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Review Article

An Overvriew of Systemic Lupus Erythematosus (SLE) Screening, Prevalence and Incidence

Muhhammad Mahmood Akhtar[1]*, Fayez Mubarak Albishi[2], Ibraheem Abdulrahman Alhabeeb[3], Ziyad Mohammed Al-Rawiyah[2], Ahmad Zuhair Abid[4], Yousof Osama Rayes[5], Ahmed Mohammed Al-Asmari[2], Moneer Dhafir Alqashaneen[2], Ghaida Ali Aljdhaa[2], Ahmad Mohamad Almohamady[6], Rawan Maatouk Kheimi[7] and Israa Musaddif Salman[7]

[1]*Department of Internal Medicine, East Jeddah General Hospital, Jeddah, Saudi Arabia*

[2]*College of Medicine, King Khalid University, Abha, Saudi Arabia*

[3]*College of Medicine, Qassim University, Qassim, Saudi Arabia*

[4]*College of Medicine, University of Jeddah, Jeddah, Saudi Arabia*

[5]*College of Medicine, King Abdulaziz University, Rabigh, Saudi Arabia*

[6]*College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia*

[7]*College of Medicine, Ibn Sina National College, Jeddah, Saudi Arabia*

***Corresponding Author:** Muhhammad Mahmood Akhtar, Department of Internal Medicine, East Jeddah General Hospital, Jeddah, Saudi Arabia.

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Abstract

The systemic lupus erythematosus (SLE) is a prototype autoimmune disease with serious possible consequences. We performed an extensive literature search of the Medline, Cochrane, and EMBASE databases. Papers discussing the prevalence and incidence of SLE were screened for relevant information. There were no limits on date, language, age of participants or publication type. The occurrence of SLE is strongly related to gender, race, age at disease onset and socioeconomic class. There was a wide variation in both the incidence and prevalence of SLE in different countries. Moreover, gender showed significant differences with females have much higher rates compared to males.

Keywords: *Systemic Lupus Erythematosus; SLE; Incidence; Prevalence*

Introduction

The systemic lupus erythematosus (SLE) is a prototype autoimmune disease in which disturbance in the immune system precedes the clinical disease by years and wide autoantibody and immune complex production eventually lead to organ damage [1]. The science is far from understanding the immunopathology of SLE, but steps forward have been made especially in the roles of genetics, epigenetics, immune signaling and associated accelerated atherosclerosis [2,3]. The increased knowledge of the disturbances in the immune system has connected many risk factors like sunlight exposure and fluctuation of female hormone levels to disease development at a theoretical level [2,4].

The disease course is heterogeneous and individual, and the diagnosis is often challenging. The recognition of the disease has been improved by the autoantibody testing and updated classification criteria [5,6]. Earlier diagnosis is thought to pick up milder cases, but also lead to better prognosis of the disease [7-9]. Although workability levels and the life expectancy of SLE patients are shown to be inferior to the general population [10,11], the efficacy of early scheduled diagnosis and treatment has yet to be clarified in high-quality studies [8,9,12]. Multidimensional disease features make it difficult to create therapeutic agents or a uniform treatment strategy. Most of

the drugs used in therapy have been either designed for or used first in the treatment of rheumatoid arthritis [13]. The data on strategies in initial drug therapy is almost lacking [12,14,15].

The incidence and prevalence figures are dependent on the method of identification, classification and study [16]. In general, studying the entire population is not possible, and the studies are based on samples of the population. The clinical picture of SLE is not always clear at the onset of the first signs of the disease [1].

Aim of the Study

The aim of the current study to give an overview of the prevalence and incidence of SLE.

Methods

We performed an extensive literature search of the Medline, Cochrane, and EMBASE databases on 14 December 2019 using the medical subject headings (MeSH) terms (systemic lupus erythematosus [MeSH Terms]) AND (incidence [MeSH Terms]) OR (prevalence [MeSH Terms]). Papers discussing the prevalence and incidence of SLE were screened for relevant information. There were no limits on date, language, age of participants or publication type.

Incidence and prevalence of SLE

The occurrence of SLE is strongly related to gender, race, age at disease onset and socioeconomic class [17,18]. Because twin studies on SLE patients have reported a higher concordance in monozygotic contrast to dizygotic twins [19], genetic factors most likely influence the incidence of SLE. SLE is more prevalent in females. About 80 - 90% of the patients are females [16]. This preponderance is already seen in children, although not as strongly as in adults [20]. The impact of race on the epidemiology of SLE is hard to separate from socioeconomic factors [18]. Age at disease onset varies between races.

In people of African- American background, SLE is 2 to 4 more prevalent than in white people and the highest peaks of incidence are seen in females at childbearing age. In contrast, in Europe, the highest incidence rates in females are reported after 40 years of age. The antinuclear antibody (ANA) testing and improved classification criteria enable more precise case ascertainment nowadays [18,21]. The division of SLE patients into adults and children by the age differs between studies [22]. SLE in children is not as common as in adults but is more aggressive already at diagnosis [22,23].

The worldwide prevalence of SLE

The worldwide prevalence of SLE is summarized in table 1 [24-26]. There was wide variation with the highest reported prevalence was zero among 847 individuals in a study conducted in Yarrabah, North Queensland, Australia [27]. In contrast, the highest reported prevalence was 241 per 100,000 people; according to a national survey in the USA [28].

The worldwide incidence of SLE

The worldwide prevalence of SLE is summarized in table 2 [24-26]. Like in incidence, there was a wide variation with the highest incidence reported in North America of 23.2 per 100,000 people [29] and the lowest report was Africa of 0.3 per 100,000 person-years [30] and Ukraine pf 0.3 per 100,000 person-years [31].

Gender variations in prevalence and incidence of SLE

The reported incidence and prevalence of SLE in females found to be higher than males [32-36]. In the USA, the reported age-adjusted incidence in White females found to be 8.8 to 14.5 times higher compared to males [33,37]. In the same context, the age-adjusted incidence of SLE in females was 7.8 to 14.8 higher in females compared to males of East Asia [36-39] (Table 3).

Continent	Country	Source	Study period	Region	Case-finding method	Prevalent cases	Prevalence, per 100,000 (95% CI) [year of study]
Europe	Denmark	Voss., *et al.*	1 January 1995	Funen	Hospital and community records	84	22.2[a]
		Laustrup., *et al.*	1 January 2003	Funen	Hospital and community records	109	28.3 (23.3, 34.2)
		Eaton., *et al.*	31 October 2006	National	National hospital patient registry	–	48
		Hermansen., *et al.*	31 Decmeber 2011	National	National hospital patient registry	1887	45.2 (43.3, 47.4)
	Finland	Helve	December 1978	National	National hospital discharge database	1427	28
	France	Arnaud., *et al.*	2010	National	National Health Insurance database	27 369	40.8[a]
	Germany	Brinks., *et al.*	2002	National	National Health Insurance database	845	36.7 (34.3, 39.3)
	Greece	Alamanos., *et al.*	31 December 2001	North-West	Hospital records	193	38.1 (36.3, 39.9)[a]
		Anagnostopoulos., *et al.*	2008	Central	Postal survey	2	110 (110, 370)
	Iceland	Gudmundsson., *et al.*	1975–84	National	Hospital registers	86	35.9[a]
	Italy	Benucci., *et al.*	June 2002	Florence	Community survey	23	71 (49, 92)[a]
		Govoni., *et al.*	2002	Ferrara	Hospital records	201	57.9
		Sardu., *et al.*	July 2009	Southern Sardinia	Community records	–	81 (50, 124)
		Tsioni., *et al.*	31 December 2012	Valtrompia	Hospital and community records	44	39.2 (28.5, 52.6)
	Lithuania	Dadoniene., *et al.*	2004	Vilnius	Hospital records and community survey	76	16.2 (12.7, 20.3)
	Norway	Nossent	1996	North	Hospital records	89	49.7 (44.3, 55)[a]
		Eilertsen., *et al.*	2007	North	Hospital records	114	64.1
		Lerang., *et al.*	1 January 2008	Oslo	Hospital records	238	52.8 (45.2, 58.4)
	Spain	López., *et al.*	31 December 2002	Asturias	Hospital records	367	34.1 (30.6, 37.6)
		Gómez., *et al.*	December 2003	Asturias	Hospital records	–	31.7 (28.3, 35.0)
		Alonso., *et al.*	31 December 2006	Lugo	Hospital records	150	17.5 (12.6, 24.1)[a]
	Sweden	Leonhardt	1955	Malmö	Hospital records	–	2.9
			1958				4.5
			1961				6.0
		Nived., *et al.*	31 December 1982	Lund and Orup	Hospital and community records	61	39 (30, 48)
		Ståhl-Hallengren., *et al.*	31 December 1986	Lund and Orup	Hospital and community records	121	42
			31 December 1991			162	68
		Simard., *et al.*	1 January 2010	National	National patient register	7929	(46, 85)
		Ingvarsson., *et al.*	31 December 2006	Lund and Orup	Hospital and community records	174	65
	Turkey	Çakır., *et al.*	–	Havsa	Community survey	10	57 (46, 70)[a]
	UK	Hochberg	1981–82	Whole UK	Community medical record survey	20	6.5
		Samanta., *et al.*	1986–89	Leicester	Hospital records	50	26.1
		Hopkinson., *et al.*	30 April 1990	Nottingham	Hospital records	147	24.6 (20.6, 28.7)[a]
		Johnson., *et al.*	1992	Birmingham	Hospital records	242	27.7 (24.2, 31.2)
		Gourley., *et al.*	1 August 1993	Northern Ireland	Hospital records	408	25.4 (22.1, 28.7)[a]
		Nightingale., *et al.*	1992–98	Whole UK	CPRD	1538	25.0 (23.4, 26.7) [1992]
							40.7 (37.6, 43.8) [1998]
		Rees., *et al.*	1999–2012	Whole UK	CPRD	1875	65.0 (62.1, 67.9) [1999][a]
						4413	97.0 (94.2, 99.9) [2012][a]

North America	Canada	Peschken., *et al.*	1996	Manitoba	Medical records	257	22.1 (13.2, 32.4)
		Bernatsky., *et al.*	2003	Quebec	Physician billing and hospitalization databases	3825	44.7 (37.4, 54.7)[a]
		Fatoye., *et al.*	2000-2015	Alberta	Multiple population-based data sources	1442	48
	USA	Siegel., *et al.*	1959	New York	Hospital records	–	5
		Fessel	1973	San Francisco	Hospital records	64	50.8
		Serdula., *et al.*	1975	Oahu, Hawaii	Hospital records	81	15.3[a]
		Michet., *et al.*	1 January 1980	Minnesota	Hospital records	20	40.0 (23.5, 57.5)
		Uramoto., *et al.*	1 January 1993	Minnesota	Hospital records	–	122 (97, 217)[a]
		Maskarinec., *et al.*	1989	Hawaii		454	41.8
		Post., *et al.*	1996	California	Postal survey	20	68.2
		Balluz., *et al.*	1997	Arizona	Hospital and community records	20	103 (56, 149)
		Ward	1988–94	National	US National health survey	40	241 (130, 352)
		Naleway., *et al.*	2001	Wisconsin	Medical records	64	78.5 (59.0, 98.0)[a]
		Chakravarty., *et al.*	2000	California and Pennsylvania	Hospitalization databases	–	California: 107.6 (106.1, 109.2)[a]
							Pennsylvania: 149.5 (146.9, 152.2)[a]
		Feldman., *et al.*	2000–04	National	Medicaid database	34339	143.7 (142.2, 145.3)
		Furst., *et al.*	2003–08	National	Medical claims database	15396	81.1 (78.5, 83.6) [2003]
							102.9 (100.4, 105.5) [2008]
		Lim., *et al.*	2002	Georgia	Georgia Lupus registry	1156	73.0 (68.9, 77.4)[a]
		Somers., *et al.*	2002–04	Michigan	Medical records	2139	72.8 (70.8, 74.8)[a]
		Jarukitsopa., *et al.*	1 January 2006	Rochester, MN	Rochester epidemiology project database	72	53.5 (41.1, 65.9)
Central America	Caribbean	Nossent	1 January 1990	Curaçao	Medical records	69	47.6 (34.1, 51.1)
		Deligny., *et al.*	1999	Martinique	Medical records	245	64.2 (56.2, 72.2)
		Molina., *et al.*	2003	Puerto Rico	Private health insurance database	877	159
		Reyes-Llerena., *et al.*	–	Havana, Cuba	WHO-ILAR COPCORD study	2	60 (10, 200)
		Flower., *et al.*	31 October 2009	Barbados	National hospital-based SLE registry	226	84.1 (73.5, 95.8)
	Mexico	Peláez-Ballestas., *et al.*	–	Five regions in Mexico	WHO-ILAR COPCORD study	–	60 (30, 100)[a]
South America	Argentina	Scolnik., *et al.*	1 January 2009	Buenos Aires	Private medical care database	75	58.6 (46.1, 73.5)
	Brazil	Rodrigues Senna., *et al.*	–	Montes Claros City	WHO-ILAR COPCORD study	3	98 (20, 280)
	Venezuela	Granados., *et al.*	2011	Monagos	WHO-ILAR COPCORD study	3	70 (10, 200)

Asia	China	Wigley., *et al*.	–	North (near Beijing)	WHO-ILAR COPCORD study	North: 3	10
				South (near Shantou)		South: 1	20
		Li., *et al*.	–	Beijing	Community survey	3	30 (0, 60)
	India	Malaviya., *et al*.	–	Delhi	Community survey	3	3.2 (0, 6.86)
	Iran	Davatchi., *et al*.	September 2005	Tehran city	WHO-ILAR COPCORD study	3	40
		Davatchi., *et al*.	September 2006	Five villages in NW Iran	WHO-ILAR COPCORD study	1	60 (6, 670)
	Kazakhstan	Nasonov., *et al*.	31 December 2010	Semey	Hospital records	52	17.3 (12.9, 22.6)[a]
	Malaysia	Wang., *et al*.	1974–90	Kuala Lumpur	Hospital records	539	43
	Pakistan	Farooqi., *et al*.	–	North	WHO-ILAR COPCORD study	1	50
	Russia	Nasonov., *et al*.	31 December 2010	Kursk and Yaroslavl	Hospital records	79	7.7 (6.1, 9.7)[a]
	South Korea	Ju., *et al*.	2004–06	National	National Health Insurance database	9000–11000	18.8, 21.7
		Shim., *et al*.	2006–10	National	National Health Insurance database	10080	20.6 (20.2, 21.0) [2006]
						13316	26.5 (26.0, 27.0) [2010]
		Bae., *et al*.	2005-15	National	National Health Insurance database	14049	35.5 (34.93–35.96) [2015]
	Taiwan	Chou., *et al*.	–	Cu-Tien	Community survey	1	33
		Chiu., *et al*.	2000–07	National	National Health Insurance database	15463	42.2 [2000]
							67.4 [2007]
		Kang., *et al*.	31 December 2005	National	National Health Insurance database	15753	69.3
		Yu., *et al*.	2000	National	National Health Insurance database	356	37.0 (10.0, 41.0)
		Yeh., *et al*.	2003	National	Catastrophic illness database	133488	97.5
			2008				
		See., *et al*.	2005	National	National Health Insurance database	435	43.5 (39.4, 47.6)
	Ukraine	Nasonov., *et al*.	31 December 2010	Vinnitsa	Hospital records	45	12.2 (8.9, 16.4)[a]
Australasia	Australia	Anstey., *et al*.	1January 1991	Northern Territory.	Hospital records	22	52
		Grennan., *et al*.	1993	Queensland Sydney	Hospital records	Queensland: 20	89
						Sydney: 3	13
		Bossingham	1 August 1996 to 31 August 1998	Far North Queensland	Hospital records	108	45.3
		Minaur., *et al*.	January 2002	Yarrabah, North Queensland	WHO-ILAR COPCORD study	0	0
	New Zealand	Meddings., *et al*.	–	Dunedin	Hospital records	16	14.7
		Hart., *et al*.	1980	Auckland	Hospital records	136	17.6[a]

Table 1: *Worldwide prevalence of SLE.*

a: Age standardized. CPRD: UK Clinical Practice Research Datalink.

Continent	Country	Source	Region	Case-finding method	Number of incident cases	Incidence per 100,000 person-years (95% CI) [study year]
Europe	Denmark	Voss., *et al*.	Funen	Hospital and community records	127	1.0 (0.3, 2.9)[a] [1980]
						3.6 (2.0, 6.1)[a] [1994]
		Laustrup., *et al*.	Funen	Hospital and community records	35	1.0 (0.3, 2.7)
		Hermansen., *et al*.	National	National patient registry	1644	2.35 (2.24, 2.49)
	France	Arnaud., *et al*.	National	National health insurance database	1931	3.32
	Finland	Elfving., *et al*.	Northern Savo	Hospital and community records	7	3.6 (3.0, 4.2)[a]
	Greece	Alamanos., *et al*.	North-west	Hospital records	178	1.9 (1.5, 2.3)[a]
	Iceland	Gudmundsson., *et al*.	National	Hospital registers	76	3.3
	Italy	Govoni., *et al*.	Ferrara	Hospital records	2000: 7	2.0
					2001: 4	1.2
					2002: 9	2.6
		Tsioni., *et al*.	Valtrompia	Hospital and community records	9	2.0 (0.9, 3.8)
	Norway	Nossent	North	Hospital records	83	2.9 (2.4, 3.3)[a]
		Eilertsen., *et al*.	North	Hospital records	58	3.0 (2.0, 4.0)
		Lerang., *et al*.	Oslo	Hospital records	116	3.0 (2.4, 3.5)
	Spain	López., *et al*.	Asturias	Hospital records	116	2.2 (1.8, 2.5)
		Gómez., *et al*.	Asturias	Hospital records	–	1.9 (1.1, 2.7)
		Alonso., *et al*.	Lugo	Hospital records	150	3.6 (3.0, 4.2)[a]
	Sweden	Leonhardt	Malmö	Hospital records	16	1.0[a]
		Eyrich., *et al*.	Halmstad	Hospital records	41	1.8 [1957, 1964]
						3.0 [1964, 1971]
		Jonsson., *et al*.	Lund and Orup	Hospital and community records	39	4.0 (1.6, 6.4)[a]
		Ståhl-Hallengren., *et al*.	Lund and Orup	Hospital and community records	41	4.8
		Ingvarsson., *et al*.	Lund and Orup	Hospital and community records	55	2.8 (1.4, 4.2)
	UK	Hopkinson., *et al*.	Nottingham	Hospital records	23	4.0 (2.3, 5.6)[a]
		Johnson., *et al*.	Birmingham	Hospital records	33	3.8 (2.5, 5.1)
		Nightingale., *et al*.	Whole UK	CPRD	390	3.0 (2.7, 3.3)
		Somers., *et al*.	Whole UK	CPRD	1638	4.7 (4.5, 4.9)[a]
		Rees., *et al*.	Whole UK	CPRD	2740	4.9 (4.7, 5.1)
North America	Canada	Bernatsky., *et al*.	Quebec	Physician billing database	219	3.0 (2.6, 3.4)
				Hospitalization database	203	2.8 (2.6, 3.0)
	USA	Siegel., *et al*.	New York and Alabama	Hospital records	New York: 98	1.9
					Alabama: 63	1.0
		Fessel	San Francisco	Hospital records	74	7.6
		Hochberg	Baltimore	Hospital records	302	4.6[a]
		Michet., *et al*.	Minnesota	Hospital records and death certificates	25	1.8 (1.1, 2.5)[a]
		McCarty., *et al*.	Pennsylvania	Community and hospital records	191	2.4 (2.1, 2.8)[a]
		Uramoto., *et al*.	Minnesota	Hospital records	48	5.6 (3.9, 7.2)[a]
		Naleway., *et al*.	Wisconsin	Medical records	44	5.1 (3.6, 6.6)[a]
		Feldman., *et al*.	Whole US	Medicaid database	3490	23.2 (22.4, 24.0)
		Furst., *et al*.	Whole US	Medical claims database	1557	7.2 (6.8, 7.7)[a]
		Lim., *et al*.	Georgia	Georgia Lupus registry	267	5.6 (5.0, 6.3)[a]
		Somers., *et al*.	Michigan	Medical records	399	5.5 (5.0, 6.1)[a]
		Jarukitsopa., *et al*.	Minnesota	Rochester epidemiology project database	45	2.9 (2.0, 3.7)

Central America	Caribbean	Nossent	Curaçao	Medical records	68	4.6 (0.4, 8.8)
		Deligny., *et al*.	Martinique	Medical records	180	4.7 (2.5, 6.9)
		Flower., *et al*.	Barbados	National hospital-based SLE registry	183	6.3 (5.4, 7.3)[a]
South America	Argentina	Scolnik	Buenos Aires	Private medical care database	68	6.3 (4.9, 7.7)
	Brazil	Pereira Vilar., *et al*.	Natal city	Hospital records	43	8.7 (6.3, 11.7)
		Nakashima., *et al*.	Cascavel	Medical records	14	4.8
Africa	Zimbabwe	Taylor., *et al*.	Bulawayo and Harare	Hospital records	22	0.3
Asia	China	Mok., *et al*.	Hong Kong	University hospital data-base	–	3.1
	Kazakhstan	Nasonov., *et al*.	Semey	Hospital records	4	1.3 (0.4, 3.4)[a]
	Russia	Nasonov., *et al*.	Kursk and Yaroslavl	Hospital records	12	1.2 (0.6, 2.1)[a]
	Ukraine	Nasonov., *et al*.	Vinnitsa	Hospital records	1	0.3 (0.0, 1.5)[a]
	South Korea	Shim., *et al*.	National	National Health Insurance database	1398	2.8 (2.7–2.9)[a]
	Taiwan	Chiu., *et al*.	National	National Health Insurance database	12 789	8.1
		Kang., *et al*.	National	National Health Insurance database	758	3.3
		Yu., *et al*.	National	National Health Insurance database	671	8.4 (7.7, 9.0)
		Yeh., *et al*.	National	Catastrophic illness database	6675	4.9
		See., *et al*.	National	National Health Insurance database	358	7.2 (6.5, 8.0)
Australasia	Australia	Anstey., *et al*.	Northern Territory	Hospital records	13	11

Table 2: *Worldwide incidence of SLE.*

a: Age standardized. CPRD: UK Clinical Practice Research Datalink.

Source	Country	Year	Definition of SLE	Characteristics of study group	Incidence (per 100,000 person-years)	Prevalence (per 100, 000 persons)
Uramoto., *et al*.	United States (Minnesota)	1950–1979	ACR-82 criteria	Overall	1.51	NA
				Females	2.47	NA
				Males	0.5	NA
	United States (Minnesota)	1980–1992	ACR-82 criteria	Overall	5.56	NA
				Females	9.4	NA
				Males	1.54	NA
Lim., *et al*.	United States (Georgia)	2002–2004	ACR-97 criteria	All population	5.6	73
				Females	9.2	127.6
				Males	1.8	14.7
				White People	2.7	32.7
				Females	4.7	59
				Males	0.7	7.5
				Black People	8.7	118.5
				Females	13.4	196.2
				Males	3.2	23.7
Somers., *et al*.	United States (Michigan)	2002–2004	ACR-97 criteria	All population	5.5	72.8
				Female population	9.3	128.7
				Male population	1.5	12.8

Dall'Ella., *et al*.	United States (California)	2007–2009	ACR-97 criteria	All population	4.6	NA
				Females	8.6	NA
				Males	0.7	NA
				White People	2.8	NA
				Females	5.3	NA
				Males	0.6	NA
				Black People	15.5	NA
				Females	30.5	NA
				Males	2.1	NA
				Asian /Pacific Americans	4.1	NA
				Females	7.2	NA
				Males	0.6	NA
Izmirly., *et al*.	United States (New York)	2007–2009	ACR-97 criteria	Overall	4.6	62.2
				Females	7.9	107.4
				Males	1	12.5
	United States (New York)	2007–2009	SLICC	Overall	6.2	73.8
				Females	10.3	128.3
				Males	1.7	13.8
Barnabe., *et al*.	Canada	1994–2007	Diagnosed in clinical setting (ICD-9, ICD-10)	Females	NA	27.3
				Males	NA	3.2
				First Nations females	NA	32.2
				First Nations males	NA	3.2
				non-First Nations females	NA	27.1
				non-First Nations males	NA	3.2
Somers., *et al*.	United Kingdom	1990–1999	Clinical Practice Research Datalink (CPRD)	All population	4.87	NA
				Females	8.01	NA
				Males	1.6	NA
Rees., *et al*.	United Kingdom	1999–2012	Clinical Practice Research Datalink (CPRD)	All population	4.91	64.6–97.0
				Female population	8.34	NA
				Male population	1.44	NA
Arnaud., *et al*.	France	2010	Diagnosed in clinical setting (ICD10)	All population	3.32	47
				Females	5.51	79.1
				Males	0.92	11.8
Zou., *et al*.	China	2009–2010	Diagnosed by rheumatologists (ACR-97 criteria)	All population	NA	37.6
				Females	NA	70.3
				Males	NA	6.4
Yu., *et al*.	Taiwan	2000–2008	Diagnosed in clinical setting (ICD9)	All population	8.4	37
				Females	15	66.6
				Males	1.9	8.5
Shim., *et al*.	South Korea	2009	Diagnosed (ACR-criteria) (ICD10)	All population	2.8	24.9
				Females	5.1	42.9
				Males	0.6	7
Yamamoto., *et al*.	Japan	1972–1983	Diagnosed by a rheumatologist (ACR criteria)	All population	2	NA
				Females	3.7	NA
				Males	0.25	NA
Ohno., *et al*.	Japan	1992	Diagnosed in clinical setting (ACR-82 criteria)	All population	NA	29.1
				Females	NA	52.3
				Males	NA	5
Iseki., *et al*.	Japan	1972–1991	ACR-82 criteria	All population	3	NA
				Females	1.6–4.7	6.6–68.4
				Males	0.4–0.8	0.8–7.0

Table 3: *Incidence and prevalence of SLE in females and males*

NA: not available.

Conclusion

The SLE is very serious with multiple complications. The disease prevalence and incidence is highly variable among different geographic areas. Moreover, it is a higher prevalence in females compared to males.

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Conflicts of Interest

No conflicts related to this work.

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