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National systemic lupus erythematosus prospective cohort in Saudi Arabia

A study protocol

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Abstract

Systemic Lupus erythematosus (SLE) is a chronic multisystem, multifactorial inflammatory autoimmune disease. The SLE patients have 3 times increased risk of mortality based on international data with ethnicity playing an important impact on patients' morbidity and mortality. Descriptive studies from Saudi Arabia showed variation in clinical features from one region to another. Moreover, reliable inference from these studies is limited by study methodology and lack of translational data using biological samples to understand clinical phenotypes of Saudi SLE patients.

The aim of this report is to describe the prospective study protocol of the National Systemic Lupus Erythematosus Cohort in Saudi Arabia. The purpose of this cohort study is multifold: first, to examine clinical characteristics and molecular phenotypes of Saudi SLE patients in relation to local environment and practices/lifestyles; second, to assess long-term outcomes of SLE in Saudi population and factors that influence favorable outcomes; third, to compare the effectiveness of various treatment regimens in Saudi SLE population.

This study is a longitudinal prospective cohort study of adult, Saudi SLE patients using open cohort study design. Primary outcomes include disease-related outcomes (activity, improvement, and organ damage) and patient-reported outcomes (quality of life). Secondary outcomes include physiological and molecular modifications associated with changes in disease activity states. Results and analysis are in on-going study.

This study provides a source of reliable data for clinical and translational research. This will allow us to have a holistic approach to SLE pathogenesis especially in Saudi population and may take us a step further toward much more personalized medicine.

This protocol has been registered in NIH ClinicalTrial.gov (ClinicalTrial.gov identifier: NCT04604990) on October 27, 2020.

Abbreviations: ACR = American College of Rheumatology, DMARD = disease-modifying anti-rheumatic drugs, IRB = institutional review board, KKUH = King Khalid University Hospital, KSU = King Saud University, LupusQoL = Lupus Quality of Life, SLE = systemic lupus erythematosus, SLICC = Systemic Lupus International Collaborating Clinics , SLICC/ACR-DI = SLICC/ACR Damage Index, SPSS = Statistical Package for the Social Sciences, SRI-50 = SLEDAI-2K Responder Index, SPIRIT = Standard Protocol Items: Recommendations for Interventional Trails.

Keywords: cohort, lupus, observational, outcomes, phenotypes, Saudi Arabia

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1. Introduction

1.1. Background

Systemic lupus erythematosus (SLE) is a chronic multisystem disease in which an underlying aberrant immune system leads to inflammation in various organs, and possibly consequent damage.[1] Incidence and prevalence of the disease vary significantly from 1 to 7 per 10,000 patients to 19 to 159 per 10,000 patients, respectively, in the United States.[2] The estimated incidence in the United Arab Emirates is around 3.5 per 100,000 patients and the prevalence is 109 per 100,000 patients[3], while in Saudi Arabia the prevalence is around 19 per 100,000 patients.[4] Such variation is likely due to the use of different definitions, studies' standardization of age, and racial background.[4]

Ethnicity is an important variable in disease occurrence, severity, phenotypic presentation, and prognosis.[5] For example, patients with African, Hispanic, and Native American tend to have more severe disease and, consequently, increased mortality.[5–7] Unfortunately, national Saudi studies in SLE are sporadic and limited in addressing our unique population in a prospective standardized fashion. The majority of the studies use retrospective chart review-based designs that are threatened by potential selection and information biases. They also lack molecular and genetic data of Saudi patients with SLE. As a result, our understanding of Saudi SLE patients is limited.

Thus, our national lupus registry protocol aims to establish an extensive record of well-characterized SLE patients in Saudi population on which to develop consistent longitudinal studies. This will provide a better understanding of disease characteristics and progression in Saudi population coupled with molecular data, and, sanguinely, be a fundamental attribution for future clinical trials in Saudi Arabia.

1.2. Objectives

The main objectives of this cohort are to:

- examine the changing trends in SLE disease outcomes (activity, severity, improvement, organ-damage, mortality) and patient-reported outcomes (quality of life) over time.
- evaluate the effect of risk factors (sociodemographic, environmental, social, family, and medical histories) on disease related outcomes including disease activity and disease damage.
- investigate laboratory characteristics including molecular signatures (genetic, epigenetic, genomic, immunologic, microbiotic) to identify novel mendelian genotypes/phenotypes.
- explore drug adherence, response, side effects, and associated molecular signature profile (pharmacometabolomics).
- establish a baseline Saudi polygenic risk score and compare it to Caucasian risk score in relation of clinical and laboratory characteristics.

2. Methods

2.1. Participants, interventions, and outcomes

2.1.1. Study design and setting. This is a prospective, cohort study. (The study was initiated in November 2019 and follows an open observational registry). This study design was guided by Standard Protocol Items: Recommendations for Interventional Trails (SPIRIT) checklist.[8,9]

2.1.2. Participant recruitment. Participants are recruited from both the General and Specialized Rheumatology Clinic at King Khalid University Hospital (KKUH) in King Saud University (KSU). Referred patients from other clinics from inside or outside KKUH are also allowed. Collaboration with other local and international centres is planned in the first 5 years of the study.

2.1.3. Eligibility criteria. Patients who met the inclusion criteria are enrolled after obtaining informed consent. Inclusion criteria: patients must be Saudi (or Arab living in Saudi Arabia are also allowed), adult (over 18 years old) and diagnosed with lupus according to the classification criteria of American College of Rheumatology (ACR),[10] Systemic Lupus International Collaborating Clinics (SLICC)[11] or ACR/European League Against Rheumatism [12]; irrespective of diagnosis date or treatment plan allowing for both prevalence and inception cohort components. Exclusion criteria: patients who do not fulfil the aforementioned criteria.

2.1.4. Sample size. The expected sample size is estimated to be about 1000 patients. Sample size was calculated based on the following assumptions: SLE prevalence of 19.28 per 100,000[4] and population size of 13,147,004 Saudis aged 18 years and older (according to the Saudi Arabian 2016 Census issued by General Authority of Statistics), with confidence interval of 95%, and precision of 5%.

2.1.5. Patient cohort division. Consented patients who fulfil the SLE classification criteria are categorized as inception new (<24 months from the onset of their symptoms) and prevalent (>24 months) patients. First visit is considered the baseline visit and subsequent visits are considered follow-up visits (see Fig. 1). Each patient has a standard follow-up visit every 3 months unless otherwise clinically indicated. Research assistants ensure patients follow protocol including attending visits and survey completion. Any missed follow-ups are handled by direct communication with patients (phone or email) to reschedule visits or investigate reasons for withdrawal.

2.1.6. Exposure.

- Sociodemographic information (age, gender, nationality, marital status, education level, employment, income, residency region).

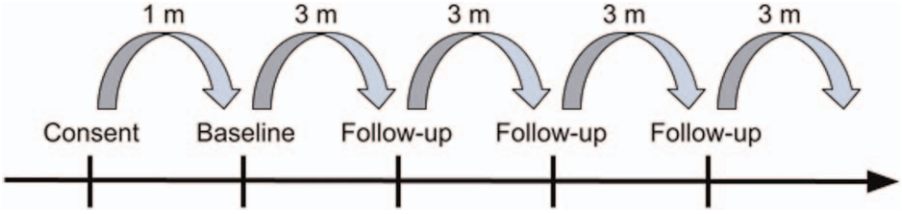

Figure 1. Timeline of enrollment and visits for participants. m = months(s).

- Patient and family medical history (autoimmunity including SLE, other seropositive diseases, hospitalization, and pregnancy).
- Environmental factors (smoke inhalation, smoking, sun exposure, fasting, physical activity, alcohol consumption, medication- or environmental-related allergy).
- Infections including but not limited to bacterial (*Mycobacterium tuberculosis*, *Clostridium difficile*, *Helicobacter pylori*), viral (Hepatitis B, Hepatitis C, Human immunodeficiency, Cytomegalovirus, Epstein-Barr, Herpes simplex, Varicella-zoster), fungal (Candida albicans, Pneumocystis jirovecii), and protozoal.
- Medications (monotherapy or combination therapy) including conventional immunosuppressive disease-modifying anti-rheumatic drugs (DMARD), conventional non-immunosuppressive DMARD, targeted biologic DMARD, targeted synthetic DMARD, nonsteroidal anti-inflammatory drug, steroid, supplements, other medications used for other comorbidities.

2.1.7. Primary outcomes. Clinical outcomes:

- SLE disease activity measured using SLE Disease Activity Index 2000 (SLEDAI-2K).[13,14]
- SLE Disease improvement using SLEDAI-2K Responder Index (SRI-50).[15]
- Disease-related damage measured using SLICC/ACR Damage Index (SLICC/ACR-DI).[16]

Patient-reported outcomes:

- SLE-related quality of life measured using Lupus Quality of Life (LupusQoL).[17]
- Patient-reported outcomes measured using Patient-Reported Outcomes Measurement Information System 29-item (PROMIS-29) profile version 2.1.[18]

2.1.8. Secondary outcomes. The following items are investigated according to patient's clinical indication:

- Cardiovascular/circulatory system
  - Percutaneous coronary intervention, myocardial infarction, stent thrombosis, target vessel lesion revascularizations, stroke, and death as a measure of Major Adverse Cardiovascular Event via patient history and monitoring heart-related failure hospitalizations.
  - Subclinical atherosclerosis: All patients will have a baseline electrocardiogram and echocardiogram. Those with abnormalities will be subjected to further investigations as clinically indicated. Random patients will be selected for image specific substudies that aim to identify subclinical atherosclerosis. Patients enrolled in these substudies will have baseline imaging and at 2 years interval for 6 years. Data will be collected using image-specific case report form. Images modalities include carotid artery intimal thickness, plaques size, ankle-brachial index as measure of peripheral artery disease using color duplex tomography for calcium score.
- Digestive system
  - Gastrointestinal disorders confirmed using abdomen ultrasound, gastroendoscopy, manometry, or colonoscopy as clinically indicated.
- Integumentary system/skin
  - Cutaneous Lupus Erythematosus disease activity and damage using Cutaneous Lupus Erythematosus Disease Area and Severity Index [19] index will be used if skin is affected.
- Nervous system
  - Patients with suspected neurocognitive impairments will undergo Mini-Mental State Examination and Montreal Cognitive Assessment.[20]
- Respiratory system
  - Baseline chest X-ray will be collected for all patients. Further studies will be used to confirm lung disorders when clinically indicated including pulmonary function test, high resolution computed tomography.
- Muscular and skeletal systems
  - Arthritis using Disease Activity Score-28,[21,22] 66/68-joint count of swollen and tender joints, and back examination.
  - Baseline bone density for all patients using dual-energy X-ray absorptiometry and fragility fracture using fracture risk assessment tool,[23] according to the International Society of Clinical Densitometry guidelines.[24] Repeated images will be obtaining according to clinical indications.
- Urinary system
  - Kidney biopsy for those with acute kidney injury, proteinuria >500, and or Active urinary RBC cast.
- Comorbidities
  - Metabolic syndrome using the various definitions including the harmonized definition.[25]
  - Malignancy using various imaging techniques and serological tumor markers.
- Medications
  - Medication adherence using modified Medication Adherence Response Scale.[26,27]

2.1.9. Biological specimens.

- Blood: venous blood (20 mL) is collected from each patient by the phlebotomist or assigned nurse and handled according to routine phlebotomy techniques followed at KKUH. For immunologic analysis, serum is separated from SST tube, then transferred into aliquots and stored at $-80°C$ until analysis. For proteomic analysis, plasma is separated from EDTA tube, then transferred into aliquots and stored at $-80°C$ until analysis. For genomic DNA analysis, buffy coat is isolated from EDTA tube, transferred into aliquots and stored at $-80°C$ until analysis. For RNA analysis, blood is directly collected into PAXgene Blood RNA tube and stored at $-80°C$ until analysis.
- Excreta: Patient self-collected fresh stool (15 mg) and urine (5 mL) is obtained from each patient into sterile containers and stored at $-80°C$ for microbiome analysis.

All collected biological specimens are transported to the Core Lab at the College of Medicine Research Center in KSU where they are prepared. Samples are then transferred to the College of Medicine Biobank where they are stored indefinitely and/or processed for current or ancillary studies in the future. All biosamples are maintained using sample identification labels that contain protocol ID, patient unique research ID, initials of derived sample type and collected tube, aliquot number, time and date of collection. All biosamples and related data are stored securely in soft and hard copies, while the key for patient's identification is kept with the principal investigator.

2.2. Data collection, management, and analysis

2.2.1. Data collection schedule. Patients are examined by the attending physician and treated with a standard of care as determined by the standardized clinical care procedures followed at KKUH. After a patient's initial visit (baseline), follow-up visits

are divided into short (follow-up) and long (annual) visits. Schedule of data collection for variables is shown in Table 1.

2.2.2. Data management. Data is collected by trained clinic staff (physician and/or nurse) according to the standard operating procedure for data entry in each clinical visit. Case report forms and surveys for data collection are built using Research Electronic Data Capture [28] hosted by KSU. A copy of the data dictionary is provided (see Supplemental Material, http://links.lww.com/MD/G297). Then, all data is transferred and stored into Caisis-KSU innovation hub, a data manager program, based at the Deanship of Electronic Communication at KSU. Entered data undergo validation and quality checks on quarterly basis prior to exporting data.

Database is governed by the protocol committee members consisting of principal investigator and coinvestigator. The principal investigator has full access and the key for patient identification; however, specific research members, appointed by the principal investigator, may be granted limited access to data as necessary.

2.2.3. Statistical methods. The data collected in this study is a longitudinal-type data which lists completed and missed data. Missed data may include complete random, random, and nonrandom deletions. Loss of data will be accounted and analyzed for impact on outcome variables accordingly. Multiple imputation will be used to account for missing data as appropriate.

For descriptive statistics, qualitative data will be described using frequency tables and percentages, while quantitative data will be described using mean, standard deviation, median, and lower and upper quartiles. Parametric and nonparametric tests will be used to assess continuous variables for significant differences between groups. A Student t test and Pearson χ^2 show presence of correlation among variables. Univariate and multivariate logistic and linear regression models will be used to examine the association between exposure and outcome variables and identify independent predictors of outcomes.

The hypothesis test will be a 5% of a 2-sided significance expressed with 95% confidence intervals. A P value of less than .05 will be considered statistically significant. All analyses will be performed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Inc, Armonk, NY).

2.3. Ethics and dissemination

2.3.1. Research ethics. Research ethical approval for this study was obtained from the Institutional Review Board (IRB) of KSU in Riyadh, Saudi Arabia (IRB approval no. E-19-3955/58) and was registered in ClinicalTrial.gov (ClinicalTrial.gov identifier: NCT04604990).

2.3.2. Protocol amendment. Any modifications to the protocol will be communicated to relevant parties.

2.3.3. Consent. This study is carried out in accordance with the principles of the Declaration of Helsinki set forth by the World Medical Association. All informed, assented patients are enrolled using a signed written consent form according to IRB of KSU guidelines.

2.3.4. Data availability. The data repository generated during the study are not publicly available due to IRB restrictions. However, analyzed datasets that support study findings will be available upon publication from the corresponding author on reasonable request.

3. Discussion

Our current understanding of SLE has been fostered by ongoing efforts of long-term observational cohorts, such as John Hopkins University and University of Toronto lupus cohorts, that have enriched our knowledge of disease presentation, course, and outcomes. These cohorts serve as exemplary models and stand at the cornerstones of many SLE studies, such as investigation of disease manifestations, organ-specific outcomes, prognosis, risk factor, clinical–laboratory correlations, and therapeutic efficacy and tolerability studies that promote a deeper understanding of disease behavior.[29,30]

The SLICC group is, also, no stranger to this effort, where it has taken up the challenge of putting together standardized clinical assessments and indices used by rheumatologists worldwide today,[14–16,31] as well as establishing International Inception Cohort by recruiting real-world data regarding the outcomes of atherosclerosis, nervous system, lupus nephritis, and metabolic involvement in SLE.

Although these studies have contributed much insight into the disease as we know it, more are necessary to fill our knowledge gap regarding descriptive clinical characteristics, qualitative-type research of patient-related outcomes, genotype-phenotype correlation, and pharmacometabolomics in Saudi patients.

The current nature of SLE highlights the importance of a multidimensional approach to assess the disease. Translational research suggests that when pathophysiological factors related to disease outcomes have been managed, genomic approaches may be a worthwhile path of study to integrate novel therapeutic

Table 1

Data collection schedule.

Variables/visits	Baseline (w/in 1 m)	Follow-up (3 m ± 2 w)	Follow-up (6 m ± 2 w)	Follow-up (9 m ± 2 w)	Annual (12 m ± 2 w)
Informed consent	✓				
Demographic and medical history	✓				✓
Biological specimens	✓				✓
SLE classification criteria	✓				✓
Physiological status	✓	✓	✓	✓	✓
Clinical outcome assessments	✓	✓	✓	✓	✓
PRO questionnaire	✓	✓	✓	✓	✓
Medications and adherence scale	✓	✓	✓	✓	✓
Labs and images (±1 m accepted)	S & L	S	S	S	L

L = long (annual) protocol, m = month(s), PRO = patient-reported outcome, S = short (follow-up) protocol, SLE = systemic lupus erythematosus, w = week(s), y = year(s).

regimens effective for patient populations. For instance, researchers have proved the usefulness of genetic analysis in predicting flare in SLE.[32] The results showed that patients who had a higher interferon-regulated gene expression profile had a higher level of disease activity at the time of the study. Thus, utilizing such robust demonstration in disease detection and control is perhaps a promising avenue worth venturing in cohorts.

Although evidence of ethnicity has shown to be an important factor of disease outcome in SLE patients, a fair representation of Middle Eastern or Arabs remains scarce. Thus, extrapolated data from international cohorts are often generalized to all SLE patients. This evokes the importance of establishing longitudinal cohorts encompassing these ethnicities.

Additionally, SLE disease in Saudi Arabia has yet to be well defined, especially in a population with high consanguinity and high inbreeding coefficient.[33] Until now, there has been no prospective cohort study for SLE patients in Saudi Arabia. As a result, the current published literature is focused on retrospective chart reviews which are subjected to many forms of bias.[6,34] Thus, these studies are difficult to utilize for translational research because clinical data are not complemented by simultaneously collected biological data.[35]

The importance of a national prospective cohort study to address the aforementioned knowledge gaps is high, especially in the context of assessing the burden of long-term outcomes and growing national interest in drug development programs, in the current time.

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Author contributions

Ibrahim A. Almaghlouth and Lena M. Hassen equally contributed to study protocol design. Hana Alahmari, Asma Bedaiwi, Rana Albarrak piloted study protocol plan. Maha Daghestani, Eman Alqurtas, Abdulaziz Alkhalaf, Mohammed Bedaiwi, Mohammed Omair, Sultan Almogairen, Hussein Alarfaj, Abdulrahman Alarfaj reviewed study protocol manuscript.

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