TITLE PAGE

Title of the article: A study of the influence of ethnicity on serology and clinical features in lupus.

Shortened version of the title: Influence of ethnicity in lupus.

Authors: Sandra A. Morais[1], David A. Isenberg[2]

1 – Internal Medicine Department, Hospital Pedro Hispano, Matosinhos, Portugal

2 – Centre for Rheumatology, University College London Hospitals, London, UK

Corresponding author:

Full name: David A. Isenberg

Postal address: Centre for Rheumatology, University College London, Room 424, 4th Floor Rayne Building, 5 University Street, London WC1E 6JF, UK

E-mail: d.isenberg@ucl.ac.uk

Fax number: + 44 20 7380 9278

Keywords:

Systemic lupus erythematosus, ethnicity, serological expression, clinical expression.

ABSTRACT

Objective: To review the links between ethnicity, serology and clinical expression in systemic lupus erythematosus (SLE), in a single cohort followed over a 36 year period.

Patients and methods: Patients with SLE treated at UCLH between January 1978 and December 2013 formed the cohort. Demographic, clinical and serological data were assessed. Standard methods were used for laboratory testing. Student T-test and Mann-Whitney U test were used for continuous variables and Fisher's exact test for categorical variables.

Results: 624 SLE patients were studied, 571 women (91.5%, mean age at diagnosis: 29.0±6.5 years) and 53 men (8.5%, mean age was 29.4±15.3 years). Ethnically, 369 patients were European, 100 Afro-caribbean, 77 East Asian, 56 South Asian and 21 mixed ethnicity.

East Asian patients developed the disease younger than the other ethnic groups ($p<0.0001$). Afro-caribbean patients were less frequently associated with the presence of rash and photosensitivity, and non-european patients were more likely to have alopecia and renal involvement. South Asian patients were significantly associated with musculoskeletal and neurological involvement, serositis, sicca syndrome and haematological features.

Afro-caribbeans had the highest prevalence of anti-Smith, anti-RNP, anti-Ro and anti-La antibodies. Anti-IgG anticardiolipin antibodies were significantly associated with the non-East Asian groups and hypocomplementemia was common on East Asians.

Rash, alopecia, mouth ulcers, serositis, neurological, joints and renal involvement were significantly associated with the presence of anti-Smith and anti-RNP antibodies in the Afro-caribbean group, and an association of joint involvement and presence of anti-Ro and anti-La was also observed on this group.

Conclusion: East Asian patients developed the disease younger than the other ethnic groups. Cutaneous involvement was more frequent in non-afro-caribbeans, with serosistis, joint and neurological involvement being more frequently diagnosed on South Asians. Anti-ENA antibodies were frequently associated with Afro-caribbeans.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease of complex, incompletely understood aetiology, with a wide spectrum of clinical and immunological manifestations (1, 2). The pathogenesis and expression of the disease is likely to be influenced by genetic, environmental or sociodemographic factors. This multiplicity of factors helps to explain the variability observed in the expression of the disease, between individuals, and ethnic groups (2). Ethnic differences may influence the clinical expression of the disease and the presence of autoantibody profiles (1). Several studies have demonstrated that non-white individuals present at a younger age, have a higher frequency of severe renal disease and ultimately a worse prognosis when compared with Caucasians (3-7).

In SLE, the most distinctive laboratory feature is the presence of autoantibodies to nuclear antigens including double stranded DNA (dsDNA), histones, ribonucleoprotein (RNP), and the Sm antigen (1, 8). Autoantibodies in SLE may be diagnostic and/or markers of disease activity, and may be detected before the diagnosis of the disease (8-10).

Many studies have been shown substantial ethnic disparities in the burden of SLE, with consequent influence on the severity and final outcome of disease (11). Earlier studies reported a higher proportion of renal disease (40.5%) and renal failure (15.3%) in black SLE patients, who were also diagnosed at younger age (34.4±14.9 years) when compared to white patients (18.8%, 4.5% and 41.9±21.3 years, respectively)(11). A recent study of 42 221 SLE patients revealed that SLE was more frequently diagnosed in white (20.17%) and black (24.13%) individuals than in Asian (5.18%) patients. In addition, a higher mortality risk was observed in black patients (HR 1.21 [95% CI 1.10-1.33]) compared to whites and conversely, the risk was significantly lower among Asian (hazard ratio 0.59 [95% CI 0.40-0.86]) when compared with white patients. A similar result also observed in patients with lupus nephritis where the mortality risk was lower in Asian patients compared with white patients (12).

Other differences between ethnic groups include the demonstration of African-American SLE women expressing higher serum levels of specific Toll-like receptors (TLR-9) and pro-inflammatory cytokines (IL-6 and TNF-α) when compared to European-American women (13). In addition, meta-analysis studies revealed that FcyRIIIA-F158 allele, a Fcy receptor subtype,

predisposed to lupus nephritis in Asian patients (14), and also, higher rates of lupus nephritis-associated autoantibodies have been described in this ethnic group when compared with White patients (15).

In this study we have sought to take advantage of a relatively large cohort of diverse ethnicity SLE patients followed up very carefully over a long period (up to 36 years). We have thus been able to make direct comparisons in the same cohort between the four ethnic groups.

METHODS AND PATIENTS

PATIENTS: An audit of all the SLE patients followed up in the Rheumatology department at University College of London Hospital (UCLH) between January 1978 and December 2013 was performed. Demographic, clinical and serological data were collected and reviewed.

The study population included a total of 624 patients (571 females and 53 males) attending UCLH, who fulfilled the revised criteria of the American College of Rheumatology for SLE (16).

Demographic information collected included gender, ethnicity and age at diagnosis. Information on ethnicity was self-designated and patients were divided according to geographical origin: European (which include all white patients of European ancestry), Afro-caribbean (which include all black patients of African descent, and also patients from the Bahamas, Belize, Bermuda, Anguilla, Antigua and Barbuda, British Virgin Islands, Dominica, Montserrat, Saint Kitts and Nevil, Barbados, Grenada, Saint Lucia, Saint Vincent and the Grenadines, Cayman Islands, Guyana, Jamaica, Trinidad and Tobago, Turks and Caicos Islands), South Asian (which include patients from the South Asia, composed by the current territories of Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka; the British Indian Ocean Territory, Mauritius and the Tibet Autonomous Region were included as well) and East Asian (which include patients from the territories of China, Japan, North Korea, South Korea, Mongolia, Taiwan and Vietnam). Patients of mixed origin were excluded from the analysis as well as patients from the countries of Somalia and Eritrean (based on the difficulty of categorisation and the small number of patients).

METHODS: The routine laboratory serology results were analysed by standard methods. From 1978 to 1988, a radioimmunoassay (Amersham, UK) was used in the serial measurement of anti-DNA antibody levels. From April 1988, we have used an ELISA (Cambridge Life Sciences). In each case, we regarded twice the upper limit of normal (25 and 100U, respectively) recommended by the manufacturers as a raised level. Three raised levels were required or a positive Crithidia lucida test before a patient was recorded as DNA antibody positive. Patients had approximately 5-yearly re-assessments of antibodies to Ro/SSA, La/SSB, Sm and RNP [originally by counter-immunoelectrophoresis, and since 1988 by ELISA (Shield Diagnostics, Dundee)] as well as repeated Coombs' tests, rheumatoid factor assessments and lupus anti-coagulants. The assays used have been described in detail elsewhere (17, 18). For the long-term follow-up serological part of this study, we have used the routine DNA antibody and serum C3 results (measured by laser nephelometer using UK approved standards, normal range 0.75-1.75 ug/ml; three reduced levels were required before the patient was regarded as being 'low' C3). The C3 levels were expressed as a proportion of the lower limit of normal and (because of the change in assay) the DNA binding antibodies as a fraction of the upper limit of normal (i.e. irrespective of the assay). Solid-phase assays for anti-Ro/SSA (17, 19), anti-La/SSB (17, 20) and anti-U1 RNP and anti-Sm (17) were performed using affinity-purified antigens prepared from calf thymus tissue extract. Solid-phase assays for anti-ribosomal 'P' and Western blotting were performed as previously described (17, 21). RF was detected using the latex fixation method (Becton Dickinson, Sparks, Maryland, USA). Titres of ≥1:80 were considered positive. The presence of antinuclear antibodies (ANA) was tested using dilutions of serum on a human epithelial cell line (HEp-2). Fluorescence at a titre ≥1:80 was considered positive. Ig and IgM anti-cardiolipin tests were done by commercial ELISE and lupus anti-coagulant by the dilute Russell's viper venom time and the anti-thyroid antibody tests by immunofluorescence.

The autoantibody profiles were obtained at or shortly after diagnosis. As previously published (????), 17% of patients with positive ANAs in our group become negative over a decade. In addition, high dsDNA antibody levels likewise tend to normalise over time, whereas, ENA antibody profiles presented some fluctuation but overall most of these patients tended to keep the same patterns over the time (????).

The disease manifestations of the study group were collected at diagnosis, with the new clinical features been cumulatively added over time.

STATISTICAL ANALYSIS: Descriptive results are presented as frequencies (%), mean or standard deviation. Comparisons between continuous variables were made using student T test and Mann-Whitney U test. Fisher's exact test was used for categorical variables when it was appropriate. Values of $p<0.05$ (two tailed) were considered significant.

RESULTS

A total of 624 SLE patients were studied, 571 patients were women (91.5%), with a mean age at diagnosis of 29.0±12.3 years (7 to 77 years) and 53 patients males (8.5%), with a mean age at diagnosis of 29.4±15.3 years (1 to 63 years). No significant differences were found between gender and the age at diagnosis (T-value=0.256, p=0.798).

369 SLE patients were European (59.1%), 100 patients were Afro-caribbean (16.0%), 77 patients were East Asian (12.3%) and 56 patients were South Asian (9.0%). Twenty patients were of mixed ethnicity and in 1 patient the information was missing.

Females were more frequently affected in all ethnic groups, with no significant difference found between genders in the different ethnic groups (p=0.324-1.00) (Table 1).

East Asian patients developed the disease younger than the European, Afro-caribbean and South Asian patients (T-value=4.154-5.597, p<0.0001) (Table 1). No statistically significant differences were observed in the age at diagnosis between genders.

The clinical profile analysis of the ethnic groups is described on Table 2, and shows a significant association of musculoskeletal involvement in the South Asian group, presented in all patients, when compared to the other ethnic groups (100% vs 81.0% to 92.9%, respectively, p=0.0002-0.039); been a less frequent clinical feature in Afro-caribbean patients (81.0% vs 92.2% to 100%, respectively, p=0.0002-0.049).

The European group was significantly associated with the presence of rash (70.9%, compare to 46.9% in Afro-caribbean and 63.6% in East Asian, respectively, p<0.0001) and photosensitivity (49.2% vs 8.2% in Afro-caribbean, p<0.0001). In contrast, these patients were less likely to

have alopecia than the other ethnic groups (16.0% vs 28.6% to 38.0%, respectively, p=0.0001-0.014). Afro-caribbean patients complained less frequently of photosensitivity when compared with the other ethnic groups (8.2% vs 37.7% to 49.2%, respectively, p<0.0001).

Notably, renal involvement was less frequently diagnosed in European patients than in Afro-caribbean and East Asian patients (24.1% vs 36.4% and 49.4%, respectively, p=0.0001-0.021).

Interestingly, South Asian patients developed more frequently ocular lesions (sicca syndrome) when compared to Afro-caribbean and East Asian patients (16.1% vs 3.1% and 3.9%, respectively, p=0.009-0.029); as well as, serositis (55.4% compared to 31.2% in East Asian, 35.0% in Afro-caribbean and 37.8% in European patients, respectively, p=0.007-0.019), neurological symptoms (39.3% compared to 15.8% in East Asian, 19.6% in European and 20.0% in Afro-caribbean patients, respectively, p=0.002-0.014) and leukopenia (50.0% compared to 25.3% in Afro-caribbean, 27.6% in East Asian and 27.9% in European patients, respectively, p=0.002-0.011).

The Afro-caribbean group presented less frequently thrombocytopenia when compared to European and South Asian patients (7.1% vs 15.3% and 21.4%, respectively, p=0.012-0.032).

No other statistical significant differences where observed in the other clinical categories.

Analysing the serological data, the frequency of ANA and anti-dsDNA antibodies was similar in all groups (table 3), with a mean variation ranging between 89.0 to 96.4% and 61.6 to 67.6%, respectively.

Afro-caribbean patients had the greatest prevalence (1/3 of the patients) of anti-Smith antibodies, when compared to the other ethnic groups (37.5% vs 9.5% to 17.6%, respectively, p=0.0001-0.006).

In addition, in comparison to European patients the Afro-caribbean group had a higher prevalence of anti-Ro (53.1% vs 32.2%, respectively, p=0.0002) and anti-La (20.8% vs 11.7%, respectively, p=0.028) antibodies.

The Afro-caribbean group as also the higher prevalence of anti-RNP antibodies (53.1% compared to 20.3% in European, 28.6% in South Asian and 34.7% in East Asian patients, respectively, p=0.0001-0.012), being a less frequent expression in European patients (20.3% compared to 34.7% in East Asian and 53.1% in Afro-caribbean patients, respectively, p=0.0001-0.013).

In the European group, hypocomplementemia (low C3) is a less common feature, occurring in 38.9% of the patients (compared to 65.8% of the East Asian patients and 50.5% of the Afro-caribbean patients, respectively, p=0.0001-0.039).

The anti-IgG anticardiolipin is detected less frequently in the East Asian patients when compared to European and South Asian patients (7.9% vs 21.8% and 25.0%, respectively, p=0.004-0.012).

The analysis of clinical and serological links between the ethnic groups (table 4) revealed a significantly association in the development of several clinical features and presence of anti-Sm and anti-RNP in Afro-caribbean patients when compared to the other ethnic groups, namely, development of rash (34.1% vs 9.2% to 14.9% of anti-Smith antibodies positivity, respectively, p=0.001-0.049; and 56.8% vs 19.2% to 31.9% of anti-RNP antibodies positivity, respectively, p=0.0001-0.027), alopecia (anti-Smith positivity in 45.9% compared to 11.9% of European patients, respectively, p=0.0003; and anti-RNP positivity in 64.9% of Afro-caribbean and 50% of East Asian compared to 20.3% of European, respectively, p=0.0001-0.019), mouth ulcers (36.8% of Afro-caribbean and 26.3% of South Asian vs 0% of East Asian and 5.2% of European patients with anti-Sm positivity, respectively, p=0.0005-0.047; and 57.9% compared to 15.5% of European group with anti-RNP, respectively, p=0.0002), musculoskeletal involvement (36.7% vs 9.7% to 17.6% with anti-Smith, p=0.0001-0.016; and 53.2% vs 19.6% to 34.8% with anti-RNP positivity, respectively, p=0.0001-0.03), serositis (45.5% compared to 10.1% in European and 16.1% in South Asian patients with anti-Sm, p=0.0001-0.015; and with anti-RNP positivity 57.6% compared to 21.6 and 32.3% on the same groups, respectively, p=0.0002-0.049), renal involvement (42.9% vs 11.2% of European patients with anti-Smith, p=0.0002; and 60% compared to 18% in European and 33.3% in East Asians with anti-RNP, p=0.0001-0.033), neurological involvement (with anti-Sm 47.4% vs 5.6% of European and 13.6% of South Asians, p=0.0001-0.037; and 42.1% vs 15.3% of Europeans with anti-RNP positivity, respectively, p=0.022), leukopenia (with anti-Smith positivity 33.3% vs 10.9% of European patients, respectively, p=0.011) and lymphopenia (39.4% vs 10.2% to 18.2% of the other groups with anti-Sm positivity, p=0.0001-0.021; and 60.6% vs 21.4% to 37.0% with anti-RNP, respectively, p=0.0001-0.022). In addition, Afro-caribbean patients have high serological expression of anti-Ro and anti-La in association with rash (54.4 and 27.3% compared to 33.0%

and 12.6% in European patients, respectively, p=0.01 and 0.019), alopecia (56.8% vs 33.9% in Europeans with anti-Ro positivity, p=0.035), musculoskeletal involvement (49.4 and 22.8% vs 31.9 and 11.1% in European patients, respectively, p=0.004 and 0.009), neurological involvement (63.2% with anti-Ro positivity compared to 18.2% of East Asian and 33.3% of European patients, p=0.026) and lymphopenia (57.6% compared to 34.1% of Europeans with anti-Ro positivity, respectively, p=0.001).

In East Asian patients hypocomplementemia was a common presentation been associated with cutaneous symptoms (rash, photosensitivity or alopecia) (64.6%, 67.9% and 77.2% compared to 36.9%, 35.8% and 40.7% in Europeans, respectively, p=0.0004, 0.002 and 0.005), mouth ulcers (70.6% vs 34% of European patients, p=0.007), musculoskeletal involvement (65.7% compared to 38.1% in European and 49.4% in Afro-caribbeans, respectively, p=0.0001-0.049), serositis (70.8% vs 38.8% of Europeans, p=0.006), neurological involvement (91.7% compared to 47.2% of Europeans and 50% of Afro-caribbeans, respectively, p=0.004-0.023) and haematological features (leukopenia, lymphopenia and thrombocytopenia) (85.7%, 70.7% and 80% compared to 45.4%, 41.5% and 43.6% of European patients, respectively, p<0.0001 to 0.044).

Interestingly, East Asian patients less frequently express anti-IgG anticardiolipin antibodies when compared to European or South Asian patients, observed in patients with rash (8.3% vs 22.8 and 26.3%, respectively, p=0.02-0.038), photosensitivity (3.6% vs 21.7% of Europeans, p=0.02), musculoskeletal involvement (7.1% vs 22% and 25%, respectively, p=0.003-0.011), serositis (4.2% compared to 25.9% of Europeans, p=0.017), renal involvement (5.3% vs 20.9% and 25%, respectively, p=0.034-0.047) and lymphopenia (5.3% vs 22.1% and 20.5%, respectively, p=0.003-0.029).

DISCUSSION

We have studied a relatively large number of SLE patients followed carefully over a long period using broadly similar assays throughout to review ethnic diversity in this disease. Although as discussed below, there have been other studies of this nature they were mostly multi-sites often

using different assays to measure for example dsDNA antibodies, of much shorter duration and usually in involving just two or three ethnic groups.

As expected, females were more affected by SLE (22) in each ethnic group. In our study, European, South Asian and Afro-Caribbean patients developed the disease later than the East Asian group. This result was consistent with previous reports (eg from Leicester, UK) where a younger age at diagnosis was observed in Asian patients (24±6 years) compared to white patients (31±5 years) (23). Interestingly, and unlike our experience, previous reports have found that African-American females with SLE had a younger mean age at diagnosis compared with white females (24).

Skin lesions in SLE are frequent (about 75% of patients) and often polymorphic (25, 26). In the present study skin lesions (namely rash and photosensitivity) were less frequent in the Afro-Caribbean group features that have been observed in previous reports (7, 27-29) perhaps being less easily recognized in this group (30).

A negative association with renal involvement was observed in the European patients when compared with the other ethnic groups, a result consistent with previous reports (6, 27, 31-33). In a systematic review of SLE in Asia, higher rates of renal involvement were described in Asian patients (21-65% at diagnosis and 40-82% at follow-up) when compared with White patients (6, 31). Renal disease was also more common in Black SLE patients in our study as has previously been reported (7, 27, 32).

All of our South Asian patients present musculoskeletal involvement (100%), a feature less frequent on the rest of the ethnic groups. Interestingly, Jasmin et al (33) showed that arthritis was a common clinical manifestation (52.3%) in a multi-ethnic Malaysian population, with Indians having a higher risk of arthritis compared to Malays and Chinese Malaysians.

ANA and anti-dsDNA antibodies are the most frequent autoantibodies detected in all groups.

Analysis of individual autoantibody specificities in the anti-ENA spectrum revealed significant differences among ethnic groups. Reports in Afro-Caribbean SLE patients indicate that anti-Sm, anti-RNP and anti-Ro were more prevalent than in those with European ancestry (28, 29, 32).

As previously observed (27-29, 32, 34) that the Afro-caribbean SLE patients in our study had the greatest prevalence of anti-Sm antibodies (37.5%), which was much less common in the other groups (European 9.5%, East Asian 17.6%, South Asian 14.3%).

Curiously, Li and co-workers (2014) (35) studied a Chinese SLE population of 2170 and observed a positivity of 44.1% for anti-phospholipid antibodies (anticardiolopin, anti-B2 glucoprotein I antibody and LAC), a significant high number when compared to our group of East Asian patients where the frequency of anti-IgG and IgM anticardiolipin and LAC were of 7.9%, 6.6% and 13% (with a total of 24.7%, 19/77, p=0.0007), respectively, and a significantly association between our non-East Asian patients with positivity for anti-IgG anticardiolipin antibodies and several clinical features (namely, rash, photosensitivity, musculoskeletal and renal involvement, serositis and lymphopenia). In contrast, Li and co-workers found an association between anti-phospholipid antibodies and haematological involvement, interstitial lung disease and a lower prevalence of oral ulcerations ($p<0.05$) (35), a result not consistent with our findings.

In this study we observed that Afro-caribbeans with kidney involvement have higher positivity for ENA antibodies (anti-Sm and anti-RNP), as reported previously (1). In addition, in this ethnic group a significant association was observed between anti-Ro positivity and presence of cutaneous manifestations (skin rash) as previously described in literature (36, 37).

A previous study showed that Asian ethnicity was significantly associated with a more clinically severe SLE, with patients being more likely to have renal disease (OR 2.9, 95% CI 1.4-5.98; p=0.004), a significantly higher proportion of autoantibody positivity to anti-RNP and anti-Sm, and an increased likelihood of hypocomplementaemia (38) which is in agreement with our findings.

It is important to mention that the apparent differences observed in phenotypic expression, severity and even frequency of SLE between the different ethnic groups may be due to genetic or environmental (including cultural) factors or a combination of both (39). As the LUMINA (Lupus in Minorities, Nature vs nurture) study has shown, rather than ethnicity per se, a lower income and the socioeconomic status are independent risk factors for the disease progression and outcome (40). In parallel, a study has also revealed that income (but not ethnicity or education level) was strongly associated with renal damage in a SLE cohort of patients (41). Unfortunately in studies from the USA it is hard to disentangle genetic and socio-economic factors. However, a study from the UK (where healthcare is free at the point of access to the system) clearly showed that renal disease and renal failure were much more common in the

black population (compared to the Caucasian group) strongly suggesting that genetic factors were highly significant in determining clinical outcome (42).

Much discussed in literature has been the use of self-reported ethnicity in genetic and epidemiologic studies, which may be seen as an important bias and could lead to misleading information (5, 43). Of major importance, as demonstrated when examining ancestry informative markers, it is clear that no homogeneous racial groups exist within the human race (44).

The key findings in this audit of ethnic differences in an SLE cohort followed for a period of up to 36 years were that East Asian patients developed the disease younger than the other ethnic groups. Anti-ENA antibodies were shown to be higher in the Afro-caribbeans, and the disease was commonly accompanied by low C3 levels in the East Asian patients. Renal involvement was more frequent in non-caucasians (23) and was frequently associated with anti-ENA antibodies in Afro-caribbeans.

Understanding the influence of ethnicity in disease expression, may provide a way for an individualised approach to risk assessment, management and monitoring of SLE.

REFERENCES

1. Alba P, Bento L, Cuadrado MJ, Karim Y, Tungekar MF, Abbs I, et al. Anti-dsDNA, anti-Sm antibodies, and the lupus anticoagulant: significant factors associated with lupus nephritis. Annals of the rheumatic diseases. 2003;62(6):556-60.
2. Vila LM, Alarcon GS, McGwin G, Jr., Friedman AW, Baethge BA, Bastian HM, et al. Early clinical manifestations, disease activity and damage of systemic lupus erythematosus among two distinct US Hispanic subpopulations. Rheumatology (Oxford, England). 2004;43(3):358-63.
3. Piram M, Maldini C, Mahr A. Effect of race/ethnicity on risk, presentation and course of connective tissue diseases and primary systemic vasculitides. Current opinion in rheumatology. 2012;24(2):193-200.
4. Pons-Estel GJ, Alarcon GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Seminars in arthritis and rheumatism. 2010;39(4):257-68.
5. Sanchez E, Rasmussen A, Riba L, Acevedo-Vasquez E, Kelly JA, Langefeld CD, et al. Impact of genetic ancestry and sociodemographic status on the clinical expression of systemic lupus erythematosus in American Indian-European populations. Arthritis and rheumatism. 2012;64(11):3687-94.
6. Jakes RW, Bae SC, Louthrenoo W, Mok CC, Navarra SV, Kwon N. Systematic review of the epidemiology of systemic lupus erythematosus in the Asia-Pacific region: prevalence, incidence, clinical features, and mortality. Arthritis care & research. 2012;64(2):159-68.
7. Flower C, Hennis AJ, Hambleton IR, Nicholson GD, Liang MH. Systemic lupus erythematosus in an African Caribbean population: incidence, clinical manifestations, and survival in the Barbados National Lupus Registry. Arthritis care & research. 2012;64(8):1151-8.
8. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine. 1993;72(2):113-24.
9. Urowitz MB, Gladman DD, Ibanez D, Fortin PR, Bae SC, Gordon C, et al. Evolution of disease burden over five years in a multicenter inception systemic lupus erythematosus cohort. Arthritis care & research. 2012;64(1):132-7.
10. Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. The New England journal of medicine. 2003;349(16):1526-33.
11. Somers EC, Marder W, Cagnoli P, Lewis EE, DeGuire P, Gordon C, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis & rheumatology (Hoboken, NJ). 2014;66(2):369-78.
12. Gomez-Puerta JA, Barbhaiya M, Guan H, Feldman CH, Alarcon GS, Costenbader KH. Racial/Ethnic variation in all-cause mortality among United States medicaid recipients with systemic lupus erythematosus: a Hispanic and asian paradox. Arthritis & rheumatology (Hoboken, NJ). 2015;67(3):752-60.
13. Lyn-Cook BD, Xie C, Oates J, Treadwell E, Word B, Hammons G, et al. Increased expression of Toll-like receptors (TLRs) 7 and 9 and other cytokines in systemic lupus erythematosus (SLE) patients: ethnic differences and potential new targets for therapeutic drugs. Molecular immunology. 2014;61(1):38-43.
14. Jeon JY, Kim KY, Kim BS, Jung JY, Kim HA, Suh CH. FcgammaRIIB Gene Polymorphisms Are Associated with Disease Risk and Clinical Manifestations of Systemic Lupus Erythematosus in Koreans. The Tohoku journal of experimental medicine. 2015;236(3):185-91.
15. Mok MY, Li WL. Do Asian patients have worse lupus? Lupus. 2010;19(12):1384-90.
16. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis and rheumatism. 1997;40(9):1725.
17. Isenberg DA, Garton M, Reichlin MW, Reichlin M. Long-term follow-up of autoantibody profiles in black female lupus patients and clinical comparison with Caucasian and Asian patients. British journal of rheumatology. 1997;36(2):229-33.
18. Isenberg DA, Williams W, Le Page S, Swana G, Feldman R, Addison I, et al. A comparison of autoantibodies and common DNA antibody idiotypes in SLE patients and their spouses. British journal of rheumatology. 1988;27(6):431-5.

19. Yamagata H, Harley JB, Reichlin M. Molecular properties of the Ro/SSA antigen and enzyme-linked immunosorbent assay for quantitation of antibody. The Journal of clinical investigation. 1984;74(2):625-33.
20. Harley JB, Yamagata H, Reichlin M. Anti-La/SSB antibody is present in some normal sera and is coincident with anti-Ro/SSA precipitins in systemic lupus erythematosus. The Journal of rheumatology. 1984;11(3):309-14.
21. Hulsey M, Goldstein R, Scully L, Surbeck W, Reichlin M. Anti-ribosomal P antibodies in systemic lupus erythematosus: a case-control study correlating hepatic and renal disease. Clinical immunology and immunopathology. 1995;74(3):252-6.
22. Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus. Lancet (London, England). 2014;384(9957):1878-88.
23. Samanta A, Feehally J, Roy S, Nichol FE, Sheldon PJ, Walls J. High prevalence of systemic disease and mortality in Asian subjects with systemic lupus erythematosus. Annals of the rheumatic diseases. 1991;50(7):490-2.
24. McCarty DJ, Manzi S, Medsger TA, Jr., Ramsey-Goldman R, LaPorte RE, Kwoh CK. Incidence of systemic lupus erythematosus. Race and gender differences. Arthritis and rheumatism. 1995;38(9):1260-70.
25. Obermoser G, Sontheimer RD, Zelger B. Overview of common, rare and atypical manifestations of cutaneous lupus erythematosus and histopathological correlates. Lupus. 2010;19(9):1050-70.
26. Lipsker D. The need to revisit the nosology of cutaneous lupus erythematosus: the current terminology and morphologic classification of cutaneous LE: difficult, incomplete and not always applicable. Lupus. 2010;19(9):1047-9.
27. Levy DM, Peschken CA, Tucker LB, Chedeville G, Huber AM, Pope JE, et al. Influence of ethnicity on childhood-onset systemic lupus erythematosus: results from a multiethnic multicenter Canadian cohort. Arthritis care & research. 2013;65(1):152-60.
28. Cooper GS, Parks CG, Treadwell EL, St Clair EW, Gilkeson GS, Cohen PL, et al. Differences by race, sex and age in the clinical and immunologic features of recently diagnosed systemic lupus erythematosus patients in the southeastern United States. Lupus. 2002;11(3):161-7.
29. Weckerle CE, Franek BS, Kelly JA, Kumabe M, Mikolaitis RA, Green SL, et al. Network analysis of associations between serum interferon-alpha activity, autoantibodies, and clinical features in systemic lupus erythematosus. Arthritis and rheumatism. 2011;63(4):1044-53.
30. Petit A, Dadzie OE. Multisystemic diseases and ethnicity: a focus on lupus erythematosus, systemic sclerosis, sarcoidosis and Behcet disease. The British journal of dermatology. 2013;169 Suppl 3:1-10.
31. James JA, Danda D. New perspectives and insights to Asian systemic lupus erythematosus: renal disease, genetic predisposition and disease activity. International journal of rheumatic diseases. 2013;16(6):611-4.
32. Alarcon GS, Friedman AW, Straaton KV, Moulds JM, Lisse J, Bastian HM, et al. Systemic lupus erythematosus in three ethnic groups: III. A comparison of characteristics early in the natural history of the LUMINA cohort. LUpus in MInority populations: NAture vs. Nurture. Lupus. 1999;8(3):197-209.
33. Jasmin R, Sockalingam S, Cheah TE, Goh KJ. Systemic lupus erythematosus in the multiethnic Malaysian population: disease expression and ethnic differences revisited. Lupus. 2013;22(9):967-71.
34. Santos MJ, Capela S, Figueira R, Nero P, Matos AA, Silva C, et al. [Characterization of a Portuguese population with systemic lupus erytematosus]. Acta reumatologica portuguesa. 2007;32(2):153-61.
35. Li J, Leng X, Li Z, Ye Z, Li C, Li X, et al. Chinese SLE treatment and research group registry: III. association of autoantibodies with clinical manifestations in Chinese patients with systemic lupus erythematosus. 2014;2014:809389.
36. Wang CL, Ooi L, Wang F. Prevalence and clinical significance of antibodies to ribonucleoproteins in systemic lupus erythematosus in Malaysia. British journal of rheumatology. 1996;35(2):129-32.
37. Tikly M, Burgin S, Mohanlal P, Bellingan A, George J. Autoantibodies in black South Africans with systemic lupus erythematosus: spectrum and clinical associations. Clinical rheumatology. 1996;15(3):261-5.

38. Golder V, Connelly K, Staples M, Morand E, Hoi A. Association of Asian ethnicity with disease activity in SLE: an observational study from the Monash Lupus Clinic. Lupus. 2013;22(13):1425-30.
39. Crosslin KL, Wiginton KL. The impact of race and ethnicity on disease severity in systemic lupus erythematosus. Ethnicity & disease. 2009;19(3):301-7.
40. Duran S, Apte M, Alarcon GS. Poverty, not ethnicity, accounts for the differential mortality rates among lupus patients of various ethnic groups. Journal of the National Medical Association. 2007;99(10):1196-8.
41. Cooper GS, Treadwell EL, St Clair EW, Gilkeson GS, Dooley MA. Sociodemographic associations with early disease damage in patients with systemic lupus erythematosus. Arthritis and rheumatism. 2007;57(6):993-9.
42. Adler M, Chambers S, Edwards C, Neild G, Isenberg D. An assessment of renal failure in an SLE cohort with special reference to ethnicity, over a 25-year period. Rheumatology (Oxford, England). 2006;45(9):1144-7.
43. Sinha M, Larkin EK, Elston RC, Redline S. Self-reported race and genetic admixture. The New England journal of medicine. 2006;354(4):421-2.
44. Gonzalez LA, Toloza SM, McGwin G, Jr., Alarcon GS. Ethnicity in systemic lupus erythematosus (SLE): its influence on susceptibility and outcomes. Lupus. 2013;22(12):1214-24.

Table 1 – Demographic characteristics of SLE patients per ethnic group.

Ethnic groups	Number of patients (%)	Age at diagnosis		Gender (%)	Age at diagnosis / gender
European	369 (59.1)	30.6 ± 13.2	**F**	334 (90.5)	30.3 ± 12.9
			M	35 (9.5)	33.3 ± 15.7
Afro-caribbean	100 (16.0)	28.4 ± 10.9	**F**	94 (94.0)	28.6 ± 11.0
			M	6 (6.0)	24.7 ± 7.2
East Asian	77 (12.3)	21.6 ± 10.6	**F**	69 (89.6)	21.9 ± 10.4
			M	8 (10.4)	18.9 ± 12.9
South Asian	56 (9.0)	30.3 ± 10.1	**F**	53 (94.6)	30.4 ± 10.0
			M	3 (5.7)	27.7 ± 14.6

Legends: F – Female; M – Male.

Table 2 – Clinical characteristics of SLE patients per ethnic group.

Manifestations	**Total N = 624**	**Ethnic Group**				
		European N = 369	**Afro-Caribbean N = 100**	**East Asian N = 77**	**South Asian N = 56**	**P value**
Musculoskeletal	91,3% (569/623)	**92,9% (342/368)**	**81,0% (81/100)**	**92,2% (71/77)**	**100% (56/56)**	p = 0.0002-0.049
Cutaneous						
Alopecia	22,8% (142/624)	**16,0% (59/369)**	38,0% (38/100)	28,6% (22/77)	30,4% (17/56)	p = 0.0001-0.014
Photosensitivity	40,1% (247/616)	49,2% (179/364)	**8,2% (8/97)**	37,7% (29/77)	41,1% (23/56)	p < 0.0001
Malar rash (butterfly lesions)	66,0% (410/621)	**70,9% (261/368)**	**46,9% (46/98)**	**63,6% (49/77)**	**67,9% (38/56)**	p = 0.0001-0.012
Oral/nasal ulcers	25,8% (160/620)	26,3% (97/369)	19,4% (19/98)	22,1% (17/77)	33,9% (19/56)	p = 0.053-0.709
Ocular lesions (Sicca syndrome)	8,6% (53/615)	9,3% (34/364)	**3,1% (3/96)**	**3,9% (3/76)**	**16,1% (9/56)**	p = 0.009-0.029
Serositis (pleuritic and/or pericarditis)	38,2% (238/623)	37,8% (139/368)	35,0% (35/100)	31,2% (24/77)	**55,4% (31/56)**	p = 0.007-0.019
Renal	31,6% (197/623)	**24,1% (89/369)**	**36,4% (36/99)**	**49,4% (38/77)**	42,9% (24/56)	p = 0.0001-0.021
Neurologic	20,9% (130/621)	19,6% (72/367)	20,0% (20/100)	15,8% (12/76)	**39,3% (22/56)**	p = 0.002-0.014
Hematologic						
Hemolytic anemia	3,7% (23/619)	3,3% (12/367)	4,1% (4/97)	5,2% (4/77)	1,8% (1/56)	p = 0.397-1.0
Leukopenia	29,6% (183/618)	27,9% (102/365)	25,3% (25/99)	27,6% (21/76)	**50,0% (28/56)**	p = 0.002-0.011
Lymphopenia	75,1% (464/618)	75,6% (276/365)	68,7% (68/99)	76,3% (58/76)	78,6% (44/56)	p = 0.195-1.0
Thrombocytopenia	14,9% (92/618)	**15,3% (56/365)**	**7,1% (7/99)**	13,2% (10/66)	**21,4% (12/56)**	p = 0.012-0.032

Table 3 – Serological characteristics of SLE patients per ethnic group.

Variable	Total N = 624	Ethnic group				
		European N = 369	Afro-Caribbean N = 100	East Asian N = 77	South Asian N = 56	P value
ANA	93,8% (574/612)	93,6% (339/362)	96,0% (95/99)	89,0% (65/73)	96,4% (54/56)	p = 0.127-1.0
High-anti-dsDNA	63,4% (391/617)	62,0% (227/366)	61,6% (61/99)	67,6% (50/74)	64,3% (36/56)	p = 0.429-1.0
Anti-U1-nRNP	28,3% (174/615)	**20,3% (75/369)**	**53,1% (51/96)**	**34,7% (25/72)**	**28,6% (16/56)**	p = 0.0001-0.020
Anti-Smith	15,4% (95/616)	9,5% (35/368)	**37,5% (36/96)**	17,6% (13/74)	14,3% (8/56)	p = 0.0001-0.006
Anti-Ro (SSA)	36,9% (227/616)	**32,2% (119/369)**	**53,1% (51/96)**	41,1% (30/73)	39,3% (22/56)	p = 0.0002
Anti-La (SSB)	14,0% (86/616)	**11,7% (43/369)**	**20,8% (20/96)**	15,1% (11/73)	16,1% (9/56)	p = 0.028
Lupus anticoagulant	15,7% (96/611)	17,8% (64/360)	11,3% (11/97)	13,0% (10/77)	12,5% (7/56)	p = 0.164-1.0
Anti-IgG anticardiolipin	19,6% (120/612)	**21,8 % (79/362)**	15,6% (15/96)	**7,9% (6/76)**	**25,0% (14/56)**	p = 0.004-0.012
Anti-IgM anticardiolipin	8,0% (49/612)	**9,7% (35/362)**	**3,1% (3/96)**	6,6% (5/76)	5,4% (3/56)	p = 0.038
Coombs positive	22,1% (138/624)	19,5% (72/369)	29,0% (29/100)	27,3% (21/77)	19,6% (11/56)	p = 0.054-1.0
Anti-thyroid microsome	9,8% (61/624)	10,8% (40/369)	6,0% (6/100)	6,5% (5/77)	12,5% (7/56)	p = 0.185-1.0
Anti-thyroglobulin	4,3% (27/624)	**5,7% (21/369)**	**2,0% (2/100)**	5,2% (4/77)	0% (0/56)	p < 0.0001
RF	21,9% (129/589)	21,0% (74/352)	20,7% (19/92)	29,4% (20/68)	23,2% (13/56)	p = 0.152-1.0
Low C3	38,0% (236/621)	**38,9% (143/368)**	**50,5% (50/99)**	**65,8% (50/76)**	51,8% (29/56)	p = 0.0001-0.039

Legends: ANA - antinuclear antibodies; dsDNA - doublestranded DNA; RF – rheumatoid factor.

Table 4 – Clinical and serological characteristics of SLE patients according to ethnic group.

Variables	Ethnic groups				
	European	Afro-caribbean	East Asia	South Asian	P value
Rash vs anti-Sm	9.2% (24/261)	**34.1% (15/44)**	14.9% (7/47)	13.2% (5/38)	p = 0.0001-0.049
Rash vs anti-RNP	19.2% (50/261)	**56.8% (25/44)**	31.9% (15/47)	31.6% (12/38)	p = 0.0001-0.027
Rash vs anti-Ro	**33.0% (86/261)**	**54.4% (24/44)**	44.7% (21/47)	42.1% (16/38)	p = 0.01
Rash vs anti-La	12.6% (33/261)	**27.3% (12/44)**	12.8% (6/47)	15.8% (6/38)	p = 0.019
Rash vs low C3	**36.9% (96/260)**	53.3% (24/45)	64.6% (31/48)	55.3% (21/38)	p = 0.0004-0.047
Rash vs IgG	**22.8% (58/254)**	19.0% (8/42)	**8.3% (4/48)**	**26.3% (10/38)**	p = 0.02-0.038
Photosen. vs anti-Sm	**7.8% (14/179)**	12.5% (1/8)	**21.1% (6/28)**	8.7% (2/23)	p = 0.036
Photosen. vs anti-RNP	**19.0% (34/179)**	37.5% (3/8)	**37.0% (10/27)**	34.8% (8/23)	p = 0.044
Photosen. vs low C3	**35.8% (64/179)**	37.5% (3/8)	**67.9% (19/28)**	**60.9% (14/23)**	p = 0.002-0.024
Photosen. Vs IgG	**21.7% (38/175)**	28.6% (2/7)	**3.6% (1/28)**	21.7% (5/23)	p = 0.02
Alopecia vs anti-Sm	**11.9% (7/59)**	**45.9% (17/37)**	20.0% (4/20)	23.5% (4/17)	p = 0.0003
Alopecia vs anti-RNP	**20.3% (12/59)**	**64.9% (24/37)**	**50.0% (10/20)**	41.2% (7/17)	p = 0.0001-0.019
Alopecia vs anti-Ro	**33.9% (20/59)**	**56.8% (21/37)**	35.0% (7/20)	29.4% (5/17)	p = 0.035
Alopecia vs low C3	**40.7% (24/59)**	**65.8% (25/38)**	**77.2% (17/22)**	70.6% (12/17)	p = 0.005-0.022
MouthU vs anti-Sm	**5.2% (5/97%)**	**36.8% (7/19)**	**0% (0/17)**	**26.3% (5/19)**	p = 0.0005-0.047
MouthU vs anti-RNP	**15.5% (15/97)**	**57.9% (11/19)**	29.4% (5/17)	31.6% (6/19)	p = 0.0002
MouthU vs low C3	**34.0% (33/97)**	52.6% (10/19)	**70.6% (12/17)**	52.6% (10/19)	p = 0.007
Musc. vs anti-Sm	9.7% (33/341)	**36.7% (29/79)**	17.6% (12/68)	14.3% (8/56)	p = 0.0001-0.016
Musc. vs anti-RNP	**19.6% (67/342)**	**53.2% (42/79)**	**34.8% (23/66)**	28.6% (16/56)	p = 0.0001-0.030
Musc. vs anti-Ro	**31.9% (109/342)**	**49.4% (39/79)**	38.8% (26/67)	39.3% (22/56)	p = 0.004
Musc. vs anti-La	**11.1% (38/342)**	**22.8% (18/79)**	14.9% (10/67)	16.1% (9/56)	p = 0.009
Musc. vs low C3	**38.1% (130/341)**	**49.4% (40/81)**	**65.7% (46/70)**	51.8% (29/56)	p = 0.0001-0.049
Musc. Vs IgG	**22.0% (74/336)**	16.3% (13/80)	**7.1% (5/70)**	**25.0% (14/56)**	p = 0.003-0.011
Serositis vs anti-Sm	**10.1% (14/139)**	**45.5% (15/33)**	21.7% (5/23)	**16.1% (5/31)**	p = 0.0001-0.015
Serositis vs anti-RNP	**21.6% (30/139)**	**57.6% (19/33)**	39.1% (9/23)	**32.3% (10/31)**	p = 0.0002-0.049
Serositis vs low C3	**38.8% (54/139)**	48.6% (17/35)	**70.8% (17/24)**	58.1% (18/31)	p = 0.006
Serositis vs IgG	**25.9% (36/139)**	17.6% (6/28)	**4.2% (1/24)**	22.6% (7/31)	p = 0.017
Renal vs anti-Sm	**11.2% (10/89)**	**42.9% (15/35)**	24.3% (9/37)	20.8% (5/24)	p = 0.0002
Renal vs anti-RNP	**18.0% (16/89)**	**60.0% (21/35)**	**33.3% (12/36)**	33.3% (8/24)	p = 0.0001-0.033
Renal vs IgG	**20.9% (18/86)**	19.4% (7/36)	**5.3% (2/38)**	**25.0% (6/24)**	p = 0.034-0.047
Neurologic vs anti-Sm	**5.6% (4/72)**	**47.4% (9/19)**	16.7% (2/12)	**13.6% (3/22)**	p = 0.0001-0.037
Neurologic vs anti-RNP	**15.3% (11/72)**	**42.1% (8/19)**	**45.5% (5/11)**	36.4% (8/22)	p = 0.022-0.032

Neurologic vs anti-Ro	**33.3% (24/48)**	**63.2% (12/19)**	**18.2% (2/11)**	40.9% (9/22)	p = 0.026
Neurologic vs low C3	**47.2% (34/72)**	**50.0% (10/20)**	**91.7% (11/12)**	68.2% (15/22)	p = 0.004-0.023
Sicca synd. vs anti-Ro	**70.6% (24/34)**	**0% (0/3)**	100% (3/3)	44.4% (4/9)	p = 0.037
Sicca synd. vs anti-La	44.1% (15/34)	0% (0/3)	**100% (3/3)**	**22.2% (2/9)**	p = 0.045
Leukop vs anti-Sm	**10.9% (11/101)**	**33.3% (8/24)**	14.3% (3/21)	14.3% (4/28)	p = 0.011
Leukop vs anti-RNP	**19.6% (20/102)**	37.5% (9/24)	33.3% (7/21)	**39.3% (11/28)**	p = 0.044
Leukop vs low C3	**45.4% (46/101)**	56.0% (14/25)	**85.7% (18/21)**	**50.0% (14/28)**	p = 0.003-0.015
Lymphop vs anti-Sm	10.2% (28/275)	**39.4% (26/66)**	16.1% (9/56)	18.2% (8/44)	p = 0.0001-0.021
Lymphop vs anti-RNP	**21.4% (59/276)**	**60.6% (40/66)**	**37.0% (20/54)**	34.1% (15/44)	p = 0.0001-0.022
Lymphop vs anti-Ro	**34.1% (94/276)**	**57.6% (38/66)**	47.3% (26/55)	38.6% (17/44)	p = 0.001
Lymphop vs low C3	**41.5% (114/275)**	58.2% (39/67)	70.7% (41/58)	59.1% (26/44)	p = 0.0001-0.034
Lymphop vs IgG	**22.1% (60/271)**	15.2% (10/66)	**5.3% (3/57)**	**20.5% (9/35)**	p = 0.003-0.029
Thrombocyt. vs anti-Ro	**19.6% (11/56)**	50.0% (3/6)	**60.0% (6/10)**	50.0% (6/12)	p = 0.014
Thrombocyt. vs anti-La	**3.6% (2/56)**	0% (0/6)	10.0% (1/10)	**25.0% (3/12)**	p = 0.035
Thrombocyt. vs low C3	**43.6% (24/55)**	57.1% (4/7)	**80.0% (8/10)**	58.3% (7/12)	p = 0.044

Legend: vs – versus; Photosen. – Photosensitivity; Musc. – Musculoskeletal; Thrombocyt. – Thrombocytopenia; IgG – anti-IgG anticardiolipin; MouthU – Mouth ulcers; Sicca synd. – Sicca syndrome; Leukop – Leukopenia; Lymphop – Lymphopenia.