UNIVERSITY OF CRETE


# Impact of residential environment on Systemic Lupus Erythematosus outcomes in a south European population

A Master Thesis

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*In memory of my father, Nikolaos*

*"We shall not cease from exploration and the end of all our exploring will be to arrive where we started and know the place for the first time"*

*T. S. Eliot*

## ABSTRACT

**Background** Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease that originates from a complex interplay between genetic, epigenetic and environmental factors.

**Objectives** To study the effect of rural versus urban place of residency in SLE patients with regards to: i) disease occurrence (relative risk); ii) clinical manifestations, severity, organ damage; and, iv) comorbidities and hospitalization rates.

**Methodology** Cross-sectional study which analyzed data collected from questionnaires of SLE patients (n=401) at their enrolment in Cretan Lupus registry in Crete, from 2012-2015 and from their medical records' review. We compared SLE occurrence and outcomes of the patients by their residential history thus having lived exclusively in a rural (<10.000 inhabitants) or urban (>10,000 inhabitants) or mixed environment, through their entire lifespan.

**Results** The relative risk of developing SLE in an urban versus a rural region was 2.08 (95% Confidence Interval 1.66-2.61, *p<0.001*). Notably, patients who had exclusively lived in urban regions were significantly younger at SLE diagnosis (mean± SD, 38.3 ± 13.1 years old), as compared to patients who lived exclusively in rural (45.0 ± 15.3 years, *p=0.024*) and lower female-to-male ratio (6.5:1 *vs*. 15:1, *p=0.03*). Antiphospholipid antibodies were found positive in 20.5% of the patients in urban vs. 14.1% in rural SLE population *(p=0.04).* In multivariable logistic regression analysis, urban living was associated with lower risk (Odds ratio [OR]) 0.5, CI 95% 0.27-0.9 for moderate/severe forms of SLE, independent of the effects of other disease-related factors including the total number of ACR classification criteria. On the contrary, the place of residency was not predictive of organ damage accrual. Further, hospitalizations differed slightly (38.5% in rural vs. 37.6% in urban, *p=0.003*).

**Conclusion** Given the rather homogenous genetic background of the population, these results suggest an important effect of the living environment on SLE risk and phenotype, which warrants further investigation.



**Key words** SLE; rural urban disparities; place of residency; health disparities; access to care; utilization of health services.

**Η επίδραση του αστικού συγκριτικά με το αγροτικό περιβάλλον στην έκβαση του Συστηματικού Ερυθηματώδους Λύκου, σε πληθυσμό Νότιας Ευρώπης.**


## ΠΕΡΙΛΗΨΗ

**Υπόβαθρο** Ο Συστηματικός Ερυθηματώδης Λύκος (ΣΕΛ) είναι μια αυτοάνοση νόσος που οφείλεται σε αλληλεπιδράσεις γενετικών, επιγενετικών και περιβαλλοντικών παραγόντων.

**Σκοπός** Η μελέτης επίδρασης αστικού έναντι. αστικού τόπου διαμονής αναφορικά με i) το σχετικό κίνδυνο ανάπτυξης ΣΕΛ, ii) τις κλινικές εκδηλώσεις iii)τη σοβαρότητα iv) τη βλάβη σε όργανα και v) τις απαιτούμενες νοσηλείες.

**Μεθολογία** Συγχρονική μελέτη στην οποία αναλύθηκαν δεδομένα του Αρχείου ΣΕΛ Κρήτης που συλλέχθηκαν από ανασκόπηση ιατρικών φακέλων και ερωτηματολόγια σε ασθενείς ΣΕΛ (n=401) κατά την εισαγωγή τους στη μελέτη (2012-2015) και τα οποία συγκρίθηκαν με βάση τον τόπο διαμονής: αποκλειστικά αγροτικός (<10.000 κατοίκους), αποκλειστικά αστικός (>10,000 κατοίκους) ή και τα δύο κατά τη διάρκεια της ζωής των ασθενών.

**Αποτελέσματα** Ο σχετικός κίνδυνος ανάπτυξης ΣΕΛ σε μια αγροτική συγκριτικά με μια αστική περιοχή ήταν 2.08 (95% Διάστημα Εμπιστοσύνης 1.66-2.61, *p<0.001*). Οι ασθενείς που είχαν αποκλειστικά ζήσει σε αστικές περιοχές είχαν μικρότερη ηλικία στη διάγνωση, συγκριτικά με εκείνους που είχαν ζήσει αποκλειστικά σε αγροτική περιοχή (μέση τιμή ± SD, 38.3 ± 13.1 vs. 45.0 ± 15.3 ετών, *p=0.024*) και χαμηλότερη αναλογία γυναικών:ανδρών (6.5:1 στις αστικές *vs.* 15:1 στις αγροτικές περιοχές, *p=0.03*). Τα αντιφωσφολιπιδικά αντισώματα ήταν θετικά στο 20.5% στο αστικό vs. 14.1% στο αγροτικό περιβάλλον *(p=0.04)*. Στην πολυπαραγοντική ανάλυση παλινδρόμησης το αστικό περιβάλλον συσχετίστηκε με χαμηλότερο κίνδυνο εμφάνισης μετρίων/σοβαρής μορφών ΣΕΛ (Odds ratio [OR]) 0.5, CI 95% 0.27-0.9), ανεξάρτητα από την επίδραση άλλων παραγόντων που σχετίζονται με την νόσο και οι οποίοι περιλαμβάνουν τον συνολικό αριθμό των ACR κριτηρίων ταξινόμησης. Αντίθετα, ο τόπος διαμονής δεν ήταν προγνωστικός της μη αναστρέψιμης βλάβης. Επιπρόσθετα, το ποσοστό των νοσηλειών διέφερε ελαφρά (38.5% στο αγροτικό vs. 37.6% στο αστικό, *p=0.003*).

**Συμπέρασμα** Με δεδομένο το σχετικά ομοιόμορφο γενετικό υπόβαθρο του υπό μελέτη πληθυσμού, τα αποτελέσματα υποδηλώνουν σημαντική επίδραση του περιβάλλοντος διαμονής στην εκδήλωση και τους φαινοτύπους του ΣΕΛ, που χρήζει περαιτέρω διερεύνησης.



**Λέξεις κλειδιά** ΣΕΛ; ανισότητες αγροτικού αστικού; τόπος διαμονής; πρόσβαση στην υγεία; χρήση υπηρεσιών υγείας;

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*This work is dedicated to my family and especially my daughter who inspired me to keep exploring my academic interests and supported me in every possible way.*

**TABLE OF CONTENTS**

**Chapter** **Page**

**LIST OF TABLES**

LIST OF FIGURES

## CHAPTER I: Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with important clinical, societal and economical concenquences[1]. SLE aitiopathogenesis is yet not fully clarified.[2] Although it is well established that genetics influence SLE susceptibility, environmental factors and epigenetics are also suggested to play an important role. [3] Notably, increasing trends of SLE in different parts of the world, within the second half of the twentieth century have been explained, at least partially, by environmental triggers[4 5].

Furthermore, demographic and socio-economical attributes of a population can have an important effect, not only on SLE occurrence, but also on clinical features and overall prognosis.[1 6 7] Illustratively, prevalence of the disease differ considerably across gender (female-to-male ratio 9-15:1)[8], race/ethnicity[7] (2- to 3-fold increased in black individuals) or geographical area (9/100,000 in Ukraine[9] to 300/100,000 cases in USA[10]). Disparities and inequalities are not uncommon in SLE populations[11 12] without having been elucidated to what extent socioeconomic disadvantage or ethnicity is the main key driver. [13 11 14] Characteristically, non-whites with SLE have mortality rates up to 3 times higher than whites and they disproportionally suffer from more aggressive disease[7].[13]

Although a number of population-based studies have contributed in understanding the influence of socio-environmental determinants on the disease, the role of place of residence per se, has been addressed infrequently. More specifically, despite being an important health determinant, the urban versus rural place of living, has not been extensively studied, as far as the effects both on SLE expression and its long term outcomes. A few relevant studies have reported higher activity at diagnosis, higher occurrence of renal disease over time[15] and more depression[16] in rural vs. urban regions, but similar rates regarding the delay in the diagnosis[17], disease activity over the disease course, hospitalizations, damage or mortality[15]. As expected, findings from some previous studies, most of them performed in heterogeneous multiethnic environments with enormous inequalities, suggest that patients from unprivileged residential areas may

experience worse clinical outcomes due to their low socioeconomic status, educational level or inadequate access to health care.[18] [17] [11]. On the other hand, studies suggest that SLE is more frequent in urban than rural regions[19] [20] and furthermore that neighbourhood poverty is related to depression in SLE patients independently of individual socioeconomic status.[21]

As the literature supporting the impact of living environments and, in particular, urbanization on health grows, the issue is re-emerging as one of the biggest public health challenges of the 21st century. [22] [23] [24] [25] In that context, it would be important to update the identification of any urban-rural patterns in the occurrence or outcomes of SLE, a prototype autoimmune disease and the recognition of possible modifiable risk factors that may contribute in health disparities or imply a role in pathogenesis.

The aim of our study was to estimate the effects of urban-versus-rural residency on SLE in patients living in Crete, a Mediterranean island with a population that is monoethnic and relatively homogenous, both genetically and socio-demographically.

## CHAPTER II: Background and Literature Review

### *SLE clinical and epidemiological overview*

SLE is a multisystem autoimmune disease with diverse presenting manifestations.[26] Patients may present with typical or atypical constellation of symptoms that practically can affect any organ or tissue and include fatigue, butterfly (malar) rash, alopecia, Raynaud phenomenon, sun sensitivity, livedo reticularis, oral ulcers, arthritis, myalgias, serositis (pleuritis or pericarditis), nephritis or neurological symptoms (psychosis, seizures, mood disorders). Due to the main pathogenetic mechanism which is loss of self-tolerance and inflammation, a vast array of immunological disturbances can be detected in lupus patients. Most common such features are the increase of antibodies (anti-nuclear antibodies, anti-Sm, antiphospolipid antibodies), various cytopenias (anaemia, leucopenia or thrombocytopenia) and decreased complement (C3 and C4). [26]

Diagnosis is currently based on strong clinical expertise acumen, since no diagnostic criteria have been validated[27]. Interestingly, manifestations and serological abnormalities do not always occur at the same time, leading to a continuum of a disease from a milder connective tissue syndrome (CTD) or pre-lupus to the full-spectrum of a severe case. Symptoms can vary from person to person, may be intermittent (flares and reemissions) and can be mild, moderate, or severe. SLE is a chronic disease which can cause damage to main organs and tissues leading to non-reversible consequences such as End-Stage Renal Disease (ESRD). Comorbidities and particularly cardiovascular disease, infections and cancer can further complicate the course of the disease[28], leading to a multimorbid complex disease status.[29] Although survival rates have increased (the five-year survival has improved to over 90% from a low of 50% in the 1950s), due to early recognition of the disease and better management, the unmet needs of ameliorating quality of life of the patients and improved morbidity and overall prognosis remain[30].

Further, a consistent finding in SLE studies is that gender and race/ethnicity[14] [7] are important determinants of the disease frequency and course.[5] [14] Some ethnic groups (African Americans, Hispanics, Canadian aboriginals) have more severe disease and poorer prognosis.[31] [32] [33] SLE occurrence differs considerably across the globe,[1] with prevalence rates ranging from 9[9] to 300 cases[10] per 100,000, and incidence rates from 0.3[9] to 23.7[34] per 100,000 person-years as reported in studies conducted during the last ten years.[5] In Greece, the prevalence estimates reported from previous studies range from 50[35] to 110[36] per 100,000 people but more recent data from Cretan Lupus Cohort suggest higher prevalence up to 123 per 100,000 (Gergianaki et al, unpublished data). Together, these findings are suggesting that SLE should no longer be considered a rare disease (defined from European Union as no more than 50 patients per 100,000).[37]

**Environmental factors and SLE**

Multiple environmental factors have been implicated in the pathogenesis and the course of SLE. Robust epidemiologic evidence provides association of silica, cigarette smoking, oral contraceptives, postmenopausal hormone therapy and endometriosis, with SLE occurence.[38] A number of studies have also provided evidence of the association between alcohol consumption and decreased SLE risk[38]. Additionally, there are mixed data that other factors (ultraviolet light, air pollution, infections, solvents, pesticides, cosmetics and heavy metals such as mercury and vaccinations) are related to SLE risk. [39] [38] [40]

Interestingly, in a recent study, Simoniello M. et al[41] aimed at assessing the possible effect of environmental pesticide mixtures in 89 patients with SLE, 46% of whom came from areas highly sprayed with pesticides, comparing them with patients from urban areas. In order to identify factors that could predict DNA damage and oxidative stress, a binary logistic regression model was developed revealing that place of residence ($p = 0.007$) has 75% of positive predictive value and that lupus patients living in villages presented 3.52 times more oxidative DNA damage compared to those living in the city. [41]

***Place of residency and Health: Urban vs. Rural effects***

Over the past decades, there has been an unprecedented urbanization of the word's population[24] creating new dynamics and challenges but also new disparities and inequalities.[42] Urbanization has been a growing concern in most of the developed world. The estimations predict that in 2050 the urban population will be 70% of the global population.[25] Residential instability, migration[43] and mega-cities are some more of the very important aspects of the enormous effect that place can have to the health of the populations in the near future, moving the focus of the research interest "from the gene code to the ZIP code".

These characteristics influence the magnitude and types of health problems that communities face. This ongoing demographic alteration inevitably leads to the emerging need for epidemiology to be more closely linked to research that uses surrogate markers than the traditional individual-based health determinants of socioeconomic status (SES), education or other health-related risk factors. On the other hand, the explosion of geographic information systems (GIS) and other relevant innovations and technological improvements in regional science and geovisualization[44 45] have largely facilitated the attempt to update our knowledge through sophisticated disease mapping. Of course, such approaches are not something new: from the era that John Snow, the father of epidemiology, unravelled the cause of cholera by mapping the pumps of water in London to the current innovative research in non-communicable diseases, the living environment matters and can be a simple but sometimes neglected way to enlighten us regarding disease pathogenesis[23 46].

In this context, place probably should not be treated under simplistic approaches because, in fact, it is a dynamic measure of both built and social environment and of the way people interact with environment and with each other. In other words, living environment should not be handled merely as a traditional constellation of risk factors (i.e physical inactivity-sedentary life in cities vs. remoteness and difficult access to care in villages). A multidisciplinary approach in relevant research could undoubtedly lead to a better

understanding of disease processes, identify vulnerable populations and generate results for interventionists and policy makers.

Generally, the place of residency is associated with the "Lifestyle" of people. Although the strict definition of lifestyle is complex, it can by simplified by "the way in which a person lives" (Oxford Dictionary; www.oxforddictionaries.com), being mainly a sociological term which potentially carries health implications including psychological, cultural, historical, socio-economic and environmental factors that influence the habits that characterize the living mode of a group of individuals. In this concept, the residential area i.e. a mega city or a metropolitan city[47], a small town or a village[48] should also be seen as surrogate lifestyle measure.

Furthermore, the area of residency (urban or rural) can be particularly important given the uneven spatial distribution of goods, services and resources, education and health included [25]. Numerous studies have revealed the impact of residential area on health, regarding non-communicable diseases[47 49 50 51 52], mental disease included, with most striking the double occurrence percentage of schizophrenia in urban regions.[53 54]

Although rural–urban differences do not exist for many health measures or outcomes, there is a gradient in a large number of health conditions. For example, dwellers in the cities, on average, can theoretically receive improved sanitation, nutrition and specialized health care. Urban living is on the other hand associated with poor air quality, increased crime, injuries, a more stressful working and social environment and increased homicides.[23] Asthma prevalence and morbidity is more frequent in urban areas. A possible explanation is that rural residents are exposed early in life to stables and to farm milk production and such exposures are being protective against asthma morbidity.[55] Importantly, the increasing trend of "urban poors" shapes various vulnerabilities since availability and access to health care does not ensure affordability and utilization of health services [23 22 45 56].

On the contrary, people living in rural areas also have a "rural disadvantage".[23 57] The 2014 Update of the US Rural-Urban Chart Book provides useful insights. More specifically, differences in urban and rural mortality rates exist across the entire lifespan, with the lowest rates in fringe counties of large metro areas and the highest in the most rural ones[58]. If fact, urban-rural gap in life expectancy and all-cause mortality has widened during the last decade as "*The rural poor and rural blacks currently experience survival probabilities that urban rich and urban whites enjoyed 4 decades earlier*"[59 60]. Obesity also varies by urbanization level and increases with increasing rurality[58]. Ischemic heart disease death rates for both men and women at least 20 years old were also higher in the most rural counties[58]. Furthermore, suicide rates for both sexes increased with increasing levels of rurality, while age-adjusted activity limitation rates due to chronic health conditions were also higher in the most rural counties.[58]

Interestingly, research supports that rural vs. urban health patterns are not always "monotonic", meaning that the most rural and the most urban areas have higher rates of adverse health effects in comparison with suburban areas[2]. Furthermore, the risk-factor burden is occasionally "paradoxically" associated with the actual prevalence of the disease. Most characteristic paradigm is the asymmetry of cardiovascular risk factors and case fatality from cardiovascular events, which is mainly explained by socioeconomic differences (such as residents' awareness, healthcare quality, and medical services availability and affordability.[61])

***The effect of residency on SLE***

A limited number of studies have explored the effect of urbanization vs. rurality on SLE. The main findings from these studies reveal the association of rural areas with increased age at diagnosis, lower female-to-male ratio (5:1 compared to typical 9:1) but not significant different clinical characteristics, disease severity and mortality.[15] Further it has been reported that a major disadvantage of SLE patients living in non-urban regions is the limited availability of health care experts. A more recent study examined the role of the place of residency on the expression and outcome of SLE in the largest multi-national

Latin American cohort, GLADEL[15]. The authors reported that patients from rural areas had lower socioeconomic status, educational level and medical insurance coverage[15]. These patients experienced more active disease at the time of diagnosis and a more renal disease occurrence over time[15]. In the same study, on the contrary, there were no poorer outcomes in terms of disease activity over time, renal or overall damage and mortality.[15] The explanation given by researchers was that patients may have presented to the rheumatologists only when the disease was evident and active. To this end, Ward *et al* also showed that SLE patients who had more limited care access, had increased risk to developing ESRD.[62]

In addition, a residential area is possibly associated with environmental exposures that may trigger different patterns of SLE expression.[63] Most characteristic factors include: work-related increase in the levels of sun light[64] and exposures to pesticides[65] or insectides[66] which are more likely to occur in rural areas. In contrast, other factors like air pollution levels[67], occur more frequently in cities. Finally, factors such as smoking[68 69 70] or infections associated with lupus -such as Epstein Barr virus[71] may be observed equally in urban and rural areas.

A more recent study was performed in Egypt to examine the influence of the neighbourhood environment and rural residency on outcomes in an SLE cohort[16] and reported that rural residency was associated with higher depression symptoms and disease activity[16], explaining this association by the fact that the rural residents in Egypt may not have had the same medical specialized care, probably presenting to rheumatologists when the disease was quite active. On the contrary, a study from Austria showed no association of delay in diagnosis and rural or urban residency.[17]

Furthermore, scarce data exist regarding the comparison of occurrence of SLE among rural and urban regions. Most studies suggest that SLE is more frequent in urban than rural regions. [19 20 72] In Crete, the point prevalence of SLE (December 2013) was significantly higher in urban ($165/10^5$) than rural ($123/10^5$) areas ($p<0.001$) (Gergianaki *et al*, under peer review). Al Maini et al. used GIS to create a map of incidence rates for

SLE patients in Toronto [73] and identified a hot spot, suggesting that ethnicity *per se* did not increased risk of SLE, but it was mainly the interaction of ethnicity with residential area that significantly increased SLE risk.[73] Other rheumatic diseases such as Rheumatoid Arthritis is also found to be more common in urban regions in both developed and under-development countries[74] [75] in contrast to scleroderma that has been reported to be more frequent in rural areas.[72]

# CHAPTER III: METHODOLOGY

## Settings

Crete is the third largest and southernmost island in the Mediterranean with a relatively stable, genetically homogeneous population of ~0.6M inhabitants, thus offering the opportunity to study the natural history of complex diseases such as systemic lupus erythematosus (SLE). In Crete, 61% of the inhabitants reside in rural areas (villages and small towns of up to 10,000 dwellers) and 39% in urban areas (>10. 000 dwellers) according to 2011, National Census (ELSTAT) http://www.statistics.gr/. Mean age of inhabitants of rural areas is 43.9 and urban 37.8 years.[76] The Department of Rheumatology, University of Crete, http://www.rheumatology-uoc.gr/en/ serves as the referral center for patients with rheumatic diseases on the island.

The Epidemiology & Surveillance SLE Project "Leto" was established in 2012 as a research registry database with the primary aim to estimate the disease occurrence and burden of SLE in the community. The registry includes 1500 patients from the region diagnosed by a rheumatologist -950 with SLE and 550 with SLE-like or Undifferentiated Connective Tissue Disease (UCTD) syndromes- diagnosed from 1999 to date. Main Inclusion criterion for the registry is any definite or possible lupus over 15 years old at diagnosis and exclusion criteria include diagnoses other than systematic forms of lupus (cutaneous lupus only, drug-induced).

## Data Source

The collection of the data used for the present analysis was performed both retrospectively (for the time period 1999-2012) and prospectively (2012-2015). Data were derived both from medical records review i.e the SLE classification criteria (ACR-1997 [77] and SLICC-2012 [77] classification criteria) and main disease outcomes (severity, activity, organ damage scores) as well as patient-reported data on the patients' consecutive visits upon their first enrollment (up to date n=460 patients were enrolled in 2012-2015, 410 of whom with SLE and 50 with UCTD).

This is a cross sectional study assessing data from consecutive patients ≥15 years old with an SLE diagnosis who are regularly followed and being regularly treated for at the referral Rheumatology Clinic (University of Crete, Heraklion, Crete Greece. More specifically, the inclusion criteria for the present study were: to be diagnosed with Systemic Lupus Erythematosus with any of the three ways (clinical diagnosis by expert rheumatologist, fulfilling at least either 4 ACR-1997 classification criteria[77] or fulfilling SLICC-2012 classification crieria[77] *(Supplementary Table I, Appendix Section)*. The patients were clinically and serologically reassessed and invited to enrol in the SLE registry which was approved by Research Ethics Committee of the University of Crete. Exclusion criteria: if the patients did not meet either the classification criteria or clinical diagnosis for SLE or were not living permanently in Greece; patient refusal to participate or failure to provide relevant information i.e. due to language or communication difficulties. Data were collected through medical charts reviews, laboratory assessments and face to face structured questionnaires. All participants were included in this study after an informed consent. From the 460 patients enrolled, 410 met inclusion criteria. Nine more patients' datasets were removed due to the inconsistent questionnaires (incomplete residential history data). The final number of the sample analyzed was 401.

**Variables**

From the questionnaire datasets the following variables were analysed:

Main variable of interest was if patients lived exclusively in rural, in urban or in both ("mixed") areas through their lives, up to the enrolment. Relevant residential history variables included place of current residency (urban-rural), place of upbringing (urban-rural), immigration (yes/no) emigration (yes/no), number of years lived in urban and rural settings. Demographic parameters that were used in analysis include: gender, ethnicity, education level, marital status, employment status, decent (Cretan, other) and lifestyle variables such as smoking (current, never, ever, pack-years), BMI ($Kg/m^2$) and cosmetics (frequent ever use, y/n). Most common SLE manifestations were also assessed in the questionnaire (ever, yes/no).

Regarding the disease presentation: time lag from symptoms to diagnosis (1-5months, 6-12 months, >1 year, >2 years), Twenty four comorbidities (allergic rhinitis, asthma, urticaria, diabetes, hypertension, dyslipidemia, thyroid nodules, Hashimoto disease, cancer, infections, fibromyalgia, osteoporosis, osteoporotic fracture, neurologic disease, kidney disease, lung disease, liver disease, gallbladder disease, ulcer, blood disorders, tuberculosis, AIDS syndrome, urinary tract infections, dermatologic disease and five comorbidities for mental health (generalized anxiety disorder, depression, eating disorder, alcohol dependence, suicidal attempt).A crude "comorbidity count" was calculated scoring one point to every comorbid status.

Regarding gyn/obs history the patients were asked about: number and gender of children, any miscarriages (number, trimester), pregnancy problems: preterm birth, diabetes, low birth weight (yes/no), menstruation status, age of menarche, age of menopause and prevention measures as were indicated by age and gender: immunizations (influenza, pneumoniococcus), pap smear, mammography, colonoscopy and sun protection measures.

Data derived from the medical records review included: clinical diagnosis (SLE, CTD), date of clinical diagnosis, ACR 1997 classification criteria, nephritis (Biopsy Proven), Neuropsychiatric Disease (defined by multidisciplinary consensus and attribution models [78]).

*Severity.*

There are no validated scores or consensus on characterizing the severity of an SLE patient. A number of registries use Katz Index[79] which is rather obsolete, the presence of more severe manifestations such as nephritis or neurophychiatric disease, or ACR classification criteria[80] or the presence or more severe phenotype as nephritis. The characterization of SLE as "mild", "moderate" or "severe" in our study was determined by the number and severity of disease manifestations (based on the BILAG[81] glossary) and the use of lupus medications (Bertsias et. unpublished data, *Appendix Supplementary Table II).*

*Non-reversible Organ Damage*.

As damage was considered one of the main objectives of the present study, that is to evaluate the role of the place of residency in the cumulative chronic damage in SLE patients, we used the SLICC/ACR-DI score (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index) for Systemic Lupus Erythematosus as main methodological tool (*Appendix. Supplementary Table III*.). The SDI score has been extensively validated [82], widely used and remains a well-accepted score for chronic non reversible cumulative damage because of SLE itself, or treatments used. SDI items represent irreversible damage that has occurred after the diagnosis of SLE [83]. Items should be present for at least 6 months. Once recorded in the score they are permanent so that the score can only increase. The mean SDI tends to increase over time [84] and in the long run, a large proportion of SLE patients will cumulatively accrue damage. A number of factors have been associated with higher SDI scores, including older age at SLE onset, Hispanic and African ancestry race/ethnicity, chronic disease activity and flares[85]. A number of studies have confirmed an association between higher scores and mortality[84]. SDI is the most powerful predictor of long-term prognosis in SLE (ie, for further damage accrual and survival). It is therefore important to better understand factors related to the development of the damage.

**Statistical analysis**

A power sample calculation was performed by online calculators http://clincalc.com/stats/samplesize.aspx A sample size of at least 196 patients were needed to ensure 80% power for detecting a significant difference (a=0.05) of 60% vs 40% as was our initial hypothesis.

SLE patients with exclusively urban (>10.000 inhabitants) or rural residence (<10.000 inhabitants) or mixed residence through the entire lifespan up to their enrolment were compared regarding disease risk (relative risk)[86 87] and disease characteristics. Baseline characteristics were expressed as the mean (±SD) or percentages (%) as appropriate. Students t- test or Mann-Whitney test was applied for comparison between continuous

variable as well as Chi-Square or Fisher exact test for categorical variables. Bonferroni correction was used in case of multiple comparisons, getting the adjusted p value, by dividing the original 0.05 by the number of analyses on the dependent variable.[88]

Missing values were mostly due to poor data in medical charts. In case of more than 20% incomplete answers in the questionnaire or adequate information on residence, the data were not included. (complete case analysis method).[89]

A stepwise binary logistic regression analysis (unadjusted and adjusted for gender, age at diagnosis, disease duration, total number of ACR and smoking was performed to determine if the place of residence influences damage accrual (SDI=0, no damage accrual, SDI≥1 any damage accrual up to last follow-up). In a second regression model, SLE severity was treated as outcome and was categorized in mild/moderate vs. severe disease and was adjusted for total ACR criteria, gender, disease duration and age at disease onset). The results from the multivariate logistic regression are presented as the exp (B) coefficient with 95% Confidence Interval and p-values.

Analyses were performed using SPSS.22 software packages as needed.

## CHAPTER IV: RESULTS

### *Place of Residency of SLE Patients: Double Risk in those lived in cities*

Out of the 401 SLE patients, included in our study, a hundred and seventy three (43,1%) had lived in urban and a hundred and thirty patients (32,4%) in a rural region through their entire lifespan. The rest 98 patients (24.4%) had lived in both urban and rural areas, having moved at least once in their lives from rural to urban (68.7%), from rural to urban (20.3%) while 10% reported other patterns of translocations (immigration, emigration). The majority of the total participants (90%) have never left Crete Island to live or work in another region or country and there were spatially distributed in all 4 prefectures of the Crete Island as shown in *Figures 1 and 2.*

The relative risk of developing SLE in an urban versus a rural region was estimated to be 2.08 (95% Confidence Interval 1.66-2.61, $p<0.001$).

### *Lower educational, employment and lower female-to-male ratio in SLE patients of rural areas.*

The main demographics of the patients are described in Tables 1-3. SLE patients living in rural areas differ in several socio-demographic characteristics as they have lower education (only 9.2% vs. 39.9% have more than 12 years' education, $p<0.001$), and lower employment rates (51.6% vs. 68.1% in paid work vs. 31.9% in urban, $p<0.001$). Notably, patients who had exclusively lived in urban regions had lower female-to-male ratio (6.5:1 in urban *vs.* 15:1 in rural, $p=0.03$) (*Figure 3*). There were no important differences in ethnicity (Greek in 98,5% in rural and 96,5% in urban areas, p=0.3). Although the majority of the patients were of Cretan descent there was a greater percentage in villages (80% in rural vs.63.6% in urban, p=0.001).

***Pesticides use and obesity prevalence higher in rural while smoking percentage higher among urban dwellers.***

Farming was the most usual occupational activity in working rural SLE patients (23.1% vs. 2.3% in urban, p=0.005) with the ever use of pesticides to largely differ from urban areas (36.5% vs. 10.0% in urban, p<0.001) as shown in *Table 4.* Furthermore, the prevalence of pesticides reached up to 28,3% in SLE patients that have grown up in a village in comparison with less than half in patients that have spent their childhood years in a town (13%, p=0.01) *(Table 5).*

Regarding lifestyle, obesity (BMI>30) was more common in rural than urban SLE patients (39.4% vs. 28.5%, *p<0.049*) as shown in Figure 3 and the opposite results were found for smoking (36.9% in rural vs. 50.0% in urban were smoking either currently or in the past, *p=0.76. Figure 5*). Differences were also found in the use of cosmetics (frequent use, ever 20.2% in rural vs 42.6. p=0.001).

***Lower age of diagnosis in urban lupus patients and in those grown at cities without significant differences in diagnosis delay as compared with rural dwellers***

A significantly lower age of disease diagnosis was found among patients that lived exclusively in urban (mean± SD, 38.3 ± 13.1 years) as compared to those exclusively in rural (45.0 ± 15.3 years, *p=0.024*). As expected, SLE patients from villages were older at enrollment but the difference was not statistically significant (mean ±SD 52.4 ± 13.9) vs. 45±13.1, *p=0.07*). Notably SLE patients whose upbringing was at urban place (n=185) had about 8 years earlier diagnosis, compared to those that had grown up in a village (mean± SD, 38.09 ± 14.2 vs. 46,37 ± 12,19 years, *p<0.001*).

About half of the rural living patients had a delay more than 2 years from the symptoms onset to SLE diagnosis but this was only 10% more than the urban dwellers (49.4.% in rural vs. 39.1% in urban (*p=0.5*)., as shown in more details in table 6.

**Photosensitivity more frequent in rural SLE dwellers while antiphospholipids more frequent in urban areas.**

Regarding the ACR-1997 classification criteria as reviewed from the medical records, photosensitivity was decreasing in prevalence from the exclusively rural living (90.6%), to mixed rural/urban (83.5%) and exclusively urban living (79.8%) *(p=0.03) (Figure 6).* There were no significant differences in other clinical manifestations as defined by the ACR-1997 criteria (cumulatively up to the enrolment date) *(Table 7).* Manifestations from the skin (malar rash, ulcers) and the musculoskeletal system (arthritis) were more prevalent in rural patients both individually and so was this disease "pattern" that include all of these mucocutaneus and musculoskeletal features (25.8% in rural vs 16.4% in urban environment, $p<0.046$). However, the total number of ACR-1997 criteria at the enrolment did not differ significantly (mean ±SD 4,62 ± 1.4 in rural vs 4.51±1.33 in urban areas ($p=0.8$).

Specific immunologic characteristics for SLE (anti-dsDNA, anti-Sm, anti-phopholipid antibodies, as described in ACR-1997 criteria) were found to differ in urban (positive in 39.2 % in urban vs. 32.2.1% in rural vs. 9.3% in mixed, *p=0.5*). Antiphospolipids antibodies were found positive in 20.5% urban vs. 14.1% in rural SLE population *(p=0.04).* Anti-nuclear antibodies were found in 93.6% of rural and 84.2% of urban areas *(p=0.03). (Table 8)*

Neuropsychiatric disease was more prevalent (14.6% *vs*. 10.4%) in rural than urban patients and in mixed environments (6%) but these comparisons were not statistically significant (*p=0.1).* Nephritis prevalence (biopsy-proven) was also examined at the residency level and no significant differences were revealed (10.0% vs 10.4% in urban, *p =0.9*). Symptoms related to SLE as they were assessed by the patient questionnaire, are shown in *Table 9* presenting no significant differences across geographies.

**Comorbidities: Thyroid disease and other chronic diseases are more frequent in rural areas whereas viral infections are more prevalent in urban areas.**

Among comorbidities assessed, most common among patients was thyroid disease and it was more frequent in rural patients (44.6% vs. 37.0%, *p=0.015*) (Table 9). On the contrary, allergic rhinitis was 3-fold higher in cities 13.9 vs. 4.6, *p=0.027*). Hypertension, diabetes and dyslipidemia, heart disease and cancer were all more frequent in villages as shown in Table 10, although differences were not statistically significant. Further, osteoporosis was more frequent in rural women (22.3% vs. 15.6 %, *p=0.1*) while menopause prevalence was 46.9% in rural and 26.0% in urban SLE women *(p<0.001*). Furthermore, the total comorbidity count was found not statistically different among the rural-urban category (mean 1,87±1.62 vs. 1,63±1,53, p=0.4) if only physical comorbidities were counted and 2.24±1.81 vs. 2.00 ±1.77, p=0.19 if mental comorbidities were added. Last, fibromyalgia prevalence did also not differ significantly among the rural-urban category (20.8% vs. 16.2%, p=0.4).

Notably, patients assessed had differences in infections in their medical history (ever) with urban dwellers reporting greater percentages in rubella (15.6% vs. 6.9%, *p=0.033*) and chicken-pox (25.4% vs 12.3%, *p=0.025*). Infectious mononucleosis was also higher in urban SLE patients (6.4% vs. 1.5%, *p=0.1*), as well as measles (27.7% vs. 21.5%, p=0.2) and mumps (23.7 vs. 17.7, p=0.95) but these differences were not statistically significant.

**Severity**

In a crude, unadjusted analysis, SLE patients derived from rural environments had less mild and more moderate/severe disease (40.8% and 59.2%, respectively) as compared to 52.9% and 47.1% in those from urban areas (p=0.1) as Table 11 depicts.

In bivariable logistic regression analysis, urban living was associated with lower risk (Odds ratio [OR] 0.5) CI 95% 0.27-0.9 for moderate/severe forms of SLE, as compared

with rural living, independent of the effects of other factors such as the total number of ACR classification criteria (*data not shown*)

**Damage and Hospitalizations**

In univariate analysis, 45.3% of the patients living in urban and 51.9% of patients in rural areas were free of organ damage (SDI=0) at the last follow-up (*p=0.89*). In multivariable regression analysis adjusting for the effects of gender, age, disease duration and smoking, the place of residency was not predictive of organ damage accrual (data not shown). Hospitalizations due to active lupus differed significantly between the two groups (38.5% in rural versus 37.6% in urban, *p=0.003*).

**Preventive measures**

Rural dwellers had greater percentages in all preventive measures: pap-smear test (52.3% vs. 48.0%, *p=0.001*), mammography 46.9% vs. 41.65, *p=0.007*), colonoscopy (13.1 vs. 11.6, p=0.7) immunizations against influenza (39.2% vs. 24.9%, *p=0.009*) and against pneumoniococcus (32.3% vs. 23.7%, *p=0.014*). Although non-statistical significant, sun protection was higher in urban inhabitants (46.8 vs.39.2, p=0.1).

## CHAPTER VI: DISCUSSION

In our study, we have examined the role of the place of residency on the expression and outcome of SLE, in a genetically homogenous south European population.

We demonstrated that having lived in an urban environment almost doubles the relative risk of SLE diagnosis in comparison to rural living. This result is consistent with previous studies in Northern Greece (Ioannina Region), where Alamanos et al [19] showed that disease incidence was higher among the urban population in all districts (2.25 in the urban vs. 1,68 per 100,000 in the rural population). In an older study in US[20] SLE incidence and prevalence rates were two to three fold higher in New York City than in Jefferson county region. In Canada, Barnade et al[72] suggested a trend toward higher overall SLE prevalence in female and male urban dwellers, however the 95% CI for these estimates overlap, so that no strong conclusion could be made[72].

Urban versus rural place of living has not been frequently studied for the regarding possible effects on SLE expression and long term outcomes. In GLADEL cohort[15], because of the presence of large rural areas in the Latin American countries, researchers supported that the patients who were identified as living in rural areas were significantly more frequently younger at diagnosis; they had fewer years of formal education, lower SES and medical coverage than those living in urban areas[15]. As far as the clinical features, comorbid conditions such as hypertension and renal involvement were more frequent among villagers, as we also showed, although in our study the age at diagnosis was higher. When multivariable logistic regression models were performed in GLADEL study, they observed that rural residency was associated with high levels of disease activity at diagnosis and renal disease occurrence but no impact on the rates of hospitalization, disease activity over the disease course, renal damage, overall damage and mortality was found[90]. We confirm that even though in our region patients residing in rural area had lower educational level and work employment they did not present worse outcomes as estimated by damage.

In a smaller cohort of Egyptian patients, rural place of residence was associated with lower physical function, increased depressive symptoms and higher scores in activity indexes. [16]

Socioeconomic factors have been recognized as important mediators of less favorable outcomes. Results from multiethnic cohorts as GLADEL [15] suggests that, in fact, these factors could play a more important role than the place of residency *per se* in terms of their impact on outcomes of this SLE. However, i.e in GLADEL study even after adjusting for the socioeconomic parameters examined, place of residency had an important impact on terms of disease activity at diagnosis and the occurrence of renal disease over the disease course. These data may reflect the fact that rural residents in Latin America may not have the same access to specialized care, the end result being that they may present to the rheumatologists only when the disease is quite evident and active. This has been clearly shown by Ward *et al.* who found that SLE patients with limited access to care, perhaps a subrogate variable for place of residency, were more likely to develop end stage renal disease. [62]

However, in the Greek heath care system we did not demonstrate that patients in the rural areas experienced a significant lag time in diagnosing SLE, as compared to those living in urban settings. In our study SLE population is rather homogenous not only genetically but also socio-demographically. No ethnicity or race effect could act toward a biased estimation because of these two strong confounders. In addition, access both to primary and rheumatogical care is not so hampered in Crete due to the health care system which is characterized by a public large referral clinic, geographically approximately in the centre of the island, a network of private rheumatologists and general physicians working in rural health centers. Distances across the island are not quite long and public transportation systems are well developed. This accessibility is probably shown indirectly by no significant differences in mean delay between urban and rural districts in diagnosis.

The fact that in our registry, as GLADEL cohort did not find differences in the rates of overall damage may actually reflect that once patients enter the health system, their course is somewhat comparable to the one of those patients living in urban areas. This is

a likely explanation given that once they are diagnosed they are followed and treated by either rheumatologists or internists with a great degree of experience in the management of SLE. In addition, it is possible that after their diagnosis may have become proactive in their care, seeking help when their disease was active which may have resulted in avoidable hospitalizations as hypothesized by Ward [18].

One the other hand, place of residency may also reflect environmental exposures that may trigger or influence different patterns of disease expression in SLE. Our finding that SLE in people who spend all their life in a village have more than 6 years later occurrence in SLE can lead us to the assumption that maybe there are protective factors in rural lifestyles or a triggering urban lifestyle. A previous study in multiple sclerosis in Crete island[91] also showed that the women mainly affected were those living in towns or having relocated from a countryside to a city[91]. MS rose markedly over three decades in Cretan genetical stable population in tandem with a transition from rural to urban living[91].

The primary limitation of our study is that we were unable to include in our analyses detailed data on environmental exposures. However, place of residency may be a surrogate measure for these variables in multivariable models thus our study offers a picture of the similarities and differences present in SLE patients living in urban and rural south European settings. Among the strengths of our study was that because of the monoethnic and genetically homogenous environment with low rates of translocations there was a limitation of any bias due to ethnicity/race.

## CHAPTER VI: CONCLUSION

Communities at different urbanization levels differ in their demographic, environmental, economic, and social characteristics. The components and interactions of this landscape that combines risk and protective factors remain largely uncharacterized. Current research aims at better understanding this continuum, with the rural remote or geographically isolated areas on one edge and the intra-urban neighbourhood on the other, that influence the health and well being of dwellers. Continued health research will document progress toward eliminating the health disadvantage of rural areas[23] and provide information to policymakers who seek more efficient targeting of limited public health resources. Of course, rural residence does not always confer a health disparity; urban areas fare worse than other areas on some health indicators.

In our study, we report that urban living environment is probably associated with increased risk of SLE, earlier age of disease onset and more serological abnormalities. SLE patients living in rural areas smoke less and have adopted more preventive measures, but they have higher rates of severe disease and hospitalizations. Given the rather homogenous genetic background of the population, these results suggest an important effect of the living environment on SLE risk and phenotype, which warrants further investigation

# TABLES

**TABLE 1. Educational level of SLE patients by the residential place.**

| EDUCATIONAL ATTAINEMENT | | | SLE PATIENS' LIVING PLACE* | | | |
|---|---|---|---|---|---|---|
| | | | Mixed | Rural | Urban | Total |
| | Missing | No | 3 | 4 | 8 | 15 |
| | | % | 3,10% | 3,10% | 4,60% | 3,70% |
| | Illiterate | No | 2 | 5 | 4 | 11 |
| | | % | 2,00% | 3,80% | 2,30% | 2,70% |
| | Elementary School | No | 26 | 65 | 25 | 116 |
| | | % | 26,50% | 50,00% | 14,50% | 28,90% |
| | High School | No | 35 | 44 | 47 | 146 |
| | | % | 35,70% | 33,90% | 38,70% | 36,40% |
| | College | No | 13 | 6 | 18 | 37 |
| | | % | 13,30% | 4,60% | 10,40% | 9,20% |
| | University | No | 19 | 6 | 51 | 76 |
| | | % | 19,40% | 4,60% | 29,50% | 19,00% |
| Total | | No | 98 | 130 | 173 | 401 |
| | | % | 100,00% | 100,00% | 100,00% | 100,00% |

*****Mixed= They have lived both in rural or urban areas. Rural, Urban=they have been living all their lives up to enrollment day in a rural (<10.000 inhabitants) or an urban region (>10,000). P-value 0.05

**TABLE 2.**
**Marital Status of SLE patients by their living environment**

| MARITAL STATUS | | | SLE PATIENS' LIVING PLACE | | | |
|---|---|---|---|---|---|---|
| | | | Mixed | Rural | Urban | Total |
| | Missing | No | 1 | 2 | 2 | 5 |
| | | % | 1,0 | 1,5 | 1,2 | 1,2 |
| | Unmaried | No | 10 | 13 | 33 | 56 |
| | | % | 10,2 | 10,0 | 19,1 | 14,0 |
| | Divored | No | 5 | 3 | 13 | 21 |
| | | % | 5,1 | 2,3 | 7,5 | 5,2 |
| | Married | No | 78 | 96 | 121 | 295 |
| | | % | 79,6 | 73,8 | 69,9 | 73,6 |
| | Widow | No | 4 | 16 | 4 | 24 |
| | | % | 4,1 | 12,3 | 2,3 | 6,0 |
| Total | | No | 98 | 130 | 173 | 401 |
| | | % | 100,0 | 100,0 | 100,0 | 100,0 |

*P=0.03*

**TABLE 3. Employment Status of SLE patients by their residential place**

| J0B CATEGORIES | | Mix | Rural | Urban | |
|---|---|---|---|---|---|
| | No | 3 | 4 | 7 | 14 |
| | % | 3,1% | 3,1% | 4,0% | 3,4% |
| Farmers | No | 5 | 30 | 4 | 39 |
| | % | 5,1% | 23,1% | 2,3% | 9,7% |
| Unemployed | No | 10 | 9 | 20 | 39 |
| | % | 10,2% | 6,9% | 11,6% | 9,7% |
| Self-employed | No | 13 | 11 | 18 | 42 |
| | % | 13,3% | 8,5% | 10,4% | 10,5% |
| Trainees | No | 1 | 2 | 10 | 13 |
| | % | 1,0% | 1,5% | 5,8% | 3,2% |
| Public/Private Servants | No | 22 | 22 | 66 | 110 |
| | % | 22,4% | 16,9% | 38,2% | 27,4% |
| Howsewives | No | 17 | 27 | 23 | 67 |
| | % | 17,3% | 20,8% | 13,3% | 16,7% |
| Retired | No | 27 | 25 | 25 | 70 |
| | % | 27,5% | 19,2% | 14.5% | 17,5% |
| Total | No | 98 | 130 | 173 | 401 |
| | % | 100,0% | 100,0% | 100,0% | 100,0% |

$P<0.001$

**TABLE 4. Pesticides use in SLE patients by their urban/rural residency region.**

| | | | Residency | | | |
|---|---|---|---|---|---|---|
| | | | Mixed | Rural | Urban | Total |
| Pesticides | NO | Count | 62 | 54 | 117 | 233 |
| | | % within EVER | 79,5% | 63,5% | 90,0% | 79,5% |
| | YES | Count | 16 | 31 | 13 | 60 |
| | | % within EVER | 20,5% | 36,5% | 10,0% | 20,5% |
| Total | | Count | 78 | 85 | 130 | 293 |
| | | % within EVER | 100,0% | 100,0% | 100,0% | 100,0% |

p<0.001

**TABLE 5. Pesticides Use from SLE patients by their urban/rural upbridging.**

| | | | UpBridging Place | | | |
|---|---|---|---|---|---|---|
| | | | MIXED | RURAL | URBAN | Total |
| Pesticides | NO | Patients (N) | 2 | 103 | 127 | 232 |
| | | % | 100,0 | 71,5 | 87,0 | 79,5 |
| | YES | Patients (N) | 0 | 41 | 19 | 60 |
| | | % | 0,0 | 28,5 | 13,0 | 20,5 |
| Total | | Patients (N) | 2 | 144 | 146 | 292 |
| | | % | 100,0 | 100,0 | 100,0 | 100,0 |

*P=0.04*

**TABLE 6. Delay from symptoms to diagnosis, by residency.**

| | | | EV ER | | | |
|---|---|---|---|---|---|---|
| | | | Mix | Rural | Urban | Total |
| Delay | >1year | Patients (N) | 5 | 8 | 14 | 27 |
| | | % | 6,8 | 9,0 | 10,1 | 9,0 |
| | >2yrs | Patients (N) | 39 | 44 | 54 | 137 |
| | | % | 52,7 | 49,4 | 39,1 | 45,5 |
| | 1-5months | Patients (N) | 25 | 32 | 57 | 114 |
| | | % | 33,8 | 36,0 | 41,3 | 37,9 |
| | 6-12months | Patients (N) | 5 | 5 | 13 | 23 |
| | | % | 6,8 | 5,6 | 9,4 | 7,6 |
| Total | | Patients (N) | 74 | 89 | 138 | 301 |
| | | % | 100,0 | 100,0 | 100,0 | 100,0 |

**TABLE 7. Comparison of ACR-1997 criteria in SLE patients that lived in a Rural as compared to an Urban region.**

| Criterion | Rural | Urban | p-value |
|---|---|---|---|
| Malar Rash | 57,0% | 51,5% | *0.33* |
| Discoid Rash | 6,3% | 14,0% | *0.03* |
| Photosensitivity | 90,6% | 79,5% | *0.009* |
| Oral Ulcers | 55,5% | 42,1% | *0.02* |
| Arthritis | 90,6% | 87,1% | *0.36* |
| Pleuritis/Pericarditis | 10,9% | 11,1% | *0.90* |
| Neurologic | 10,2% | 10,5% | *0.90* |
| Haematologic | 28,1% | 31,0% | *0.60* |

**TABLE 8. Immunological Differences of SLE patients across rural-urban areas**

| Immunologic Feature* | Rural | Urban | p-value |
|---|---|---|---|
| Anti-nuclear antibodies (ANA) (>1/160 titre) | 93.6% | 84.2% | 0.03 |
| Anti-dsDNA, anti-Sm, anti-phopholipid antibodies | 32.2% | 39.2% | 0.5 |
| Antiphospolipids antibodies | 14% | 20.5% | 0.04 |

***ACR-1997 classification criteria defined*

**Table 9. Patient-reported SLE symptoms and manifestations.**

| Symptoms/Manifestations | Rural | Urban | Total | p-value |
|---|---|---|---|---|
| Fever | 15,4% | 19,1% | 17,5% | 0.4 |
| Weight Loss | 12,3% | 15,0% | 13,9% | 0.6 |
| Anorexia | 10,8% | 12,1% | 11,6% | 0.8 |
| Lymphadenopathy | 12,3% | 15,6% | 14,2% | 0.5 |
| Tiredeness | 55,4% | 61,3% | 58,7% | 0.3 |
| Dermatological | 26,9% | 23,7% | 25,1% | 0.5 |
| Sunsensitivity | 79,2% | 63,0% | 70,0% | 0.002* |
| Butterfly rash | 70,0% | 53,8% | 60,7% | 0.004* |
| Ulcers | 40,8% | 38,7% | 39,6% | 0.7 |
| Alopecia | 60,8% | 68,2% | 65,0% | 0.1 |
| Arthgralgias | 83,1% | 78,6% | 80,5% | 0.3 |
| Myalgias | 42,3% | 44,5% | 43,6% | 0.7 |
| Fibromyalgia | 20,8% | 16,2% | 18,2% | 0.3 |
| Tentonosynovitis | 20,8% | 24,9% | 23,1% | 0.4 |
| Cardiovascular Accident | 4,6% | 1,7% | 3,0% | 0.1 |
| Neurologic Symptoms | 13,8% | 10,4% | 11,9% | 0.3 |
| Epilepsy | 2,3% | 2,3% | 2,3% | 1.0 |
| Memory Disturbances | 10,0% | 9,8% | 9,9% | 1.0 |
| Depressive Symptoms | 22,3% | 23,7% | 23,1% | 0.7 |

| | | | | |
|---|---|---|---|---|
| Cataract | 15,4% | 6,9% | 10,6% | 0.023 |
| Xeropthalmia | 19,2% | 15,6% | 17,2% | 0.04 |
| Glaukoma | 1,5% | 0,0% | ,7% | 0.18 |
| Retinopathy | 1,5% | 0,0% | ,7% | 0.18 |
| Dyspepsia | 5,4% | 11,6% | 8,9% | 0.06 |
| Ulcer/gastroesophagic reflux | 3,8% | 5,8% | 5,0% | 0.5 |
| Chronic Diarrhea | 1,5% | 2,9% | 2,3% | 0.7 |
| Pericarditis | 10,0% | 6,4% | 7,9% | 0.2 |
| Acute Myocardial Infarction | ,8% | 1,7% | 1,3% | 0.63 |
| Arrythmia | 6,9% | 6,4% | 6,6% | 1.00 |
| Hearth Valve-Disease | 4,6% | 3,5% | 4,0% | 0.7 |
| Deep Vein Thtombosis | 3,8% | 3,5% | 3,6% | 1.0 |
| Pleuritis | 3,8% | 4,6% | 4,3% | 0.7 |
| Respiratory Infections | 10,0% | 8,1% | 8,9% | 0.6 |
| Kidney problems | 10,8% | 8,7% | 9,6% | 0.5 |
| Leukopenia | 12,3% | 19,1% | 16,2% | 0.1 |
| Anemia | 16,9% | 13,9% | 15,2% | 0.1 |

P<0.001 Bonferoni adjusted

**TABLE 10. SLE Comorbidities across residential place.**

| Comorbid Status | Mixed | Rural | Urban | Total | p-value |
|---|---|---|---|---|---|
| Allergic Rhinitis | 12,2% | 4,6% | 13,9% | 10,5% | 0.027 |
| Asthma | 5,1% | 6,2% | 4,0% | 5,0% | 0.7 |
| Knidosis | 4,1% | 3,1% | 3,5% | 3,5% | 0.9 |
| Hypertension | 28,6% | 29,2% | 18,5% | 24,4% | 0.05 |
| Diabetes | 9,2% | 12,3% | 3,5% | 7,7% | 0.1 |
| Dislipidemia | 36,7% | 37,7% | 24,9% | 31,9% | 0.03 |
| Thyroid Disease | 55,1% | 44,6% | 37,0% | 43,9% | 0.015 |
| Hashimoto | 4,1% | 1,5% | 12,1% | 6,7% | 0.01 |
| Thyroid Nodules | 20,4% | 14,6% | 9,2% | 13,7% | 0.035 |
| Osteoporosis | 13,3% | 22,3% | 15,6% | 17,2% | 0.1 |
| Osteop. Fracture | 8,2% | 7,7% | 4,0% | 6,2% | 0.28 |
| Heart Disease | 15,3% | 13,8% | 8,7% | 12,0% | 0.1 |
| Neurologic Disease | 9,2% | 7,7% | 9,2% | 8,7% | 0.8 |
| Cancer | 6,1% | 5,4% | 3,5% | 4,7% | 0.5 |
| Kidney Disease | 13,3% | 8,5% | 8,1% | 9,5% | 0.3 |
| Lung Disease | 9,2% | 12,3% | 6,9% | 9,2% | 0.2 |
| Lung Disease | 8,2% | 2,3% | 3,5% | 4,2% | 0.07 |
| Gallblader Disease | 2,0% | 5,4% | 4,0% | 4,0% | 0.044 |
| Ulcer | 10,2% | 3,1% | 5,2% | 5,7% | 0.06 |
| Blood Disorders | 2,0% | ,8% | 3,5% | 2,2% | 0.288 |
| Tuberculosis | 3,1% | 1,5% | 1,7% | 2,0% | 0.6 |
| Ulcer | 13,3% | 8,5% | 11,0% | 10,7% | 0.05 |
| Skin Disease | 7,1% | 3,8% | ,6% | 3,2% | 0.012 |
| Mental Disease | 44,9% | 30,8% | 31,8% | 34,7% | 0.049 |
| Bipolar Disease | 0,0% | 0,0% | 1,7% | ,7% | 0.079 |
| Cognitive Impairment | 3,1% | 1,5% | 1,2% | 1,7% | 0.5 |
| Anxiety (GAD) | 14,3% | 8,5% | 8,7% | 10,0% | 0.2 |
| Depression | 31,6% | 24,6% | 21,4% | 24,9% | 0.1 |
| Alcohol Depedence | 0,0% | 0,0% | ,6% | ,2% | 0.5 |
| Eating Disorder | 1,0% | 0,0% | 0,0% | ,2% | 0.2 |
| Suicidal Attempt | 6,1% | 2,3% | 4,0% | 4,0% | 0.3 |

P<0.001 Bonferoni adjusted

**TABLE 11. Residential Place effect on SLE severity**

| SEVERITY | Rural | Mixed | Urban | Total |
|---|---|---|---|---|
| Mild | 42 | 39 | 72 | 153 |
| | 40.8% | 45.9% | 52.9% | 47.2% |
| | 61 | 46 | 64 | 171 |
| Moderate/Severe | 59.2% | 54.1% | 47.1% | 52.8% |
| | 103 | 85 | 136 | 324 |
| | 100.0% | 100.0% | 100.0% | 100.0% |

**TABLE 12. Multivariable Logistic Regression Model with severity (mild vs moderate-severe) as an outcome in SLE patients from the Leto Registry**

| | B | p-value | OR | 95% C.I. | |
|---|---|---|---|---|---|
| Disease duration | .049 | .017 | 1.050 | 1.009 | 1.093 |
| Age at Diagnosis | -.011 | .265 | .989 | .970 | 1.008 |
| Gender | 1.876 | .001 | 6.527 | 2.076 | 20.514 |
| Rural Residence | | .046 | | | |
| Mixed Residence | -.102 | .747 | .903 | .484 | 1.682 |
| Urban Residence | -.691 | .021 | .501 | .278 | .901 |
| No ACR criteria | .495 | .000 | 1.640 | 1.253 | 2.146 |

*a. Adjusted with total number of ACR-1997 classification criteria,gender, age at diagnosis, disease duration,*

# FIGURES

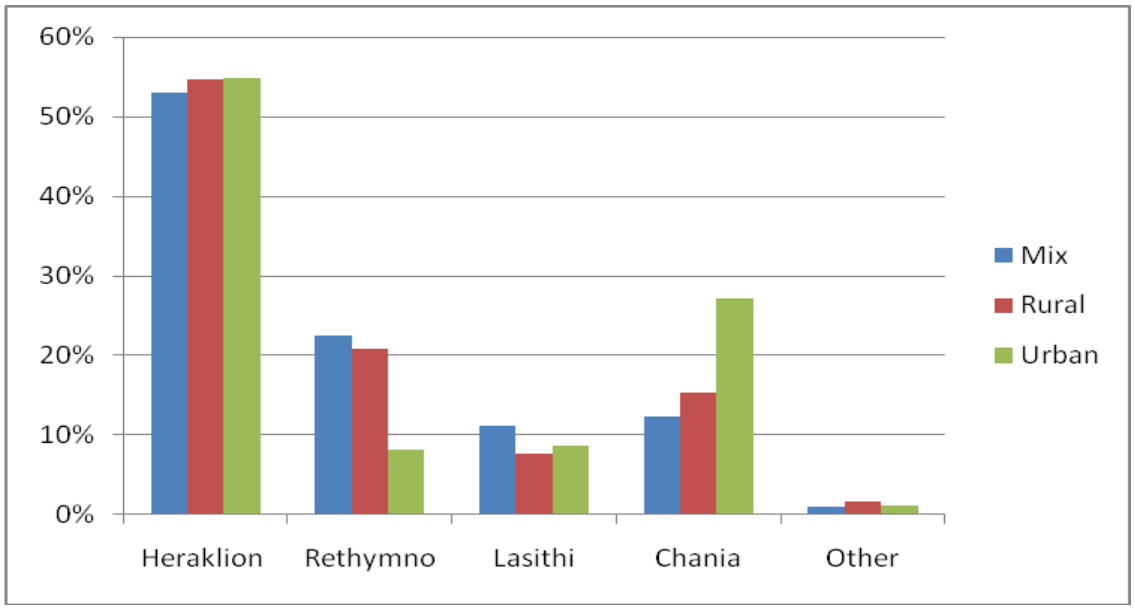


**Figure 1. Geographical Distribution of SLE patients in four prefectures of the island of Crete.** (*p=0.009*) Other, denotes Rhodos, Kasos and Kalymnos islands (*p=0.009*)

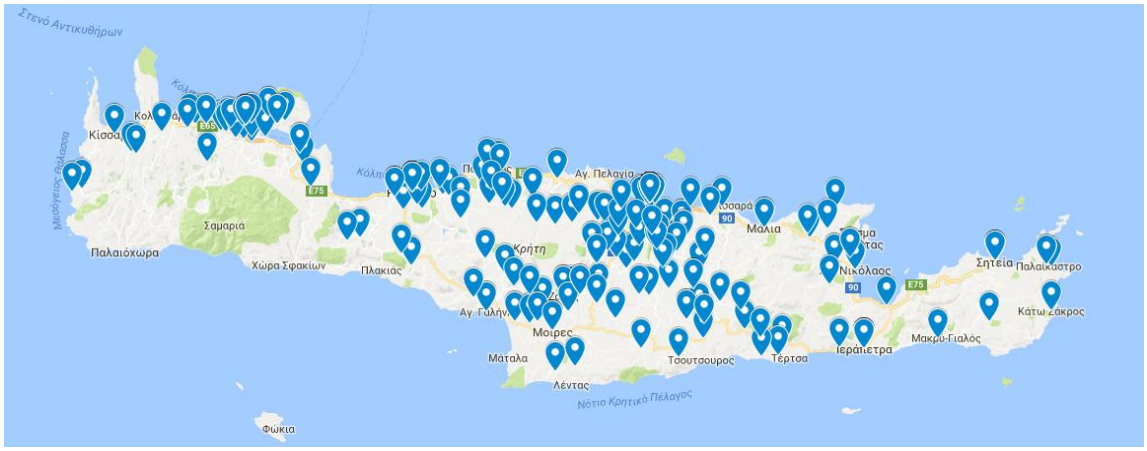


**Figure 2. Mapping of SLE patients on Crete island.**

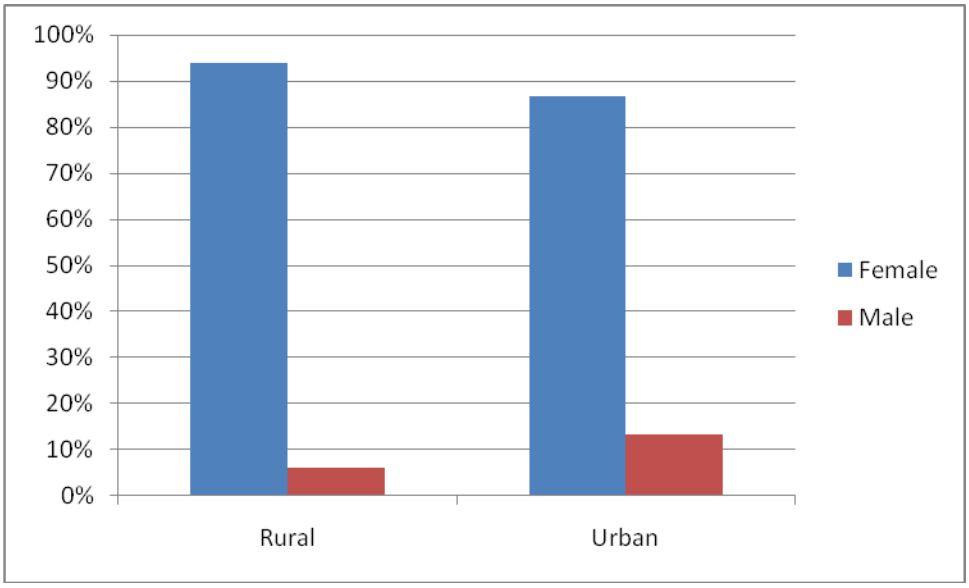


**Figure 3. Female: Male Ratio of SLE Patients by residential area (p=0.03)**

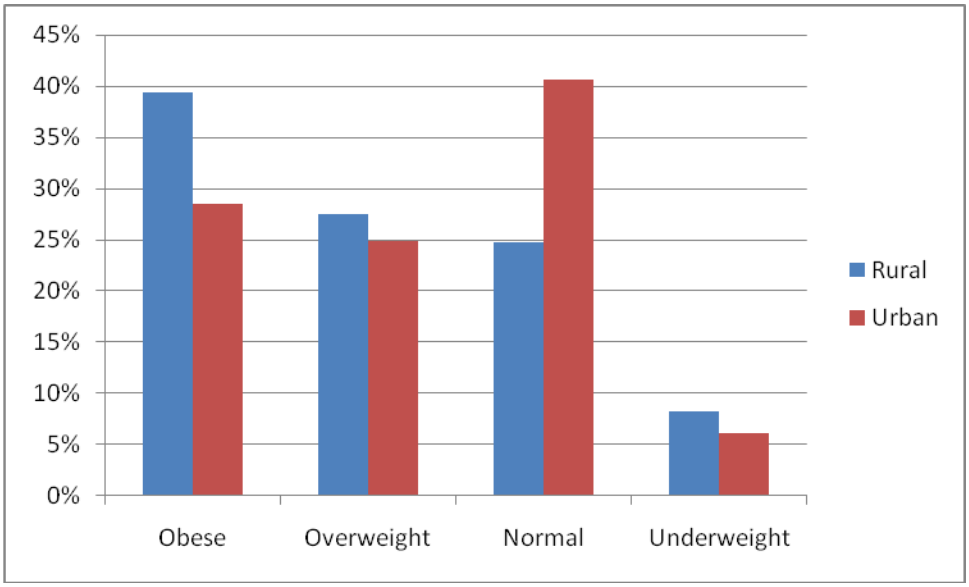


**Figure 4. Obesity categories by urban/rural place of residency (p=0.049)**

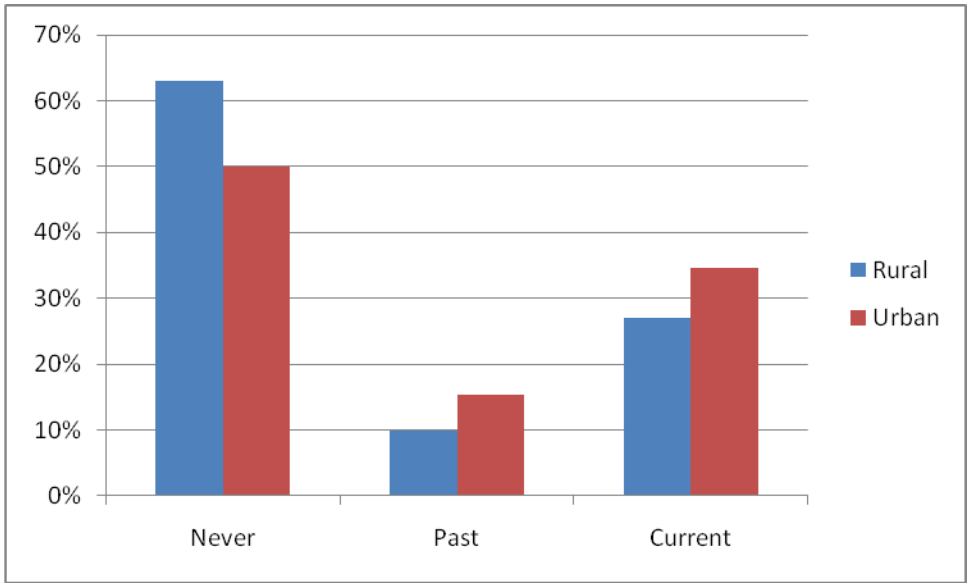


**Figure 5. Smoking by urban/rural place of residency (p=0.07)**

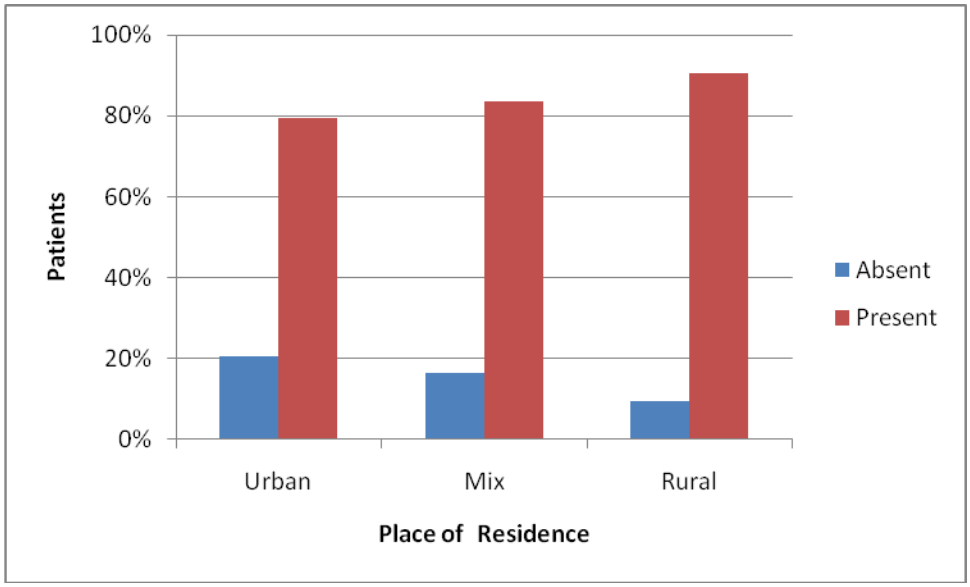


**Figure 6. Photosensitivity (as defined in ACR-19997 classification criteria) by urban/rural place of residency (p=0.03)**

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# Appendix

**Supplementary Table 1. The ACR and SLICC classification criteria for SLE**

| Criteria | *ACR criteria* (1997 update) | *SLICC criteria* (2012) |
|---|---|---|
| Skin | Malar rash. Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds | Acute cutaneous lupus (lupus malar rash [do not count if malar discoid], bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash), or subcute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring) |
| | Discoid rash. Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occur in older lesions | Chronic cutaneous lupus (classic discoid rash: localized or generalized, hypertrophic [verrucous] lupus, lupus panniculitis [profundus], mucosal lupus, lupus erythematosus tumidus, chillblains lupus, discoid lupus/lichen planus overlap |
| | Photosensitivity. Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation | Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs) |
| Ulcers | Oral or nasopharyngeal ulceration | Oral or nasal ulcers |
| Synovitis | Non-erosive arthritis involving ≥2 peripheral joints, characterized by tenderness, swelling or effusion | Inflammatory synovitis in ≥2 joints: characterized by swelling or effusion, or<br>tenderness and ≥30 minutes of morning stiffness |
| Serositis | Any of:<br>Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion<br>Pericarditis: documented by ECG or rub or evidence of pericardial effusion | Serositis: any of<br>Typical pleurisy lasting >1 day, or pleural effusions, or pleural rub<br>Typical pericardial pain (pain with recumbency improved by sitting forward) for >1 day, or pericardial effusion, or pericardial rub, or pericarditis by electrocardiography |
| Renal disorder | Any of:<br>Persistent proteinuria >0.5 g per day or >3+ if quantitation is not performed<br>Cellular casts: red cell, haemoglobin, granular tubular, or mixed | Any of:<br>Urine protein/creatinine (or 24 hr urine protein) representing ≥500 mg of protein/24 hr, or<br>red blood cell casts |
| Neurological disorder | Any of:<br>Seizures: in the absence of offending drugs or known metabolic derangements<br>Psychosis: in the absence of offending | Any of:<br>seizures,<br>psychosis,<br>mononeuritis multiplex,<br>myelitis, |

| | | |
|---|---|---|
| | drugs or known metabolic derangements | peripheral or cranial neuropathy, cerebritis (acute confusional state) |
| Haematologic disorder | Any of:<br>Haemolytic anemia with reticulocytosis<br>Lymphopenia: <1500/$mm^3$<br>Thrombocytopenia: <100,000/$mm^3$ | Haemolytic anaemia<br>Leukopenia (<4000/$mm^3$ at least once), or lymphopenia (<1000/$mm^3$ at least once)<br>Thrombocytopenia (<100,000/$mm^3$) at least once |
| Immunologic disorder | Any of:<br>Anti-DNA: antibody to native DNA in abnormal titer<br>Anti-Sm: presence of antibody to Sm nuclear antigen<br>Positive finding of antiphospholipid antibodies based on: (1) an abnormal serum concentration of IgG or IgM anticardiolipin antibodies, (2) a positive test result for SLE anticoagulant, or (3) a false positive serologic test for syphilis known to be positive for ≥6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test | Anti-dsDNA above laboratory reference range (except ELISA: twice above laboratory reference range)<br>Anti-Sm<br>Antiphospholipid antibody, lupus anticoagulant, false-positive test for syphilis, anticardiolipin (at least twice normal or medium-high titer), or anti-b2 glycoprotein 1<br>Low complement: low C3, or low C4, or low CH50<br>Direct Coombs test *in the absence of haemolytic anaemia* |
| Antinuclear antibody | Abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced SLE" syndrome | ANA above laboratory reference range |
| Diagnosis of SLE | At least 4 out of 11 criteria | Either the biopsy-proven lupus nephritis in the presence of ANA or anti-dsDNA as a "stand alone" criterion, OR<br>four criteria with at least one of the clinical and one of the immunologic/ANA criteria |

## Supplementary Table II. SLE Severity Index (Bertsias et al. unpublished data)

*Σημειώστε ποιες από τις παρακάτω εκδηλώσεις (κυκλώστε την καθεμία συγκεκριμένη εκδήλωση) έχει εμφανίσει ο ασθενής και το έτος εμφάνισης.*

**Συνολική γνώμη ιατρού**: ☐ ήπια νόσος ☐ μέτρια σοβαρή νόσος ☐ σοβαρή νόσος

| | Έτος | Βαθμός |
|---|---|---|
| ***Συστηματικές εκδηλώσεις*** | | |
| • Πυρετός >38°C, ή απώλεια βάρους >10%, ή λεμφαδενοπάθεια ενδο-κοιλιακή/θωρακική | | 1 |
| ***Βλεννογόνοι – δέρμα*** | | |
| • Εξάνθημα λύκου/δερματική αγγειΐτιδα σε 9–18% επιφάνειας σώματος [Ε.Σ.] (με/χωρίς ήπια εξέλκωση ή γάγγραινα), ή υποδερματίτιδα <9% Ε.Σ., ή αγγειοοίδημα χωρίς προσβολή αεραγωγών | | 1 |
| • Εξάνθημα λύκου/δερματική αγγειΐτιδα σε >18% Ε.Σ. με εκτεταμένη εξέλκωση ή γάγγραινα, ή υποδερματίτιδα >9% Ε.Σ., ή αγγειοοίδημα με προσβολή αεραγωγών | | 2 |
| • Εκτεταμένη τριχόπτωση με συνοδό φλεγμονή του δέρματος κεφαλής | | 1 |
| ***Γαστρεντερικό*** | | |
| • Μέτρια ασκιτική συλλογή, ή μετρίως σοβαρή εντεροπάθεια ή σύνδρομο δυσαπορρόφησης ή παγκρεατίτιδα, ή ηπατίτιδα με tot-Bil <2.5 mg/dl & κ.φ. χρόνοι πήξης | | 1 |
| • Μεγάλη ασκιτική συλλογή με σημεία οξείας κοιλίας, ή σοβαρή εντεροπάθεια ή δυσαπορρόφηση, ή παγκρεατική ανεπάρκεια, ή ηπατίτιδα με ηπατική ανεπάρκεια, ή μεσεντέρια αγγειΐτιδα | | 2 |
| ***Αναπνευστικό*** | | |
| • Μέτρια πλευριτική συλλογή (χωρίς υποξαιμία), ή μέτρια διάμεση πνευμονοπάθεια (απεικονιστικά) χωρίς διαταραχή ανταλλαγής αερίων, ή πνευμονική υπέρταση με mPAP <55 mmHg & στάδιο NYHA I-II, ή κυψελιδίτιδα/πνευμονίτιδα | | 1 |
| • Σοβαρή πλευριτική συλλογή με υποξαιμία, ή εκτεταμένη διάμεση πνευμονοπάθεια με διαταραχή ανταλλαγής αερίων, ή πνευμονική υπέρταση με mPAP >55 mmHg & NYHA III-IV, ή κυψ. αιμορραγία | | 2 |
| ***Μυοσκελετικό*** | | |
| • Πολυαρθρίτιδα με περιορισμό κινητικότητας ή προσβολή μεγάλης άρθρωσης, ή μυοσίτιδα με έκπτωση μυϊκής ισχύς έως 4/5 | | 1 |
| • Μυοσίτιδα με μυϊκή ισχύ <4/5 ή/και προσβολή μυών διαφράγματος, αυχένα-κεφαλής, φάρυγγα | | 2 |
| ***Αιματολογικό*** | | |
| • Λευκοπενία 1000-2500/μl, ή ουδετεροπενία 500-1000/μl, ή λεμφοπενία 500-1000/μl, ή θρομβοπενία 20-50$\times 10^3$/μl, ή αναιμία με αιμοσφαιρίνη 8-10 g/dl | | 1 |
| • Λευκοπενία <1000/μl, ή ουδετεροπενία <500/μl, ή λεμφοπενία <500/μl, ή θρομβοπενία <20$\times 10^3$/μl, ή αναιμία με αιμοσφαιρίνη <8 g/dl, ή Θρομβωτική θρομβοπενική πορφύρα (TTP/TTP-like) | | 2 |
| ***Οφθαλμολογικό*** | | |
| • Μετρίως σοβαρή κερατίτιδα ή πρόσθια ραγοειδίτιδα ή σκληρίτιδα/επισκληρίτιδα | | 1 |
| | | 2 |

**Supplementary Table II. SLE Severity Index (Bertsias et al. unpublished data) cont.**

| | |
|---|---|
| • Οπίσθια ραγοειδίτιδα, ή οπτική νευρίτιδα, ή πρόσθια ισχαιμική οπτική νευροπάθεια, ή σοβαρή κερατίτιδα ή πρόσθια ραγοειδίτιδα ή σκληρίτιδα/επισκληρίτιδα | |
| ***Καρδιαγγειακό*** | |
| • Μέτρια/μεγάλη περικαρδιακή συλλογή, ή μυοκαρδίτιδα, ή μη-λοιμώδης ενδοκαρδίτιδα χωρίς αιμοδυναμική αστάθεια ή καρδιακή ανεπάρκεια ή δυσλειτουργία βαλβίδων ή αρρυθμία | 1 |
| • Μεγάλη περικαρδιακή συλλογή, ή μυοκαρδίτιδα, ή μη-λοιμώδης ενδοκαρδίτιδα με αιμοδυναμική αστάθεια ή καρδιακή ανεπάρκεια ή δυσλειτουργία βαλβίδων ή αρρυθμία, ή αορτίτιδα, ή αγγειίτιδα στεφανιαίων αρτηριών | 2 |
| ***Νευρολογικό*** | |
| • Νευρολογική συνδρομή με ήπιο/μέτριο νευρολογικό έλλειμμα, ή μετρίως σοβαρή ψυχιατρική εκδήλωση, ή άσηπτη μηνιγγίτιδα, ή παροδικό ισχαιμικό αγγειακό επεισόδιο | 1 |
| • Αγγειίτιδα ΚΝΣ, ή μυελοπάθεια, ή καθέξην επιληπτικές κρίσεις/status epilepticus, ή νευρολογική συνδρομή με μέτριο/σοβαρό νευρολογικό έλλειμμα, ή σοβαρή ψυχιατρική εκδήλωση | 2 |
| ***Νεφρικό*** | |
| • Νεφρίτιδα class II ή class V με πρωτεϊνουρία <3 g/24-hr και φυσιολογική νεφρική λειτουργία | 1 |
| • Νεφρίτιδα class III/IV ή μικτή V+III/IV, ή με πρωτεϊνουρία ≥3 g/24-hr, ή με επηρεασμένη νεφρική λειτουργία (αύξηση κρεατινίνης ορού ≥30%), ή νεφρική νόσος τελικού σταδίου | 2 |
| ***Χρήση ανοσοκατασταλτικής αγωγής*** | |
| • Αζαθειοπρίνη, μυκοφαινολικό, belimumab | 1 |
| • Κυκλοφωσφαμίδη, rituximab | 2 |

**Supplementary Tale III. Systemic Lupus International Collaborating Clincs/American College of Rheumatology (SLICC/ACR) Damage Index. Score Item**

| |
|---|
| Ocular (either eye, by clinical assessment) 0,1 |
| Any cataract ever 0,1 |
| Retinal change or optic atrophy Neuropsychiatric 0,1 |
| Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) OR major psychosis 0,1 |
| Seizures requiring therapy for 6 months 0,1,2 |
| Cerebrovascular accident ever (score 2 if >1) 0,1 |
| Cranial or peripheral neuropathy (excluding optic) 0,1 |
| Transverse myelitis Renal 0,1 |
| Estimated or measured glomerular filtration rate < 50% 0,1 |
| Proteinuria > 3.5g/24h or 3 |
| OR End-stage renal disease (regardless of dialysis or transplantation) Pulmonary 0,1 Pulmonary hypertension (right ventricular prominence, or loud P2) 0,1 |
| Pulmonary fibrosis (physical and radiograph) 0,1 Shrinking lung (radiograph) 0,1 |
| Pleural fibrosis (radiograph) 0,1 |
| Pulmonary infarction (radiograph) Cardiovascular 0,1 |
| Angina OR coronary artery bypass 0,1,2 |
| Myocardial infarction ever (score 2 if > 1) 0,1 |
| Cardiomyopathy (ventricular dysfunction) 0,1 |
| Valvular disease (diastolic murmur or systolic murmur > 3/6) 0,1 |
| Pericarditis for 6 months, OR pericardectomy Peripheral vascular 0,1 |
| Claudication for 6 months 0,1 |
| Minor tissue loss (pulp space) 0,1,2 |
| Significant tissue loss ever (e.g. loss of digit or limb)(score 2 if > 1 site) 0,1 |
| Venous thrombosis with swelling, ulceration, OR venous stasis Gastrointestinal 0,1,2 |

| |
|---|
| Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever, for any cause (score 2 if > 1 site) 0,1 |
| Mesenteric insufficiency 0,1 |
| Chronic peritonitis 0,1 Stricture OR upper gastrointestinal tract surgery ever 0,1 |
| Chronic pancreatitis |
| Musculoskeletal 0,1 |
| Muscle atrophy or weakness 0,1 |
| Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis) 0,1 |
| Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis) 0,1,2 Avascular necrosis (score 2 if > 1) 0,1 |
| Osteomyelitis 0,1 |
| Tendon rupture Skin 0,1 |
| Scarring chronic alopecia 0,1 |
| Extensive scarring of panniculum other than scalp and pulp space 0,1 |
| Skin ulceration (excluding thrombosis for > 6 months) 0,1 |
| Premature gonadal failure 0,1 |
| Diabetes (regardless of treatment) 0,1,2 |
| Malignancy (exclude dysplasia) (score 2 if >1 site) |

*Adapted from Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996; 39:363-9*