The Effect of Different Ethnic Origins in Israel on the Clinical Manifestations and Outcomes of Systemic Lupus Erythematous

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ABSTRACT **Background:** Epidemiological studies have shown a connection between ethnic origin and the incidence and outcome of systemic lupus erythematosus (SLE).

Objective: To evaluate the SLE outcomes among Ashkenazi Jews, non-Ashkenazi Jews, and Arabs.

Methods: We conducted a retrospective study of patients who were diagnosed with SLE and followed in lupus clinics at two large tertiary medical centers. The data were obtained from patient medical records. Patients were stratified into three ethnic origins: Ashkenazi Jews, non-Ashkenazi Jews, and Arabs. The primary outcomes were all-cause mortality, development of end-stage kidney disease (ESKD), and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) 2K ≤ 4 at last visit.

Results: We included 570 patients in this study. The Arab group showed the highest number of SLE classification criteria at diagnosis and last encounters compared to non-Ashkenazi and Ashkenazi Jewish groups (6.0 vs. 5.0 and 4.0, respectively at diagnosis, $P < 0.001$; 8.0 vs. 7.0 and 6.0 at last visit, $P = 0.01$). In multivariate models, Arab patients had three times higher risk of all-cause mortality than Ashkenazi Jews (hazard ratio 2.99, 95% confidence interval [95%CI] 1.32–6.76, $P = 0.009$). ESKD was similar among the study groups. Low disease activity (SLEDAI 2K ≤ 4) at last visit was lower in the Arab group than the Ashkenazi Jews (odds ratio 0.50, 95%CI 0.28–0.87, $P = 0.016$), depicting a medium-to-high disease activity among the former.

Conclusions: Physicians should consider the influence of the ethnicity of the SLE patient when deciding on their care plan.

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Systemic lupus erythematosus (SLE) is an autoimmune disease that affects various systems, including the kidneys, joints, lungs, and skin [1,2]. The organ damage to these systems accumulates over time and without treatment can lead to organ failure. The etiology of this disease is not well known, yet it seems to be connected to a combination of genetic and environmental factors [3].

One of the common clinical manifestations of SLE is lupus nephritis (LN). Approximately 50–70% of the SLE patients are diagnosed with LN during their disease course, LN can eventually lead to end-stage kidney disease (ESKD). Patients with chronic kidney disease (CKD) tend to have a higher incidence of cardiovascular disease, diabetes, hypertension, and obesity compared to the rest of the population [4].

Epidemiological studies have shown that there is an association between ethnic origin and demographic characteristics with the incidence and severity of SLE [5]. For example, Asian and African American women living in the United States are diagnosed more often with SLE and LN than Caucasian women [6]. It has also been found that in non-Ashkenazi Jewish women with SLE, and especially those of Yemenite descent, had worse outcome than Ashkenazi women [7].

Since 1995, Israel has had a tax-financed national health insurance (NHI) system that covers a comprehensive package of medical services for all residents, independent of the individual's ability to pay. The Israel NHI includes primary and specialist medical consultations, medications, hospitalization, and surgical procedures. Medical services are provided through membership in one of four health funds, which are similar in many ways to health maintenance organizations [8,9].

In this retrospective study, we determined the association of SLE disease activity and the accrual of ESKD as well as mortality rate in different ethnic groups in the Israeli population.

PATIENTS AND METHODS

STUDY POPULATION

This study was comprised of patients who were diagnosed with SLE and treated in the rheumatology outpatient clinics of Soroka University Medical Center and Rabin Medical Center (Beilinson Campus) between the years of 1992 and 2018. Both fa-

cilities are university-academic centers that belong to the Clalit Health Services health maintenance organization.

We excluded patients younger than 18 years of age and those who did not fulfil the 2012 SLICC criteria as well as patients diagnosed with drug-induced SLE, discoid lupus, or lupus-like disease. We also excluded patients with less than one year of follow-up.

DATA EXTRACTION

This research was approved by Soroka and Rabin institutional ethics committees. All patients fulfilled the 1997 American College of Rheumatology classification criteria or the 2012 Systemic Lupus International Collaborating Clinics classification criteria for SLE [10].

We gathered demographic information including sex, age, birth date, death date, and socioeconomic status (SES).

Ethnic origin was stratified into three groups: Ashkenazi Jews, non-Ashkenazi Jews, and Arabs. Jewish patients with mixed origin were coded randomly between groups 1 and 2.

Medical data included the date of SLE diagnosis, additional medical conditions, SLE related medications, intensive care unit admittance, dialysis, and renal transplants.

Laboratory data included anti-nuclear antibody (ANA; by immunofluorescence), anti-double strand DNA antibody (Farr method), anti-smith (Sm), anti-Ro, complement level (C3, C4, complement hemolysis-100), and antiphospholipid antibody (APLA includes anticardiolipin and β2 glycoprotein I IgG and/or IgM antibodies and/or lupus anticoagulant). We also recorded the results of 24-hour urine protein collection and renal biopsy results. We retrospectively calculated the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) 2K and the SDI at first and last visits to the rheumatology clinics based on the medical data documented in the medical records [11]. The SLEDAI 2K score consists of 24 clinical and laboratory variables of nine organ systems, including rash, alopecia, mucosal ulcers, and proteinuria. A score greater than 4 depicts a high disease activity. The SDI is a damage index defined for 12 organ systems that assesses disease activity and irreversible damage resulting from the illness and its treatments.

MAIN OUTCOMES AND DEFINITIONS

The primary outcomes were all-cause mortality, end-stage kidney disease (ESKD) and SLEDAI 2K ≤ 4 based on last visit. Mortality date was retrieved from the CHS data warehouse [12]. We defined ESKD as estimated glomerular filtration rate (eGFR) less than 15 ml/min/1.73 m^2 (using the modification of diet in renal disease equation) or a constant use of dialysis [13]. LN was classified if there was evidence of active renal disease as depicted by 24-hour urine protein excretion of > 500 mg/day or increased urine protein-to-creatinine ratio > 500 mg/gr creatinine and/or active urinary sediment (hematuria >5 RBC/HPF and/or cellular casts) that were attributable to SLE and/or a kidney biopsy findings compatible with LN according to the 2004 International Society of Nephrology/Renal Pathological Society (ISN/RPS) classification [14].

STATISTICAL ANALYSIS

Data are expressed as mean ± standard deviation, median ± interquartile range (IQR), or number and percentage. We compared the baseline characteristics of patients according to their ethnic backgrounds. We used the chi-square, one-way ANOVA, and Kruskal-Wallis tests to compare dichotomous, parametric, and parametric continuous variables, respectively. To estimate the association between patient characteristics and all-cause mortality and ESKD, we used Kaplan-Meier curves and Cox forward stepwise conditional multivariable regression models. Each set of covariates (e.g., ethnicity, medical history, laboratory) was entered sequentially as a separate block of variables to the model. The final model was selected according to the statistical significance of coefficients, their clinical relevance, and the model discriminatory characteristic. To estimate factors associated with SLEDAI 2K ≤ 4 at last visit, we utilized multivariate logistic regression models using the same methods. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). We used the Bonferroni correction to counteract multiple comparisons in this analysis. *P*-values < 0.017 were considered statistically significant.

RESULTS

Table 1 shows the baseline characteristics of the 570 patients with SLE who were included in our cohort, stratified by ethnic backgrounds. Overall, the Arab group showed a younger age of SLE onset (29.3 ± 12.7 years) compared to the non-Ashkenazi Jews (33.7 ± 14.4 years) and Ashkenazi Jews (37.7 ± 16.2 years) ($P < 0.001$) and shorter duration of follow-up (12.0 years vs. 15.0 years, $P = 0.01$). The Arab group also showed higher number of SLE classification criteria at diagnosis and last encounters compared to the non-Ashkenazi and Ashkenazi groups (6.0 vs. 5.0 and 4.0, respectively at diagnosis with a $P < 0.001$, and 8.0 vs. 7.0 and 6.0 at last visit, $P = 0.01$). Serology markers of SLE were similar between the different ethnic groups.

Compared to the Ashkenazi and non-Ashkenazi Jews, the medication regime of the patients from Arab background included more often glucocorticoids (93.5% vs. 75.8% and 81.5%, respectively, $P = 0.01$), mycophenolate mofetil (28.6% vs. 11% vs. 15.9%, respectively, $P = 0.01$), methotrexate (33.8% vs. 13.5% and 17.2%, respectively, $P = 0.01$), and azathioprine (51.9% vs. 27.8% and 32.9%, respectively, $P = 0.01$) during their follow-up period.

SES also differed among the groups. Arabs had a grade of 2.0 while the other groups had a grade of 7.0, $P < 0.001$.

Univariate analysis is depicted in Table 1, Figures 1 and 2. All-cause mortality was highest in the Ashkenazi group (18.5%), although it was not statistically significant. Similarly, ESKD was

Table 1. General characteristics of study cohort and study outcomes stratified by ethnic origin

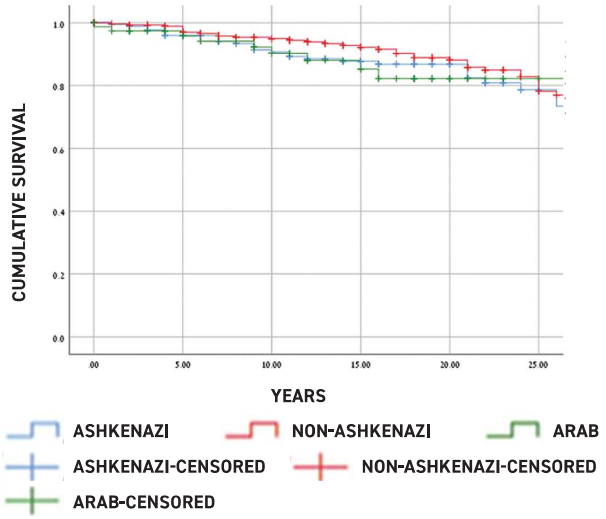
General characteristics of study cohort stratified by ethnic origin				
Variable	**Ashkenazi Jews (n=195)**	**Non-Ashkenazi Jews (n=298)**	**Arab (n=77)**	***P*-value**
Age in years at diagnosis, mean	37.7 ± 16.2	33.7 ± 14.4	29.3 ± 12.7	< 0.001
Female, n (%)	171 (87.7)	267 (89.6)	67 (87.0)	0.91
Follow-up years, median (IQR)	15.0 (8.0–22.0)	15.0 (8.0–24.0)	12.0 (5.0–18.0)	0.01
Diabetes, n (%)	26 (13.9)	40 (13.6)	15 (19.5)	0.41
Hypertension, n (%)	83 (44.1)	99 (33.6)	35 (45.5)	0.03
Smoking, n (%)	40 (21.9)	88 (30.7)	11 (15.5)	0.01
SLE classification criteria at diagnosis, median (IQR)	4.0 (4.0–6.0)	5.0 (4.0–6.0)	6.0 (4.0–7.0)	< 0.001
SLE classification criteria last visit, median (IQR)	6.0 (5.0–8.0)	7.0 (5.0–8.0)	8.0 (6.0–8.5)	0.01
Clinical manifestations, n (%)				
Arthritis	143 (73.3)	247 (82.9)	64 (83.1)	0.03
Mucocutaneous	109 (63.4)	157 (55.9)	42 (54.5)	0.23
Thrombocytopenia	75 (38.5)	102 (34.3)	32 (41.6)	0.41
Autoimmune hemolytic anemia	35 (18.4)	56 (19.5)	29 (38.7)	0.01
Pleuritis	43 (22.1)	70 (23.5)	23 (29.9)	0.38
Pericarditis	29 (14.9)	40 (13.5)	19 (24.7)	0.05
APLA syndrome	51 (27.1)	67 (22.6)	23 (29.9)	0.31
APLA obstetric	24 (13.6)	35 (12.6)	10 (13.0)	0.95
Lupus nephritis	58 (29.9)	96 (32.4)	33 (42.9)	0.11
CNS lupus	30 (15.4)	57 (19.1)	14 (18.2)	0.56
Immunological features, n positive (%)				
Anti-nuclear antibody	186 (95.4)	286 (96.6)	76 (98.7)	0.40
Double strand DNA	116 (61.1)	185 (63.1)	56 (73.7)	0.14
Anti-Smith	28 (16.1)	34 (12.4)	17 (22.4)	0.09
RO	40 (23.1)	55 (20.1)	19 (25.0)	0.58
Decreased C3	94 (48.5)	134 (45.1)	47 (61.0)	0.04
Decreased C4	46 (23.7)	69 (23.2)	26 (34.7)	0.11
aCL immunoglobulin M	26 (14.2)	40 (14.0)	14 (18.2)	0.64
aCL immunoglobulin G	44 (24.3)	83 (28.9)	24 (31.6)	0.40
Beta II glycoprotein IgM	25 (15.2)	45 (17.6)	13 (19.7)	0.66
Beta II glycoprotein IgG	29 (17.6)	40 (15.6)	10 (15.2)	0.83
Lupus anticoagulant	54 (34.2)	72 (30.1)	24 (41.4)	0.24
Therapeutic features ever, n (%)				
Glucocorticoids	147 (75.8)	242 (81.5)	72 (93.5)	0.01
Hydroxychloroquine	173 (88.7)	269 (90.6)	75 (97.4)	0.08
Cyclophosphamide	35 (18.0)	46 (15.5)	13 (16.9)	0.76
Mycophenolate mofetil (CellCept)	21 (11.0)	47 (15.9)	22 (28.6)	0.01
Methotrexate	26 (13.5)	51 (17.2)	26 (33.8)	0.01
Azathioprine	54 (27.8)	98 (32.9)	40 (51.9)	0.01
Rituximab	13 (6.7)	17 (5.7)	3 (3.9)	0.67
Belimumab	12 (6.4)	24 (8.1)	10 (13.0)	0.20
Anticoagulation	54 (30.9)	85 (30.0)	33 (42.9)	0.09
Lupus damage index, first visit, median (IQR)	0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.09
Lupus damage index, last visit, median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	3.0 (1.0–4.0)	0.10
Lupus damage index ⩾ 3, last visit n (%)	52 (26.7)	75 (25.4)	30 (39.0)	0.06
Socioeconomic status, median	7.0	7.0	2.0	< 0.001
Study outcomes stratified by ethnic origin				
All-cause mortality, n (%)	36 (18.5)	44 (14.8)	9 (11.7)	0.32
ESKD, n (%)	16 (8.2)	20 (6.7)	6 (7.8)	0.80
SLEDAI 2K at diagnosis, median (IQR)	8.0 (5.0–11.0)	8.0 (6.0–12.0)	10.0 (7.5–14.0)	0.01
SLEDAI 2K last visit, median (IQR)	3.0 (0.0–6.0)	4.0 (0.0–8.0)	5.0 (2.0–11.5)	0.01
SLEDAI 2K ⩽ 4, n (%)	127 (67.2)	174 (60.2)	37 (48.7)	0.02

aCL = anticardiolipin antibodies, APLA = antiphospholipid antibody, ESKD = end-stage kidney disease, CNS = central nervous system, IQR = interquartile range, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index

also more frequent among the Ashkenazi group (8.2% vs. 6.7% and 7.8%, log-rank in Kaplan-Meier $P = 0.32$). Figure 2 shows that the median SLEDAI 2K at diagnosis was highest among the Arab group, in contrast to the non-Ashkenazi and Ashkenazi groups (10.0 vs. 8.0, $P = 0.01$) as well as at last visit (5.0 vs. 4.0 vs 3.0, $P = 0.01$). By defining SLEDAI 2K < 4 as an endpoint for low disease activity we can see that the Arab group had the lowest percentage of patients to report a low disease activity compared to the other groups (48.7% vs. 60.2% and 67.2%, $P = 0.02$).

Figure 1. Kaplan-Meier curves
ESKD = end-stage kidney disease

[A] All-cause mortality (P = 0.39)



[B] End-stage kidney disease stratified by ethnic origin ($P = 0.32$)

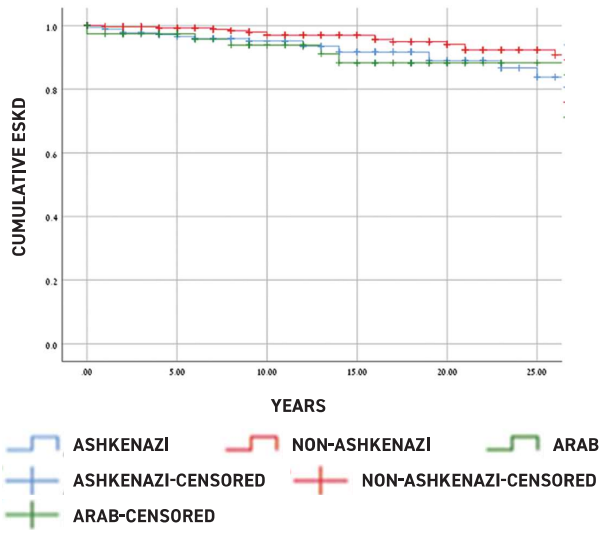
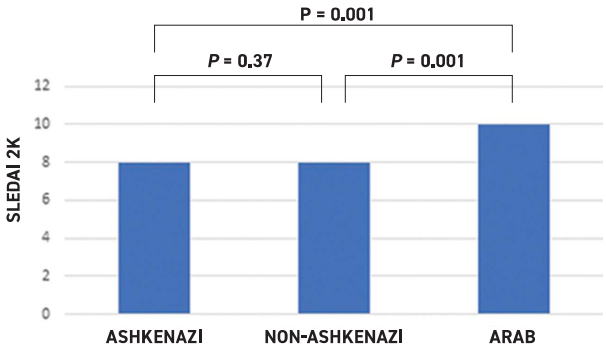
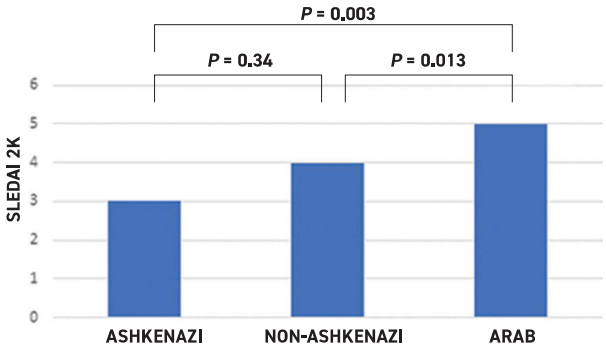


Figure 2. SLEDAI 2K stratified by ethnic origin
SLEDAI = Systemic Lupus Erythematosus Disease Activity Index

[A] FIRST VISIT



[B] LAST VISIT



The effect of ethnic origin on study outcomes with multivariate adjustment is shown in Table 2. In this model the Arab group had three times higher chance for all-cause mortality than Ashkenazi Jews, with a hazard ratio (HR) of 2.99 and $P = 0.009$. Compared to the Ashkenazi group, the Arabs with a HR of 1.07 had a slightly higher risk of developing ESKD, yet our results were not significant statistically ($P = 0.95$, 95% confidence interval [95%CI] 0.11–10.11). With an OR of 0.50, we can also see that only 50% of patients in the Arab group reported to have low disease activity as opposed to the Ashkenazi Jews ($P = 0.016$, 95%CI 0.28–0.87).

DISCUSSION

In this study, we evaluated the influence of ethnic origin on the outcomes and manifestations of SLE. We analyzed the medical records of more than 600 patients who were treated in two lupus clinics in large tertiary academic medical centers in Israel, with a median follow-up period of 15 years. Only 570 met the inclusion criteria. By stratifying our research population into three groups based on ethnic origin (Ashkenazi Jews, non-Ashkenazi

Table 2. Multivariate models

Variables	*P*-value	Hazard ratio	95% confidence interval
Model 1. Multivariate Cox regression of all-cause mortality			
Male	0.03	2.01	1.07–3.77
Age in years at diagnosis	< 0.001	1.07	1.05–1.08
HCQ ever	0.19	0.67	0.37–1.21
Malignancy	0.003	2.05	1.27–3.32
ESKD	0.002	2.49	1.41–4.42
Non-Ashkenazi Jews*	0.53	1.16	0.71–1.90
Arabs*	0.009	2.99	1.32–6.76
Model 2. Multivariate Cox regression to develop ESKD			
Male	0.13	2.79	0.72–10.86
Age in years at diagnosis	0.90	1.01	0.96–1.04
HCQ ever	0.07	0.31	0.09–1.10
CKD without LN	0.15	2.42	0.70–8.33
Non-Ashkenazi Jews*	0.37	1.71	0.52–5.62
Arabs*	0.95	1.07	0.11–10.11
Model 3. Multivariate logistic regression of SLEDAI 2K ≤ 4			
Male	0.14	1.54	0.86–2.276
Age in years at diagnosis	0.87	0.99	0.98–1.01
HCQ ever	0.19	0.63	0.32–1.25
Lupus nephritis	0.004	0.57	0.39–0.83
Non-Ashkenazi Jews*	0.16	0.75	0.50–1.12
Arabs*	0.016	0.50	0.28–0.87

*Reference is Ashkenazi Jews

CKD = chronic kidney disease, ESKD = end-stage kidney disease, HCQ = hydroxychloroquine, LN = lupus nephritis, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index

Jews, and Arabs) and reviewing their rheumatological medical history, we were able to evaluate the association of ethnic origin with all-cause mortality, ESKD, and disease activity.

Our principal findings were that the Arab patients had a three times higher chance for all-cause mortality than Ashkenazi Jews and 50% had medium to high disease activity. Consequently, the severity of the disease in among the Arab group was portrayed by the aggressive medication regime that the physicians chose to apply. The risk of developing ESKD was not found to be associated with ethnic origin in our cohort.

The results of our research are consistent with previous studies that investigated the influence of ethnic origin on SLE manifestations. For example, a study on 724 SLE patients that was conducted in California, USA, showed substantial differences in the prevalence of several clinical manifestations of SLE among different ethnicities [15]. The authors showed that African Americans, Asian/Pacific Islanders, and Hispanic patients were at an increased risk of developing severe manifestations of lupus (e.g., lupus nephritis and thrombocytopenia) than Caucasian patients. In another study that reviewed mortality in SLE patients around the world and epidemiological characteristics [16], it was found that in general non-white SLE patients had higher mortality than white patients. Similarly, a study that examined the influence of ethnicity on SLE susceptibility and outcomes [17] showed substantial variations of the clinical manifestations of SLE between ethnic groups. Compared to Caucasians, patients from ethnic minorities developed SLE more frequently, had a more acute disease onset, presented more severe clinical manifestations along with higher disease activity, showed more damage accumulation, and experienced higher mortality rates. They also found that African Americans with SLE had a two to threefold higher risk of death than Caucasians, which aligns with our core results.

Several explanations can be offered to address the difference between the different ethnic origins. First, the genetic and biological similarities among individuals that make up an ethnic group influence the way the disease affects them. A cohort of patients with SLE from different ethnic backgrounds (Hispanic, African American, and Caucasian) showed similarities and connection to the disease [18]. HLA-DR allele frequencies were studied and showed that each group held common frequencies and their presence was associated with different levels of disease damage. Another study team that investigated a connection between genetics and pericarditis in SLE patients, showed a correlation between certain genetic factors and the prevalence of pericarditis among these patients [19]. Second, research conducted in the United Kingdom showed that SES and race determined the outcome in SLE as did SES and psychosocial factors, resulting in higher incidence of end-organ damage among non-Caucasians and those with low SES [20]. Although it was not the main topic of this study, SES was part of the data we extracted to build our research database. Our results showed that the Arab group had the lowest SES. Despite Israel's NHI policy, which entitles all citizens to medical care, lower SES can be a disadvantage compared to higher SES with regard to access to private practice rather than the public health system, which is highly understaffed and underfinanced. Lower SES also affects the amount of time and means that can be invested in medical visits and treatments. Other factors that can be explained by SES and ethnic disparities may contribute to our findings but were not included in our database, such as geographical distance from lupus clinics, low education and social support, and poor adherence to medical therapy. Another proposition to these findings is that the Arabic language is

not spoken fluently by most non-Arabs in Israel, which can lead to communication difficulties between the medical staff and patients, resulting in a misunderstanding of the medical situation, as well as the treatment plan for the patient.

This study has several limitations. First, this study was designed to be observational and cannot establish causality between ethnicity and SLE outcomes. Second, we could not assess the adherence to medical therapy, we could only obtain prescription of SLE medications to patients. Third, the ethnic origins of the patients were determined based on how they described themselves and not by background or genetic tests, thus mixed ethnic backgrounds of a few generations might have been unintentionally categorized. Another limitation to this research is that our data was extracted retrospectively from the medical history of our patients. Some patients were lacking crucial information, which we were not able to obtain years later. We could only extract the data as documented by the physician during the encounter with the patient.

Notwithstanding these limitations, we found that ethnic origin was associated with outcomes and manifestations of SLE among patients. We believe that these results should be considered by the policy makers in the health field to target populations at risk and to raise awareness of SLE to ensure earlier intervention in the course of the disease. As shown in our results in Table 1, which outline the baseline characteristics of the patients included in our study, most of those who were included were female in their reproductive years. This fact emphasizes the importance of reaching out to patients from Arab or non-Ashkenazi backgrounds as early as possible and adhering to a strict follow-up regime, as it has been proven that women can experience SLE flares during pregnancy or postpartum [21]. This research can also contribute to the case managers of SLE patients from Arab or non-Ashkenazi backgrounds, possibly by taking a more aggressive therapeutic approach in earlier stages of the disease.

CONCLUSIONS

Physicians should consider the influence of the ethnicity of the SLE patient when deciding on their care and treatment plan.

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Love doesn't just sit there, like a stone, it has to be made, like bread; remade all the time, made new.
Ursula K. Le Guin (1929–2018), American author best known for her works of speculative fiction, including science fiction works set in her Hainish universe, and the Earthsea fantasy series