOTO A., VIVANCOS J., et al.: Systemic lupus erythematosus in men: Clinical and immunological characteristics. Ann. Rheum. Dis., 51 (9): 1050-2, 1992.

18- MILLER M.H., UROWITZ M.B., GLADMAN D.D. and KILLINGER D.W.: Systemic lupus erythematosus in males. Medicine (Baltimore), Sep.62 (5): 327-334, 1983.

19- KESKIN G., TOKGÖZ G., DÜZGÜN N., DUMAN M., KINIKLI G., OLMEZ U., et al.: Systemic lupus erythematosus in Turkish men. Vol. 18, Clinical and experimental rheumatology. Italy, p. 114-5, 2000.

20- ARANOW C., DEL GUIDICE J., BARLAND P. and WEINSTEIN A.: Systemic lupus erythematosus disease severity in men and women: A case-control study. J. Rheumatol., 29 (8): 1674-7, 2002.

21- SPECKER C., BECKER A., LAKOMEK H.J., BACH D. and GRABENSEE B.: [Systemic lupus erythematosus in men-a different prognosis?]. Z Rheumatol., 53 (6): 339-345, 1994.

22- LU L.J., WALLACE D.J., ISHIMORI M.L., SCOFIELD R.H. and WEISMAN M.H.: Review: Male systemic lupus erythematosus: A review of sex disparities in this disease. Lupus, 19 (2): 119-29, 2010.

23- CHANG D-M., CHANG C-C., KUO S-Y., CHU S-J. and CHANG M-L.: Hormonal profiles and immunological studies of male lupus in Taiwan. Clin. Rheumatol., 18 (2): 158-62, 1999.

24- CHAGNON P., SCHNEIDER R., HÉBERT J., FORTIN P.R., PROVOST S., BELISLE C., et al.: Identification and characterization of an Xp22.33; Yp 11.2 translocation causing a triplication of several genes of the pseudoautosomal region 1 in an XX male patient with severe systemic lupus erythematosus. Arthritis & Rheum., 54 (4): 1270-8, 2006.

25- WALLACE D.J.: A reason for the rarity of male lupus. Lupus, Jan. 1; 7 (1): 60, 1998.

26- MOLINA J.F., DRENKARD C., MOLINA J., CARDIEL M.H., URIBE O., ANAYA J-M., et al.: Systemic Lupus Erythematosus in Males A Study of 107 Latin American Patients. Medicine (Baltimore), 75 (3), 1996.

27- MOMTAZ M., FAYED A., WADIE M., GAMAL S.M., GHONIEM S.A., SOBHY N., et al.: Retrospective analysis of nephritis response and renal outcome in a cohort of 928 Egyptian lupus nephritis patients: A university hospital experience. Lupus, 26 (14): 1564-70, 2017.

28- De CARVALHO J.F., Do NASCIMENTO A.P., TESTA-GROSSA L.A., BARROS R.T. and BONFÁ E.: Male gender results in more severe lupus nephritis. Rheumatol. Int., 30 (10): 1311-5, 2010.

29- RALSTON S.H. and FRASER J.: Diagnosis and management of osteoporosis. Practitioner., Dec. 259 (1788): 15-9, 2, 2015.

30- KIM C.S., HAN K-D., JUNG J.H., CHOI H.S., BAE E.H., MA S.K., et al.: Incidence and risk factors for osteoporotic fractures in patients with systemic lupus erythematosus versus matched controls. Korean J. Intern. Med., 2019/06/26. Jan. 36 (1): 154-63, 2021.

31- REES F., DOHERTY M., GRAINGE M., LANYON P., DAVENPORT G. and ZHANG W.: Burden of Comorbidity in Systemic Lupus Erythematosus in the UK, 1999-2012. Arthritis Care Res., 68 (6): 819-27, 2016.

32- BULTINK I.E.M., HARVEY N.C., LALMOHAMED A., COOPER C., LEMS W.F., VAN STAA T.P., et al.: Elevated risk of clinical fractures and associated risk factors in patients with systemic lupus erythematosus versus matched controls: A population-based study in the United Kingdom. Osteoporos Int. J. Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA, Apr. 25 (4): 1275-83, 2014.

33- MUÑOZ-GRAJALES C., GONZÁLEZ L.A., ALARCÓN G.S. and ACOSTA-REYES J.: Gender differences in disease activity and clinical features in newly diagnosed systemic lupus erythematosus patients. Lupus, 25 (11): 1217-23, 2016.

34- TAN T.C., FANG H., MAGDER L.S. and PETRI M.A.: Differences between male and female systemic lupus erythematosus in a multiethnic population. J. Rheumatol., 39 (4): 759-69, 2012.

35- GHEITA T.A., FAWZY S.M., NOUR EL-DIN A.M. and EL-FISHAWY H.S.: Juvenile and adult onset systemic lupus erythematosus outcome in Egyptian patients. Egypt Rheumatol., 33 (2): 99-105, 2011.

36- BONAKDAR Z.S., MOHTASHAM N. and KARIMIFAR M.: Evaluation of damage index and its association with risk factors in patients with systemic lupus erythematosus. J. Res. Med. Sci., 16 (SPEC. ISSUE): 427-33, 2011.

37- SUTTON E.J., DAVIDSON J.E. and BRUCE I.N.: The Systemic Lupus International Collaborating Clinics (SLICC) damage index: A systematic literature review. Semin Arthritis Rheum., 43 (3): 352-61, 2013.

38- REES F., DOHERTY M., GRAINGE M.J., LANYON P., DAVENPORT G. and ZHANG W.: Mortality in systemic lupus erythematosus in the United Kingdom 1999-2012. Rheumatol (United Kingdom), 55 (5): 854-60, 2016.

39- RIVEROS FRUTOS A., CASAS I., RÚA-FIGUEROA I., LÓPEZ-LONGO F.J., CALVO-ALÉN J., GALINDO M., et al.: Systemic lupus erythematosus in Spanish males: A study of the Spanish Rheumatology Society Lupus Registry (RELESSER) cohort. Lupus, 26 (7): 698-706, 2017.

40- NIVED O., JÖNSEN A., BENGTSSON A.A., BENGTSSON C. and STURFELT G.: High predictive value of the Systemic Lupus International Collaborating Clinics / American College of Rheumatology damage index for survival in systemic lupus erythematosus. J. Rheumatol., 29 (7): 1398-400, 2002.

41- PRETE P.E., MAJLESSI A., GILMAN S. and HAMIDEH F.: Systemic lupus erythematosus in men: A retrospective analysis in a Veterans Administration Healthcare System population. JCR J. Clin. Rheumatol., 7 (3): 142-50, 2001.

42- CHANG D.M., CHANG C.C., KUO S.Y., CHU S.J. and CHANG M.L.: The clinical features and prognosis of male lupus in Taiwan. Lupus, 7 (7): 462-8, 1998.

43- MONGKOLTANATUS J., WANGKAEW S., KASITANON N. and LOUTHRENOO W.: Clinical features of Thai male lupus: An age-matched controlled study. Rheumatol. Int., 28 (4): 339-44, 2008.

44- SOTO M.E., VALLEJO M., GUILLÉN F., SIMÓN J.A., ARENA E. and REYES P.A.: Gender impact in systemic lupus erythematosus. Clin. Exp. Rheumatol., 22 (6): 713-21, 2004.

45- CERVERA R., DORIA A., AMOURA Z., KHAMASHTA M., SCHNEIDER M., GUILLEMIN F., et al.: Patterns of systemic lupus erythematosus expression in Europe. Autoimmun Rev., 13 (6): 621-9, 2014.

46- COOPER G.S., PARKS C.G., TREADWELL E.L., ST CLAIR E.W., GILKESON G.S., COHEN P.L., et al.: Differences by race, sex and age in the clinical and immunologic features of recently diagnosed systemic lupus erythematosus patients in the southeastern United States. Lupus, 11 (3): 161-7, 2002.

47- YAN D., JING H.E., GUO J-P., DAI Y., CHUN L.I., MIN F., et al.: Gender differences are associated with the clinical features of systemic lupus erythematosus. Chin. Med. J. (Engl), 125 (14): 2477-81, 2012.

48- JACOBSEN S., PETERSEN J., ULLMAN S., JUNKER P., VOSS A., RASMUSSEN J.M., et al.: A multicentre study of 513 Danish patients with systemic lupus erythematosus. I. Disease manifestations and analyses of clinical subsets. Clin. Rheumatol., 17 (6): 468-77, 1998.

49- FENG J.B., NI J.D., YAO X., PAN H.F., LI X.P., XU J.H., et al.: Gender and age influence on clinical and laboratory features in Chinese patients with systemic lupus erythematosus: 1,790 cases. Rheumatol. Int., 30 (8): 1017-23, 2010.

50- RENAU A.I. and ISENBERG D.A.: Male versus female lupus: A comparison of ethnicity, clinical features, serology and outcome over a 30 year period. Lupus, 21 (10): 1041-8, 2012.

51- CROSSLIN K.L., WIGINTON K.L.: Sex differences in disease severity among patients with systemic lupus erythematosus. Gend Med., 8 (6): 365-71, 2011.

52- SHAHARIR S.S., KADIR W.D.A., NORDIN F., BAKAR F.A., TING M.W.H., JAMIL A., et al.: Systemic lupus erythematosus among male patients in Malaysia: How are we different from other geographical regions? Lupus, 28 (1): 137-44, 2019.

الذئبة الحمراء فى الذكور المصريين: دراسة السمات السريرية، والأمصال، والنتائج، ومراجعة الأدبيات

الذئبة الحمراء هو مرض من أمراض المناعة الذاتية الذى يصيب النساء أكثر من الذكور فى أغلب الأحوال.

هدف الدراسة: هو دراسة الاختلاف بين الجنسين فى مرض الذئبة الحمراء بين مجموعة موحدة من نفس العرق فيما يتعلق بالمظاهر السريرية، والأمراض المصاحبة، ونشاط المرض، والأضرار، والوفيات.

المواد والطرق: تم إجراء دراسة بأثر رجعى على ٥٥٩ مريضاً مصاباً بمرض الذئبة الحمراء (٥٨ ذكور و ٥٠١ إناث) فى قسم أمراض الروماتيزم وإعادة التأهيل بكلية الطب بمستشفيات جامعة القاهرة.

شملت الدراسة مقارنة البيانات الديموغرافية للمرضى، المظاهر السريرية، الفحوصات المخبرية، حالات الأمراض المزمنة المصاحبة والأدوية المتلقاة بالإضافة إلى مؤشر نشاط مرض الذئبة الحمراء. وقد وجد أن الأعراض العامة، وإلتهاب الأغشية، وإلتهاب الكلية الذئبى، والفشل الكلوى، وإيجابية الأجسام المضادة للحمض النووى أعلى فى ذكور مرضى الذئبة الحمراء كما كانت الاضرار المتراكمة والوفيات أعلى فى الذكور عن الاناث.