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# The Burden of Various Comorbid Conditions at Initial Presentations of Systemic Lupus Erythematosus population

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## ABSTRACT

**Introduction:** Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that has various manifestations among different populations.

**Aim:** We aimed to study the various medical comorbidities associated with SLE at the time of presentation as per Rheumatologist review.

**Methods:** This is a retrospective analysis using patients' registry medical information system. All patients diagnosed with SLE were reviewed by accessing their medical records and laboratory results of investigations at the Royal hospital from 2006 to 2014. The following comorbidities were analyzed: diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, lung disease, cardiovascular disease (CVD), cerebrovascular accident (CVA), chronic kidney disease (CKD), end-stage kidney disease (ESKD), infections, thyroid disease, malignancy, and miscarriages.

**Results:** There were 966 patients diagnosed with SLE during the period from 2006 to 2014. The mean (SD) of age at presentation was 35.5 (11.5) years. Most patients were female (88.7 %) with mean age of 27.6 (1.4) years. Majority of the patients 786 (81.4%) were in the age group 18-45 years old, 40 (4.7%) patients were in age group 0-17years, 109 (11.2 %) patients were in age group 46-60 years, and 26 patients in age group >60 years.

At presentation, 30% had neuropsychiatry disorders, 24.5% had HTN, 19.1% hyperlipidemia, 12.2% miscarriages, 12.0 % with thyroid disease, 10.0% CVD, 5.81 % with DM, 5 % CVA, 4.07 % CKD, 2.8 % with ESKD, 2.5 % with lung disease, 1.49% with infections and 0.53% with malignancy.

**Conclusion:** SLE patients have a great burden of various medical co-morbidities at time of diagnosis and hence may present with CVD, stroke, CKD, ESKD and even requiring renal replacement therapy at initial encounter with health-care professionals. Strengthen health system at primary level and education of public and health work force is the main challenge to further reduce the risk of these comorbidities and the consequences.

**Keywords:** Systemic lupus erythematosus, Lupus erythematous, Comorbidities, Diagnosis, Diseases burden

## Introduction

Health inequalities are defined as "differences in the incidence, prevalence, mortality and burden of diseases and other adverse health conditions that exist among specific population groups" (National Institutes of Health [1]. Among rheumatic diseases, systemic lupus erythematosus (SLE) has one of the uppermost health discrepancy rates between populations and even among certain groups of a population [2-4] and as per LUMINA cohort, it is a disease that more severely affects disadvantaged minority population groups [5]. Hence, SLE is a complex chronic autoimmune disease with variable clinical presentations, with complex interaction and association with socioeconomic and demographic features, that is characterized by fluctuating disease activity and multiorgan involvement [6,7].

Epidemiological studies on the prevalence of SLE show a wide

range across different racial populations (21.7 to 124 per 100,000 population), that possibly related to variability in genetic and environmental factors [4,6,8]. The disease may present with acute, severe, and serious symptoms, or present as a fluctuating and chronic process that impacts several systems [7]. Lately, the survival of SLE patients had increased because of improved awareness, early diagnosis, augmented immunosuppressants and better-quality management of associated complications [4,8,9]. This improvement highlights the importance of treating comorbidities that accompany the disease or its treatment [7,9,10]. Furthermore, the known comorbidities that are associated with the disease itself and the side effects of therapy are considered as independent risk factors for morbidity and mortality [7].

SLE is categorized as a "B-cell disease. The flowing and floating lymphocytes in the blood of SLE patients show a Th2-similarform; however, Th1 lymphocytes and interferon (IFN)-γ have been verified to be an imperative for SLE pathogenesis [7,11-14]. However, chemokines and cytokines, such as interleukin (IL)-6, B lymphocyte stimulator, IL-17, type I IFNs, tumor necrosis factor (TNF)-α, and Th1 chemokines play central role in the pathogenesis of SLE. These cytokines and or chemokines are important in the arrangement, development, distinction, and initiation of several immune competent cells, that facilitate the indigenous inflammation and yield the tissue damage and injury at numerous body organs [7,11-14]. SLE causing damage that is defined as "an irreversible change in an organ or system that has occurred since the onset of SLE" [15-19]. The management of patients with SLE is aimed not just at instantaneous control of disease activity, but also at the preclusion of organ damage from various treatment modalities and associated comorbidities [6,15,20-23]. These damages of various end organs may be subtle at initial presentations but tend to progress, unless managed appropriately by multidisciplinary team of specialized clinicians [15]. In addition, studies among middleeast populations are rare, and hence we conducted this study to know the pattern and comorbidity at the time of diagnosis of SLE.

## Materials and Methods

Thiscross-sectional, of one single evaluation of each patientthat was based on data collected from Oman health information system (alshifaa system) which was launched in 2006.The Royal hospital (RH) is the main tertiary care hospital for rheumatology, majority of SLE patients are referred to RH from different parts of the country for clinical diagnosis, laboratory investigations and management.SLE diagnosis was based on the American College of Rheumatology classification criteria; ACR97; (which includes the clinical manifestation and laboratory evidence) [24]. Rheumatologist reviewed all these cases at time of diagnosis. To assure all enrollees fulfilled accurate diagnostic criteria, all laboratory tests for autoantibodies were reviewed to cross reference with the ICD classifications as obtained from medical records.

The following comorbidities were analyzed: diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, lung disease, cardiovascular disease (CVD), cerebrovascular accident (CVA), chronic kidney disease (CKD), end-stage kidney disease (ESKD), infections, thyroid disease, malignancy, and miscarriages. Demographic parameters (age and gender), the different co-morbidities, medications used, and laboratory data were collected from the systems for each patient at time of initial encounter. Stata for Windows (version 13) was used for statistical analyses.

## Results

There were 966 patients diagnosed with SLE during the period from 2006 to 2014. Mean (SD) age at presentations was 35.5 (11.5) years. The majority of patients were female which constitute 88.7 % of the total SLE patients) with mean age 27.6 (1.4) years.

Majority of the patients 786 (81.4%) were in the age group 18-45 years old (Figure 1), 40 patients (4.7%) in age group 0-17years, 109 (11.2 %) patients were in age group 46-60 years, and 26 patients in age group >60 years.

At presentation, 24.5% had HTN, 19.1% hyperlipidemia, 12.2%had miss-carriages, 12.0% had thyroid diseases, 10.0% CVD, 5.81% with DM, 5% CVA, 4.07% CKD, 2.8% with end stage kidney disease (ESKD), 2.5% with lung disease, 1.49 % with infections and 0.53% with malignancy, as shown in Table 2 and Figure 2.

Neuropsychiatric disorders including seizure, stroke, psychosis, mood and cognitive disorders, were present in 30% in patients at initial SLE presentation.

## Discussion

The present study showed that patients having significant proportion of medical comorbidities at the time of diagnosis with SLE, with a mean age of 35.5 (11.5) years. The majority (almost 90%) were young females with an average age of 27 years. Patients were suffering from various clinical manifestations and medical comorbidities with many laboratory abnormalities. These include DM, HTN, thyroid disorders, hyperlipidemia and end organ dysfunction such as CKD, CVA and CVD. These comorbidities at time of diagnosis may be a manifestation of various genetic, environmental and socioeconomic factors [25-28].

Reviewing studies from the same regions revealed similar female to male ratio of 9:1 in a Saudi study. Their mean age (±SD) were 25.3±10.5 for male and 28.5±10.9 years for female, with highest occurrence in the 20–30-year age group [29]. In Kuwait, a study reported 98 females and 10 males diagnosed as SLE, with a median age of 31.5years [30] and another study from Lebanon of 86 females and 14 male's patients with SLE, reported a median age of 26 years [31].

Internationally, the RELESSER Registry, which is a Spanish Nationwide Study, reported a median age of 34.6 years [32]. Others found that among 4,863 residents of British Columbia, Canada, with SLE, 86% were female with mean age of 48.9 years [33]. They reported the age-, sex-, and entry time-matched hazard rations (HRs) for myocardial infarction (MI), stroke, and CVD were highest during the first year after SLE diagnosis: 5.63 (95% CI 4.02-7.87), 6.47 (95% CI 4.42-9.47), and 6.28 (95% CI 4.83-8.17), respectively [33]. McCormick et al. [34] found that even years before diagnosis, SLE patients incur significantly elevated direct medical costs compared with the age- and sex-matched general population, for hospitalizations, outpatient care, and medications.

The present study found that almost six percent of patients have DM at the time of diagnosis of SLE. The co-existence of DM and SLE is a well-known phenomenon [35-37]. Chronic inflammation and oxidative stress in SLE may contribute to insulin resistance as part of autoimmune disorder, which is a significant module of DM [38,39]. Anti-insulin antibodies and chronic inflammation were

associated with hyperinsulinemia and insulin resistance and may account for the development of DM in SLE patients [40-42]. An animal mouse model of SLE suggested with insulin resistance and dysglycemia [43]. A recent study found that SLE group bi-hormone dysglycemic abnormality with amplified insulin resistance and high glucagon serum level in spite of normal glucose tolerance, preserved skeletal muscle GLUT-4 translocation and normal beta cell function [44]. Furthermore, SLE patients who are nondiabetic have signs of reduction in sensitivity to insulin [38]. Similarly, these non- diabetic patients have an increase prevalence of the metabolic syndrome up to an almost one fifth [38]. Later, as SLE progress and managed, insulin resistance and the adverse effects of immunosuppressive therapy might worsen the diabetes and its complications. Finally, SLE patients would have at least 5-fold higher risk to develop DM [40,42].

In the present study, one quarter of participants had high BP at initial presentation and diagnosis of SLE. HTN is highly co-exist among SLE population, and the immune system autoimmunity is a crucial aspect in the HTN development in laboratory-mouse-model of SLE [45-47] and that neuroimmune pathway has possible importance in the HTN development and kidney injury [45-47]. Researchers found that impaired kidney hemodynamic function, peripheral vascular function, amplified oxidative stress, and changed inflammatory cytokine production contribute to HTN in a well-known laboratory-mouse-model of SLE and hence, the autoreactive B cells and pathogenic autoantibodies mechanistically lead to the HTN pathogenesis in SLE [45,46]. They concluded that adaptive immune system dysfunction associates with HTN and that both specific activating autoantibodies and circulating antibodies to nuclear antigens correlate with BP rise in SLE patients [48,49] and suggested that creation of autoantibodies by plasma cells mechanistically leads to autoimmune-associated hypertension. Arterial HTN is reported to burden up the majority of SLE patients, especially with disease progression, and contributes significantly to augmented rise of atherosclerosis and hence increased CVD risk [50]. Therefore, research data suggest that SLE population have an increased CVD risks, recommending stringent and strict BP tight control of top priority management strategy SLE population [50].

Atherosclerosis is more frequently noted in the elderly general population whereas young women are normally group free from atherosclerosis, in part because of the protective effects of estrogen. However, in SLE, young women have increased-incidence of CVD, which is ascribed to SLE itself. In addition, hyperlipidemia, hypoalbuminemia and high blood pressure along with hypercoagulable state and associated vasculitis all play additive risk in rising the morbidity risk of CVD. In the present study, hyperlipidemia was present in almost one fifth of participants at the time of SLE diagnosis. This is in support of reported risk of atherosclerosis occurring more often among SLE patients than in the general population and advances more rapidly especially if inflammation is not well controlled [51].

Lupus patients have a higher burden of traditional CVD risk factors compared with the general population, a risk that is 2 to 10 times that of the general population, with a greater increase in relative risk generally observed in younger patient groups traditional CVD risk factors [4,52-54]. The global prevalence of CVD events in RELESSER Registry cohort was 7.4% since SLE diagnosis [55-58] and 7% in the LUMINA cohorts [59,60]. However, our study reported a higher percentage of 10% even at initial presentation at time of diagnosis. This is consistent with other European [55,58] and American cohorts [5,58,60], the frequencies of which ranged from about 9.0% to almost 20.0%.This supports the fact that lupus patients have a higher risk of accelerated atherosclerosis, comparable to that of diabetes patients, even, after controlling for traditional risk factors, individuals with SLE are at increased risk for CVD when aortic stiffness was evaluated by MRI [61]. Inflammation and autoimmune disorders seems to play an important non-traditional risk factor for CVD [62-64]. In some patients with lupus, MI may develop even before the diagnosis of SLE or shortly thereafter, suggesting that there may be a link between autoimmune inflammation and atherosclerosis [13].

The Hopkins Lupus Cohort reported that the utmost significant demographic-predictors of damage-progression were diagnosis at older age, race, ethnicity and low income [65,66]. Low income causing malnutrition, limited access to quality care and poor compliance with medication were reported as the socioeconomic status variable associated with high risk for CVD among SLE population [66]. The increased risk of progression of SLE in non-Caucasians could be attributed to by other risk markers such as income, high blood pressure and urinary protein [65]. Furthermore, researchers of Disease activity (SELENA-SLEDAI) reported a higher degree of damage progression [21,24,67,68].

End organ damage can be enhanced by co-existence of several predisposing factors. In our study, SLE patients have other risk factors for development of CKD including diabetes, hypertension and hyperlipidemia [69-71]. Jiang et al. [69] concluded that SLE population diagnosed with DM has a significantly higher risk to develop ESKD. In our study almost 7% have CKD and ESKD at initial presentation. It has been reported that around 10% to 30% of patients with severe lupus nephritis end up with ESKD within 15 years of diagnosis [72]. In developed countries, the 5, 10, and 15years incidences of ESKD in patients with lupus nephritis were reported as 11%, 17% and 22%, respectively [73]. A prospective cohort study demonstrated that insulin resistance was associated with a rapid decline in kidney function and SLE patients with DM may represent higher insulin resistance and more comorbidities, which predisposes them to develop ESKD [69,71].

In the present study, neuropsychiatry disorders were present in 30% at time of initial presentation of SLE. The occurrence of neuropsychiatric appearances varies regionally and internationally world-wide [2,29-31,74]. Regionally, studies from Saudi, Kuwait and Lebanon reported neuropsychiatry disorders in 26%, 23% and 19%, retrospectively. These findings are lower than what we reported. The diagnosis of, especially primary, manifestations are difficult, as both focal and diffuse manifestations may occur primary. Many researchers have labeled autoantibodies and cytokines as possible mediators, affecting cerebral vasculature, and/or interfering with neuronal connectivity [7,14]. International inception cohort by Hanly et al. [75] reported a 28% of SLE patients suffered at least 1 neuropsychiatric manifestation about the time of diagnosis and the existence of neuropsychiatric manifestation was linked with decreased quality of life and augmented organ damage [75]. A meta-analysis study found that CNS findings included: headache (12.2%), mood disorders (7.4%), seizures (7.0%), cognitive dysfunction (6.6%), and cerebrovascular disease (5.0%) and other syndromes arisen in less than 5% of the SLE population [74].

Our data showed that there is quite a high risk of infections and malignancy at time of diagnosis of SLE. The Spanish Rheumatology Society Lupus Registry studied a total of 3658 SLE patients and found that a total of 705 (19.3%) patients suffered ≥1 severe infection [32,57,58]. Also, they found that the time from first infection to second infection was significantly shorter than time from diagnosis to first infection ($p < 0.000$). They reported that respiratory infections were the most common (35.5%) but bloodstream infections were the most frequent cause of mortality by infection (42.0%) [32,57,58].

Cao et al. [76] analyzed 59,662 SLE patients, where malignancy was associated with SLE with higher incidence of lymphoproliferative and leukemic cancers, as well as and some non-hematologic malignancies and thyroid malignancies. They reported that the pooled RRs were 1.28 (95% CI, 1.17–1.41) for global cancer risk [76]. A multisite international SLE cohort concluded that there is small increase in risk of cancer overall in SLE compared to general population, but this risk is in early life even in childhood group [77-79] and risk would be further increased as these patients enter adulthood life and with disease progression.

The present study found that 12% of participants have thyroid disease at initial time of SLE diagnosis. A study from Kuwait found that subclinical hypothyroidism was present in13.3% of SLE patients and all were females. They found that overt hypothyroidism was present in 8.3% of SLE patients whereas biochemical hyperthyroidism was seen in 5% of SLE patients. They reported euthyroid sick syndrome in 16.7% of SLE patients and thyroid autoantibodies in 18.3% of SLE patients [80]. A study retrospectively analyzed in 1,006 Chinese SLE patients reported subclinical hypothyroidism in10.04% compared to 0.91–6.05% in general population. lupus nephritis (LN) was associated with higher incidence of subclinical hypothyroidism (13.4% in SLE with LN vs 7.3% in SLE without LN ($P = 0.001$) [81]. In multivariate analysis in a case-control study, SLE was associated with hypothyroidism (OR = 2.644, 95% CI, 2.405–2.908) [82]. Five thousand and eighteen patients with SLE and 25,090 age- and sex-matched controls were evaluated for thyroid dyfunctions. The risk of hypothyroidism in SLE patients was increased with respect to the prevalence in controls (15.58 and 5.75%, respectively, $P < 0.001$) [83].

The respiratory system can be affected by the inflammatory process of SLE, where the pleura, airways, parenchyma, vascular, and respiratory muscles could be involved [84-87]. The prevalence of various respiratory abnormalities varies among populations and races [88,89]. Pleuritis was present in 45% of patients with chronic SLE and in 3% of the initial manifestations [50,87,90,91]. Also, it has been reported that sterile pleural effusion and pneumonia, which is usually due to infection are the most common respiratory manifestations in SLE patients [56,85-87]. In addition, interstitial lung disease (ILD) occurred in variable number depending on duration of SLE but about 3% to just below 10% of patients tend to be symptomatic [87,92,93], they are found more commonly in late-onset SLE [94], where the rates are more than doubled [87,92-94] and could be even associated with malignancy [93]. However, lung function studies, have revealed an increase of abnormalities even in the absence of clinically apparent lung disease or by high resolution CT scan [95]. Furthermore, researchers even reported other manifestations such as volume restriction, decreased compliance, reduced diffusion capacity, and hyperventilation with arterial hypoxia at rest or during exercise [96]. In addition, myopathy may lead to dysfunction of the diaphragm and other respiratory muscles in patients with SLE [84,87,97]. The present study found that pulmonary lung disease occurred in 2.5% of SLE patients at time of initial presentation. This is a modest percentage but with longitudinal follow up for a decade or more it would increase significantly if the inflammatory process is not adequately controlled, as recent studies implicated plasma IL6 in the development of pulmonary manifestations and its importance in the pathogenesis of local inflammation and tissue damage [7].

SLE, both lupus nephritis and anti-phospholipid antibodies, increases the risks for maternal hypertension and premature births [98]. In the present study, miss-carriages was present in 12.2% of participants at the time of diagnosis of SLE. However, the risk of miscarriage may be dependent on disease duration and various organ involvement [98], a study of the rate of pregnancy loss in patients with active nephritis was reported to be as high as 60% [99], but recent data have shown improved outcomes, including recently quoted live birth rates in majority of pregnancies [100].

The results of this study are limited by the retrospective analysis of data that was dependent on the accurate entry and coding of patient data into the alshifaa databases, which was collected prospectively.

Although retrospective studies might under estimate the frequency of events, some of these differences are likely due to varying definitions of certain comorbidities, such as CVD events, and due to observation times, our prevalence nonetheless remained relatively high compared to other studies as discussed above. This frequency of comorbidities in our patients presented a high frequency of traditional and non-traditional risk factors, particularly DM, high BP and hyperlipidemia.

Another important limitation concerns the etiologic attribution of events. CV events in SLE, particularly heart failure and rhythm disorders, can be the result of several causes, such as lupus activity, fluid overload, anemia, and others. Nevertheless, in daily clinical practice, it is often not possible to establish the exact etiology of some CV event because of the concurrence of more than one pathogenic mechanism in the same patient.

A further limitation of our study was that we did not include important traditional risk factors, such as obesity, sedentary lifestyle and use of steroids. However, none of our female patients were ever smoker and only few men were smokers. Furthermore, we did not consider 2 subgroups of diabetes (ie, types 1 and 2 diabetes), which in the context of SLE could be totally different.

Finally, the strengths of the present study that it's the only center of all MOH in Oman that do all the laboratory investigations especially the autoantibody screen and hence capture almost all patients. However, another hospital managed SLE cases but with limited number as an educational institute and may be less than 10% of cases [101-104]. In addition, there may be some missing data for potentially confounding variables.

## Conclusion

This study identified various clinically relevant comorbidities that may warrant careful consideration in patients' clinical management. Early risk stratifications of various medical comorbidities at diagnosis should be incorporated into the management of SLE, with goal of protecting whole organs of SLE patients against inflammation, as the disease wane and wax through its natural progression process in association of various postnatal environmental risk factors.

These numerous potentially adjustable risk factors for damage accrual with an integrated and unified approach to manage SLE disease activity contributing to every organ dysfunction. However, with advancement immunosuppressive medications and multidisciplinary team approach management and support, the long-term outcome of these comorbidities is usually favorable.

## References


1. http: //www.niams.nih.gov/About_Us/Mission_and_Purpose/strat_plan_hd.asp
2. Anderson, E., Nietert, PJ., Kamen, DL., Gilkeson, GS. (2008) Ethnic disparities among patients with systemic lupus erythematosus in South Carolina. J Rheumatol, 35(5): 819-825.
3. Arroyo-Avila, M., Santiago-Casas, Y., McGwin G, Jr., Cantor, RS., Petri, M., Ramsey-Goldman, R., et al. (2015) Clinical associations of anti-Smith antibodies in PROFILE: a multi-ethnic lupus cohort. Clin Rheumatol, 34(7): 1217-1223.
4. Scalzi, LV., Hollenbeak, CS., Wang, L. (2010) Racial disparities in age at time of cardiovascular events and cardiovascular-related death in patients with systemic lupus erythematosus. Arthritis Rheum, 62(9): 2767-2775.
5. Alarcon, GS., McGwin G, Jr., Bastian, HM., Roseman, J., Lisse, J., Fessler, BJ., et al. (2001) Systemic lupus erythematosus in three ethnic groups. VII [correction of VIII]. Predictors of early mortality in the LUMINA cohort. LUMINA Study Group. Arthritis Rheum, 45(2): 191-202.
6. Adinolfi, A., Valentini, E., Calabresi, E., Tesei, G., Signorini, V., Barsotti, S., et al. (2016) One year in review 2016: systemic lupus erythematosus. Clin Exp Rheumatol, 34(4): 569-574.
7. Kaul, A., Gordon, C., Crow, MK., Touma, Z., Urowitz, MB., van Vollenhoven, R., et al. (2016) Systemic lupus erythematosus. Nat Rev Dis Primers, 2: 16039.
8. Askanase, A., Shum, K., Mitnick, H. (2012) Systemic lupus erythematosus: an overview. Soc Work Health Care, 51(7): 576-586.
9. Urowitz, MB., Gladman, DD., Tom, BD., Ibanez, D., Farewell, VT. (2008) Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol, 35(11): 2152-2158.
10. Mok, CC. (2016) Treat-to-target in systemic lupus erythematosus: are we there yet? Expert Rev Clin Pharmacol, 9(5): 675-680.
11. McMahon, M., Grossman, J., Skaggs, B., Fitzgerald, J., Sahakian, L., Ragavendra, N., et al. (2009) Dysfunctional proinflammatory high-density lipoproteins confer increased risk of atherosclerosis in women with systemic lupus erythematosus. Arthritis Rheum, 60(8): 2428-2437.
12. Santos, LL., Morand, EF. (2009) Macrophage migration inhibitory factor: a key cytokine in RA, SLE and atherosclerosis. Clin Chim Acta, 399(1-2): 1-7.
13. van Leuven, SI., Franssen, R., Kastelein, JJ., Levi, M., Stroes, ES., Tak, PP. (2008) Systemic inflammation as a risk factor for atherothrombosis.. Rheumatology (Oxford), 47(1): 3-7.
14. Antonelli, A., Ferrari, SM., Giuggioli, D., Ferrannini, E., Ferri, C., Fallahi, P. (2014) Chemokine (C-X-C motif) ligand (CXCL)10 in autoimmune diseases. Autoimmun Rev, 13(3): 272-280.
15. Bertsias, GK., Salmon, JE., Boumpas, DT. (2010) Therapeutic opportunities in systemic lupus erythematosus: state of the art and prospects for the new decade. Ann Rheum Dis, 69(9): 1603-1611.
16. Chang, NH., Li, TT., Kim, JJ., Landolt-Marticorena, C., Fortin, PR., Gladman, DD., et al. (2015) Interferon-α induces altered transitional B cell signaling and function in Systemic Lupus Erythematosus. J Autoimmun, 58: 100-110.
17. Chang, NH., McKenzie, T., Bonventi, G., Landolt-Marticorena, C., Fortin, PR., Gladman, D., et al. (2008) Expanded population of activated antigen-engaged cells within the naive B cell compartment of patients with systemic lupus erythematosus. J Immunol, 180(2): 1276-1284.
18. Landolt-Marticorena, C., Wither, R., Reich, H., Herzenberg, A., Scholey, J., Gladman, DD., et al. (2011) Increased expression of B cell activation factor supports the abnormal expansion of transitional B cells in systemic lupus erythematosus. J Rheumatol, 38(4): 642-651.
19. Nikpour, M., Dempsey, AA., Urowitz, MB., Gladman, DD., Barnes, DA. (2008) Association of a gene expression profile from whole blood with disease activity in systemic lupus erythaematosus. Ann Rheum Dis, 67(8): 1069-1075.
20. Tunnicliffe, DJ., Singh-Grewal, D., Craig, JC., Howell, M., Tugwell, P., Mackie, F., et al. (2017) Healthcare and Research Priorities of Adolescents and Young Adults with Systemic Lupus Erythematosus: A Mixed-methods Study. J Rheumatol, 44(4): 444-451.
21. Bauer, JW., Petri, M., Batliwalla, FM., Koeuth, T., Wilson, J., Slattery, C., et al. (2009) Interferon-regulated chemokines as biomarkers of systemic lupus erythematosus disease activity: a validation study. Arthritis Rheum, 60(10): 3098-3107.
22. Durcan, L., Petri, M. (2016) Why targeted therapies are necessary for systemic lupus erythematosus. Lupus, 25(10): 1070-1079.
23. Conti, F., Ceccarelli, F., Perricone, C., Leccese, I., Massaro, L., Pacucci, VA., et al. (2016) The chronic damage in systemic lupus erythematosus is driven by flares, glucocorticoids and antiphospholipid antibodies: results from a monocentric cohort. Lupus, 25(7): 719-726.
24. Gladman, DD., Urowitz, MB., Goldsmith, CH., Fortin, P., Ginzler, E., Gordon, C., et al. (1997) The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum, 40(5): 809-813.
25. Walsh, BT., Pope, C., Reid, M., Gall, EP., Yocum, DE., Clark, LC. (2001) SLE in a United States-Mexico border community. J Clin Rheumatol, 7(1): 3-9.
26. Walsh, SJ., Algert, C., Rothfield, NF. (1996) Racial aspects of comorbidity in systemic lupus erythematosus. Arthritis Care Res, 9(6): 509-516.
27. Walsh, SJ., DeChello, LM. (2001) Geographical variation in mortality from systemic lupus erythematosus in the United States. Lupus, 10(9): 637-646.
28. Walsh, SJ., Gilchrist, A. (2006) Geographical clustering of mortality from systemic lupus erythematosus in the United States: contributions of poverty, Hispanic ethnicity and solar radiation. Lupus, 15(10): 662-670.
29. Alballa, SR. (1995) Systemic lupus erythematosus in Saudi patients. Clin Rheumatol, 14(3): 342-346.
30. Al-Jarallah, K., Al-Awadi, A., Siddiqui, H., Al-Salim, I., Shehab, D., Umamaheswaran, I., et al. (1998) Systemic lupus erythematosus in Kuwait--hospital based study. Lupus, 7(7): 434-438.
31. Uthman, I., Nasr, F., Kassak, K., Masri, AF. (1999) Systemic lupus erythematosus in Lebanon. Lupus, 8(9): 713-715.
32. Rua-Figueroa, I., Lopez-Longo, FJ., Calvo-Alen, J., Galindo-Izquierdo, M., Loza, E., Garcia de Yebenes, MJ., et al. (2014) National registry of patients with systemic lupus erythematosus of the Spanish Society of Rheumatology: objectives and methodology. Reumatol Clin, 10(1): 17-24.
33. Avina-Zubieta, JA., Vostretsova, K., De Vera, MA., Sayre, EC., Choi, HK. (2015) The risk of pulmonary embolism and deep venous thrombosis in systemic lupus erythematosus: A general population-based study. Semin Arthritis Rheum. 45(2): 195-201.

34. McCormick, N., Marra, CA., Sadatsafavi, M., Avina-Zubieta, JA. (2018) Incremental direct medical costs of systemic lupus erythematosus patients in the years preceding diagnosis: A general population-based study. Lupus, 27(8): 1247-1258.

35. Molina, MJ., Mayor, AM., Franco, AE., Morell, CA., Lopez, MA., Vila, LM. (2007) Prevalence of systemic lupus erythematosus and associated comorbidities in Puerto Rico. J Clin Rheumatol. 13(4): 202-204.

36. Parker, B., Urowitz, MB., Gladman, DD., Lunt, M., Donn, R., Bae, SC., et al. (2015) Impact of early disease factors on metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort. Ann Rheum Dis, 74(8): 1530-1536.

37. Thong, B., Olsen, NJ. (2017) Systemic lupus erythematosus diagnosis and management. Rheumatology (Oxford), 56(suppl_1): i3-i13.

38. El Magadmi, M., Ahmad, Y., Turkie, W., Yates, AP., Sheikh, N., Bernstein, RM., et al. (2006) Hyperinsulinemia, insulin resistance, and circulating oxidized low density lipoprotein in women with systemic lupus erythematosus. J Rheumatol, 33(1): 50-56.

39. El-Magadmi, M., Bodill, H., Ahmad, Y., Durrington, PN., Mackness, M., Walker, M., et al. (2004) Systemic lupus erythematosus: an independent risk factor for endothelial dysfunction in women. Circulation, 110(4): 399-404.

40. Bruce, IN. (2005) 'Not only...but also': factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. Rheumatology (Oxford), 44(12): 1492-502.

41. Escarcega, RO., Garcia-Carrasco, M., Fuentes-Alexandro, S., Jara, LJ., Rojas-Rodriguez, J., Escobar-Linares, LE. et al. (2006) Insulin resistance, chronic inflammatory state and the link with systemic lupus erythematosus-related coronary disease. Autoimmun Rev, 6(1): 48-53.

42. Parker, B., Bruce, I. (2013) SLE and metabolic syndrome. Lupus, 22(12): 1259-1266.

43. Gabriel, CL., Smith, PB., Mendez-Fernandez, YV., Wilhelm, AJ., Ye, AM., Major, AS. (2012) Autoimmune-mediated glucose intolerance in a mouse model of systemic lupus erythematosus. Am J Physiol Endocrinol Metab, 303(11): 1313-1324.

44. Miyake, CNH., Gualano, B., Dantas, WS., Pereira, RT., Neves, W., Zambelli, VO., et al. (2018) Increased Insulin Resistance and Glucagon Levels in Mild/Inactive Systemic Lupus Erythematosus Patients Despite Normal Glucose Tolerance. Arthritis Care Res (Hoboken), 70(1): 114-124.

45. Mathis, KW. (2015) An impaired neuroimmune pathway promotes the development of hypertension in systemic lupus erythematosus. Am J Physiol Regul Integr Comp Physiol, 309(9): 1074-1077.

46. Mathis, KW., Venegas-Pont, M., Flynn, ER., Williams, JM., Maric-Bilkan, C., Dwyer, TM. et al. (2013) Hypertension in an experimental model of systemic lupus erythematosus occurs independently of the renal nerves. Am J Physiol Regul Integr Comp Physiol, 305(7): 711-719.

47. Mathis, KW., Venegas-Pont, M., Masterson, CW., Wasson, KL., Ryan, MJ. (2011) Blood pressure in a hypertensive mouse model of SLE is not salt-sensitive. Am J Physiol Regul Integr Comp Physiol, 301(5): 1281-1285.

48. Taylor, EB., Barati, MT., Powell, DW., Turbeville, HR., Ryan, MJ. (2018) Plasma Cell Depletion Attenuates Hypertension in an Experimental Model of Autoimmune Disease. Hypertension, 71(4): 719-728.

49. Taylor, EB., Ryan, MJ. (2017) Immunosuppression With Mycophenolate Mofetil Attenuates Hypertension in an Experimental Model of Autoimmune Disease. J Am Heart Assoc, 6(3): e005394.

50. Tselios, K., Gladman, DD., Urowitz, MB. (2017) Systemic lupus erythematosus and pulmonary arterial hypertension: links, risks, and management strategies. Open Access Rheumatol, 9: 1-9.

51. Zhang, CY., Lu, LJ., Li, FH., Li, HL., Gu, YY., Chen, SL., et al. (2009) Evaluation of risk factors that contribute to high prevalence of premature atherosclerosis in Chinese premenopausal systemic lupus erythematosus patients. J Clin Rheumatol, 15(3): 111-116.

52. Bultink, IE. (2010) Prospective cohort studies on risk factors for cardiovascular events in systemic lupus erythematosus: a major challenge. Arthritis Res Ther, 12(1): 107.

53. Frostegard, J. (2008) Systemic lupus erythematosus and cardiovascular disease. Lupus, 17(5): 364-367.

54. Scalzi, LV., Bhatt, S., Gilkeson, RC., Shaffer, ML. (2009) The relationship between race, cigarette smoking and carotid intimal medial thickness in systemic lupus erythematosus. Lupus, 18(14): 1289-1297.

55. Fernandez-Nebro, A., Rua-Figueroa, I., Lopez-Longo, FJ., Galindo-Izquierdo, M., Calvo-Alen, J., Olive-Marques, A. et al. (2015) Cardiovascular Events in Systemic Lupus Erythematosus: A Nationwide Study in Spain From the RELESSER Registry. Medicine (Baltimore), 94(29): 1183.

56. Pego-Reigosa, JM., Lois-Iglesias, A., Rua-Figueroa, I., Galindo, M., Calvo-Alen, J., de Una-Alvarez, J., et al. (2016) Relationship between damage clustering and mortality in systemic lupus erythematosus in early and late stages of the disease: cluster analyses in a large cohort from the Spanish Society of Rheumatology Lupus Registry. Rheumatology (Oxford), 55(7): 1243-1250.

57. Riveros Frutos, A., Casas, I., Rua-Figueroa, I., Lopez-Longo, FJ., Calvo-Alen, J., Galindo, M., et al. (2017) Systemic lupus erythematosus in Spanish males: a study of the Spanish Rheumatology Society Lupus Registry (RELESSER) cohort. Lupus, 26(7): 698-706.

58. Rua-Figueroa, I., Fernandez Castro, M., Andreu, JL., Sanchez-Piedra, C., Martinez-Taboada, V., Olive, A., et al. (2017) Comorbidities in Patients With Primary Sjogren's Syndrome and Systemic Lupus Erythematosus: A Comparative Registries-Based Study. Arthritis Care Res (Hoboken), 69(1): 38-45.

59. Pons-Estel, GJ., Gonzalez, LA., Zhang, J., Burgos, PI., Reveille, JD., Vila, LM., et al. (2009) Predictors of cardiovascular damage in patients with systemic lupus erythematosus: data from LUMINA (LXVIII), a multiethnic US cohort. Rheumatology (Oxford), 48(7): 817-822.

60. Toloza, SM., Uribe, AG., McGwin G, Jr., Alarcon, GS., Fessler, BJ., Bastian, HM., et al. (2004) Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXIII. Baseline predictors of vascular events. Arthritis Rheum, 50(12): 3947-3957.

61. Karp, G., Wolak, A., Baumfeld, Y., Bar-Am, N., Novack, V., Wolak, T., et al. (2016) Assessment of aortic stiffness among patients with systemic lupus erythematosus and rheumatoid arthritis by magnetic resonance imaging. Int J Cardiovasc Imaging, 32(6): 935-944.

62. Hannawi, S., AlSalmi, I., Moller, I., Naredo, E. (2017) Uric acid is independent cardiovascular risk factor, as manifested by increased carotid intima-media thickness in rheumatoid arthritis patients. Clin Rheumatol, 36(8): 1897-1902.

63. Hannawi, S., Haluska, B., Marwick, TH., Thomas, R. (2007) Atherosclerotic disease is increased in recent-onset rheumatoid arthritis: a critical role for inflammation. Arthritis Res Ther, 9(6): 116.

64. Hannawi, S., Marwick, TH., Thomas, R. (2009) Inflammation predicts accelerated brachial arterial wall changes in patients with recent-onset rheumatoid arthritis. Arthritis Res Ther, 11(2): 51.

65. Bruce, IN., O'Keeffe, AG., Farewell, V., Hanly, JG., Manzi, S., Su, L., et al. (2015) Factors associated with damage accrual in patients with

systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. Ann Rheum Dis, 74(9): 1706-1713.

66. Maynard, JW., Fang, H., Petri, M. (2012) Low socioeconomic status is associated with cardiovascular risk factors and outcomes in systemic lupus erythematosus. J Rheumatol, 39(4): 777-783.

67. Petri, M., Purvey, S., Fang, H., Magder, LS. (2012) Predictors of organ damage in systemic lupus erythematosus: the Hopkins Lupus Cohort. Arthritis Rheum, 64(12): 4021-4028.

68. Urowitz, MB., Gladman, DD., Ibanez, D., Fortin, PR., Bae, SC., Gordon, C., et al. (2012) Evolution of disease burden over five years in a multicenter inception systemic lupus erythematosus cohort. Arthritis Care Res (Hoboken), 64(1): 132-137.

69. Jiang, MY., Hwang, JC., Feng, IJ. (2018) Impact of Diabetes Mellitus on the Risk of End-Stage Renal Disease in Patients with Systemic Lupus Erythematosus. Sci Rep, 8(1): 6008.

70. Lee, PT., Fang, HC., Chen, CL., Chiou, YH., Chou, KJ., Chung, HM. (2003) Poor prognosis of end-stage renal disease in systemic lupus erythematosus: a cohort of Chinese patients. Lupus, 12(11): 827-832.

71. Plantinga, LC., Drenkard, C., Pastan, SO., Lim, SS. (2016) Attribution of cause of end-stage renal disease among patients with systemic lupus erythematosus: the Georgia Lupus Registry. Lupus Sci Med, 3(1): e000132.

72. Maroz, N., Segal, MS. (2013) Lupus nephritis and end-stage kidney disease. Am J Med Sci, 346(4): 319-323.

73. Tektonidou, MG., Dasgupta, A., Ward, MM. (2016) Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971-2015: A Systematic Review and Bayesian Meta-Analysis. Arthritis Rheumatol, 68(6): 1432-1441.

74. Unterman, A., Nolte, JE., Boaz, M., Abady, M., Shoenfeld, Y., Zandman-Goddard, G. (2011) Neuropsychiatric syndromes in systemic lupus erythematosus: a meta-analysis. Semin Arthritis Rheum, 41(1): 1-11.

75. Hanly, JG., Urowitz, MB., Sanchez-Guerrero, J., Bae, SC., Gordon, C., Wallace, DJ., et al. (2007) Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: an international inception cohort study. Arthritis Rheum, 56(1): 265-273.

76. Cao, L., Tong, H., Xu, G., Liu, P., Meng, H., Wang, J., et al. (2015) Systemic Lupus Erythematous and Malignancy Risk: A Meta-Analysis. PLoS One, 10(4): e0122964.

77. Bernatsky, S., Clarke, AE., Labrecque, J., von Scheven, E., Schanberg, LE., Silverman, ED., et al. (2013) Cancer risk in childhood-onset systemic lupus. Arthritis Res Ther, 15(6): 198.

78. Bernatsky, S., Clarke, AE., Zahedi Niaki, O., Labrecque, J., Schanberg, LE., Silverman, ED., et al. (2017) Malignancy in Pediatric-onset Systemic Lupus Erythematosus. J Rheumatol, 44(10): 1484-1486.

79. Bernatsky, S., Ramsey-Goldman, R., Labrecque, J., Joseph, L., Boivin, JF., Petri, M., et al. (2013) Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun, 42: 130-135.

80. Al-Awadhi, AM., Olusi, S., Hasan, EA., Abdullah, A. (2008) Frequency of abnormal thyroid function tests in Kuwaiti Arabs with autoimmune diseases. Med Princ Pract, 17(1): 61-65.

81. 81. Gao, H., Li, C., Mu, R., Guo, YQ., Liu, T., Chen, S., et al. (2011) Subclinical hypothyroidism and its association with lupus nephritis: a case control study in a large cohort of Chinese systemic lupus erythematosus patients. Lupus, 20(10): 1035-1041.

82. Watad, A., Mahroum, N., Whitby, A., Gertel, S., Comaneshter, D., Cohen, AD., et al. (2016) Hypothyroidism among SLE patients: Case-control study. Autoimmun Rev, 15(5): 484-486.

83. Ong, SG., Choy, CH. (2016) Autoimmune thyroid disease in a cohort of Malaysian SLE patients: frequency, clinical and immunological associations. Lupus, 25(1): 67-74.

84. Hawkins, P., Davison, AG., Dasgupta, B., Moxham, J. (2001) Diaphragm strength in acute systemic lupus erythematosus in a patient with paradoxical abdominal motion and reduced lung volumes. Thorax, 56(4): 329-330.

85. Memet, B., Ginzler, EM. (2007) Pulmonary manifestations of systemic lupus erythematosus. Semin Respir Crit Care Med, 28(4): 441-450.

86. Murin, S., Wiedemann, HP., Matthay, RA. (1998) Pulmonary manifestations of systemic lupus erythematosus. Clinics in Chest Medicine, 19(4): 641-665.

87. Orens, JB., Martinez, FJ., Lynch, JP. 3rd. (1994) Pleuropulmonary manifestations of systemic lupus erythematosus. Rheumatic Diseases Clinics of North America, 20(1): 159-193.

88. Kim, WU., Kim, SI., Yoo, WH., Park, JH., Min, JK., Kim, SC., et al. (1999) Adult respiratory distress syndrome in systemic lupus erythematosus: causes and prognostic factors: a single center, retrospective study. Lupus, 8(7): 552-557.

89. Prabu, A., Patel, K., Yee, CS., Nightingale, P., Situnayake, RD., Thickett, DR., et al. (2009) Prevalence and risk factors for pulmonary arterial hypertension in patients with lupus. Rheumatology (Oxford), 48(12): 1506-1511.

90. Crosslin, KL., Wiginton, KL. (2009) The impact of race and ethnicity on disease severity in systemic lupus erythematosus. Ethn Dis, 19(3): 301-307.

91. Merola, JF., Prystowsky, SD., Iversen, C., Gomez-Puerta, JA., Norton, T., Tsao, P., et al. (2013) Association of discoid lupus erythematosus with other clinical manifestations among patients with systemic lupus erythematosus. J Am Acad Dermatol, 69(1): 19-24.

92. Cheema, GS., Quismorio, FP.Jr. (2000) Interstitial lung disease in systemic lupus erythematosus. Curr Opin Pulm Med, 6(5): 424-429.

93. Park, JK., Yang, JA., Ahn, EY., Chang, SH., Song, YW., Curtis, JR., et al. (2016) Survival rates of cancer patients with and without rheumatic disease: a retrospective cohort analysis. BMC Cancer, 16: 381.

94. Medlin, JL., Hansen, KE., McCoy, SS., Bartels, CM. (2018) Pulmonary manifestations in late versus early systemic lupus erythematosus: A systematic review and meta-analysis. Semin Arthritis Rheum.

95. Lilleby, V., Aalokken, TM., Johansen, B., Forre, O. (2006) Pulmonary involvement in patients with childhood-onset systemic lupus erythematosus. Clin Exp Rheumatol, 24(2): 203-208.

96. Elalouf, O., Fireman, E., Levartovsky, D., Kaufman, I., Rogovski, O., Elkayam, O., et al. (2015) Decreased diffusion capacity on lung function testing in asymptomatic patients with systemic lupus erythematosus does not predict future lung disease. Lupus, 24(9): 973-979.

97. Karim, MY., Miranda, LC., Tench, CM., Gordon, PA., D'Cruz, D P., Khamashta, MA., et al. (2002) Presentation and prognosis of the shrinking lung syndrome in systemic lupus erythematosus. Semin Arthritis Rheum, 31(5): 289-298.

98. Andreoli, L., Bertsias, GK., Agmon-Levin, N., Brown, S., Cervera, R., Costedoat-Chalumeau, N., et al. (2017) EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis, 76(3): 476-485.

99. Petri, M. (1994) Systemic lupus erythematosus and pregnancy. Rheum Dis Clin North Am, 20(1): 87-118.

100. Jakobsen, IM., Helmig, RB., Stengaard-Pedersen, K. (2015) Maternal

and foetal outcomes in pregnant systemic lupus erythematosus patients: an incident cohort from a stable referral population followed during 1990-2010. Scand J Rheumatol, 44(5): 377-384.

101. Abdulla, E., Al-Zakwani, I., Baddar, S., Abdwani, R. (2012) Extent of subclinical pulmonary involvement in childhood onset systemic lupus erythematosus in the sultanate of oman. Oman Med J, 27(1): 36-39.

102. Abdwani, R., Al-Abrawi, S., Sharef, SW., Al-Zakwani, I. (2013) Geographical Clustering of Juvenile Onset Systemic Lupus Erythematosus within the Sultanate of Oman. Oman Med J, 28(3): 199-203.

103. Al Rasbi, A., Abdalla, E., Sultan, R., Abdullah, N., Al Kaabi, J., Al-Zakwani, I., et al. (2018) Spectrum of systemic lupus erythematosus in Oman: from childhood to adulthood. Rheumatol Int, 38(9): 1691-1698.

104. Al-Maini, MH., El-Ageb, EM., Al-Wahaibi, SS., Al-Farsi, Y., Richens, ER. (2003) Demographic, autoimmune, and clinical profiles of patients with systemic lupus erythematosus in Oman. Rheumatol Int, 23(4): 186-191.