

Association of rurality with disease severity and social outcomes in systemic lupus erythematosus: a regional cohort study

G. De Marchi¹, L. Occhipinti¹, P. Tomietto², F. Trentin³, M. Regis⁴,
A. Nano¹, N. Franzolini⁵, E. Mansutti⁶, M. Battellino⁷, P. Agostinis⁷,
A. Perin³, G. Emmi^{2,8,9}, L. Quartuccio¹

Affiliations: page 6.

Ginevra De Marchi, MD
Luisa Occhipinti, MD
Paola Tomietto, MD
Francesca Trentin, MD
Monica Regis, MD
Alessia Nano, MD
Nicoletta Franzolini, MD
Elisa Mansutti, MD
Michele Battellino, MD
Paolo Agostinis, MD
Antonella Perin, MD
Giacomo Emmi, MD, PhD
Luca Quartuccio, MD, PhD

Please address correspondence to:

Luca Quartuccio
Division of Rheumatology,
Department of Medicine (DMED),
University of Udine,
33100 Udine, Italy.
E-mail: luca.quartuccio@uniud.it

Received on August 26, 2026; accepted in
revised form on October 5, 2026.

J Environ Rheumatol 2026.

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EXPERIMENTAL RHEUMATOLOGY 2026.

Key words: systemic lupus erythemato-
sus, severity of illness index, rural popu-
lation, urban population, epidemiology

ABSTRACT

Objective. To investigate the associa-
tion between rurality and an opera-
tional disease-severity classification in
systemic lupus erythematosus (SLE),
and its relationship with selected clinical
and social outcomes.

Methods. This retrospective multicen-
tre cohort included adults fulfilling the
2019 EULAR/ACR SLE classification
criteria and residing in Friuli Venezia
Giulia, Italy. Disease severity was op-
erationally classified as mild, moderate
or severe according to the most severe
SLE-related manifestation documented
during the disease course, adapting
the clinical severity categories used
in the 2019 EULAR management rec-
ommendations. Rurality was defined
by distance from the referral centre,
population density and residence in a
mountainous municipality. A composite
Rurality Score (0-3) was analysed as a
continuous variable. Primary multivar-
iable models were adjusted for age at
disease onset and sex; sensitivity analy-
ses additionally accounted for partici-
pating centre and disease duration.

Results. Among 428 patients (87.9%
female; mean age at onset 37±16
years), 32.9% met the operational se-
vere category. Each 1-point increase
in Rurality Score was associated with
higher odds of the severe category af-
ter adjustment for age at disease onset
and sex (OR 1.35, 95% CI 1.01-1.81;
 $p=0.042$), and the association per-
sisted after additional adjustment for
participating centre and disease du-
ration (OR 1.49, 95% CI 1.09-2.03;

$p=0.013$). In secondary exploratory
analyses, Rurality Score was associ-
ated with certified disability (OR 1.98,
95% CI 1.20-3.25; $p=0.007$), based on
23 events. Rurality Score was not sig-
nificantly associated with SLEDAI-2K
at the last visit or with organ damage.

Conclusion. A higher composite Ru-
rality Score was associated with in-
creased odds of having experienced
severe SLE manifestations during the
disease course. An exploratory as-
sociation with certified disability was
also observed, although event numbers
were small. Geographic context may
represent an additional contextual de-
terminant of disease burden in SLE.

Introduction

Systemic autoimmune diseases arise
from a complex interplay between ge-
netic susceptibility and environmental
influences (1, 2). While classical envi-
ronmental triggers, such as infections,
ultraviolet radiation and pollutants,
have long been investigated, increas-
ing attention has been directed toward
structural and contextual determinants
of health, including social and geo-
graphic factors influencing healthcare
access and disease outcomes (3, 4).
In rheumatic diseases, the environ-
ment can therefore be considered not
only in terms of biological or chemical
exposures, but also as the geographic
and structural context in which patients
access diagnosis, specialist care, treat-
ment and social support. Among these
contextual factors, rurality is a multi-
dimensional construct encompassing

Competing interests: none declared.

geographic isolation, service accessibility, population density, and infrastructure (5). Contemporary frameworks emphasise that rural residence represents a cumulative exposure to structural constraints rather than a simple administrative classification (3, 5). Studies in cardiovascular and oncologic conditions have documented rural-urban differences in healthcare access and clinical outcomes, including mortality and disease burden (6-9). Within rheumatology, access to specialist care is influenced by travel time and geographic distribution of providers (10), and greater disability and fragmented healthcare utilisation have been described in rural patients with rheumatoid arthritis (11, 12). These findings suggest that rurality may act primarily through barriers to timely diagnosis and continuity of care.

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterised by marked variability in severity and long-term outcomes. Established predictors of severe disease include younger age at onset and male sex (13), and socioeconomic disadvantage has been linked to poorer prognosis (14). However, the independent contribution of geographic context remains insufficiently explored. Existing studies provide heterogeneous results: some report higher prevalence of SLE in urban areas (15), whereas others describe delayed diagnosis, reduced adherence and greater disease severity among rural patients (16-18). A recent systematic review highlighted major limitations in the field, including inconsistent definitions of rurality, limited control for socioeconomic confounders, heterogeneous outcome measures, and scarce data from European healthcare systems (19). The authors emphasised the need for standardised rurality metrics and well-characterised regional cohorts within unified healthcare frameworks.

To date, no Italian study has specifically examined the relationship between rural residence and SLE severity. Italy presents marked territorial heterogeneity in terms of population density, mountainous geography, and distribution of specialist services. Friuli Ven-

ezia Giulia, characterised by extensive mountainous areas and a highly fragmented municipal distribution, represents a mixed urban-rural region within a coordinated hub-and-spoke rheumatology network, providing a unique setting to explore geographic gradients in a unified public healthcare system (20). We hypothesised that increasing rurality, conceptualised as a cumulative geospatial exposure rather than a binary urban-rural distinction, would be associated with a greater likelihood of having experienced severe SLE manifestations during the disease course and with increased social burden. Accordingly, we aimed to investigate the association between a multidimensional Rurality Score and an operational disease-severity classification, and to evaluate its relationship with clinical and social outcomes after adjustment for demographic factors.

Materials and methods

Study design and population

A retrospective observational study was conducted using a multicentre regional cohort of patients with SLE residing in Friuli Venezia Giulia, Italy. The regional healthcare system is organised through a hub-and-spoke network of rheumatology units, allowing territory-wide patient capture. All consecutive adult patients (≥ 18 years) fulfilling the 2019 EULAR/ACR classification criteria for SLE (21) and followed within the regional rheumatology network were eligible. Data were extracted from institutional clinical databases updated through December 2025. Patients with incomplete information regarding the operational disease-severity classification or rurality indicators were excluded.

Rurality

Rurality was operationalised using three predefined geographic indicators designed to capture complementary dimensions of geographic isolation and territorial context. First, distance from the primary referral centre was calculated for each patient. The cohort mean distance was 22.6 km (SD 22.1 km), giving a mean-plus-one-SD value of 44.7 km; this was rounded to a >45 -km

threshold to identify patients residing substantially farther from specialised care. Unlike the other two components, this distance threshold was internally derived from the study cohort and should therefore be regarded as cohort-specific rather than an externally validated cut-off. Second, municipality-level population density <150 inhabitants/km² was used, consistent with the Organisation for Economic Co-operation and Development (OECD) territorial typology, which classifies local units with population density below 150 inhabitants/km² as rural (22). Third, residence in a municipality classified as mountainous according to the official regional classification established by Friuli Venezia Giulia Regional Law No. 33/2002 was included to capture geographic constraints related to mountainous terrain (23). Each indicator was coded as binary (present/absent), and a composite Rurality Score (range 0-3) was calculated by summing the three components. For descriptive analyses, rurality was also examined categorically (0, 1, 2, 3), whereas in regression models it was analysed as a continuous variable to preserve statistical power and estimate the association per 1-point increase in the score.

Outcomes

The primary outcome was an operational disease-severity classification categorised as mild, moderate, or severe according to the most severe SLE-related manifestation documented during the disease course (Supplementary Table S1). This classification was adapted from the clinical severity categories used in the 2019 EULAR recommendations for SLE management (24) and was not treated as a formally validated longitudinal severity instrument. In this operational scheme, lupus nephritis was classified as severe. For regression analyses, the outcome was dichotomised as severe versus mild-to-moderate disease. Secondary clinical outcomes included disease activity at the last visit, assessed by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) (25), and cumulative organ damage at the last visit, measured using the Systemic Lupus International Col-

Table I. Characteristics of the study population according to Rurality Score.

Characteristic	Overall (N=428)	Score 0 (n=285)	Score 1 (n=108)	Score 2 (n=28)	Score 3 (n=7)
Demographic characteristics					
Female sex, n/N (%)	376/428 (87.9%)	253/285 (88.8%)	94/108 (87.0%)	23/28 (82.1%)	6/7 (85.7%)
Caucasian ethnicity, n/N (%)	399/428 (93.2%)	261/285 (91.6%)	104/108 (96.3%)	27/28 (96.4%)	7/7 (100.0%)
Age at disease onset, years, mean $\pm$ SD	37.4 $\pm$ 15.6	38.9 $\pm$ 15.8	34.4 $\pm$ 14.7	35.2 $\pm$ 14.1	32.0 $\pm$ 21.4
Operational disease-severity category					
Mild, n/N (%)	195/428 (45.6%)	136/285 (47.7%)	48/108 (44.4%)	8/28 (28.6%)	3/7 (42.9%)
Moderate, n/N (%)	92/428 (21.5%)	65/285 (22.8%)	22/108 (20.4%)	4/28 (14.3%)	1/7 (14.3%)
Severe, n/N (%)	141/428 (32.9%)	84/285 (29.5%)	38/108 (35.2%)	16/28 (57.1%)	3/7 (42.9%)
Disease activity and damage					
SLEDAI-2K at last visit, median (IQR)	1.0 (0.0–3.0)	1.0 (0.0–3.0)	1.0 (0.0–3.0)	2.0 (0.0–4.0)	2.0 (1.0–2.0)
SLICC/ACR Damage Index, median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	1.0 (0.0–1.0)
SLICC/ACR Damage Index >0, n/N (%)	166/428 (38.8%)	107/285 (37.5%)	43/108 (39.8%)	12/28 (42.9%)	4/7 (57.1%)
Social characteristics					
High school education or higher, n/N (%)	222/327 (67.9%)	143/215 (66.5%)	63/86 (73.3%)	13/20 (65.0%)	3/6 (50.0%)
Employed, n/N (%)	189/349 (54.2%)	120/230 (52.2%)	53/89 (59.6%)	13/23 (56.5%)	3/7 (42.9%)
Certified disability, n/N (%)	23/428 (5.4%)	11/285 (3.9%)	8/108 (7.4%)	2/28 (7.1%)	2/7 (28.6%)
Components of the Rurality Score					
Distance from referral centre >45 km, n/N (%)	62/428 (14.5%)	0/285 (0.0%)	42/108 (38.9%)	13/28 (46.4%)	7/7 (100.0%)
Population density <150 inhabitants/km ² , n/N (%)	91/428 (21.3%)	0/285 (0.0%)	59/108 (54.6%)	25/28 (89.3%)	7/7 (100.0%)
Residence in a mountainous municipality, n/N (%)	32/428 (7.5%)	0/285 (0.0%)	7/108 (6.5%)	18/28 (64.3%)	7/7 (100.0%)

Data are presented as n/N (%) unless otherwise indicated. Disease duration was calculated from the recorded diagnosis date to 31 December 2025. High-school education or higher includes diploma, university degree and postgraduate/master education; patients with undeclared education were excluded from the denominator. Employed includes employees, self-employed professionals and manual workers; patients with undeclared employment status were excluded from the denominator. Certified disability corresponds to the dedicated disability category recorded in the database. Rurality Score ranges from 0 to 3 and is the sum of distance >45 km from the referral centre, population density <150 inhabitants/km², and residence in a mountainous municipality. IQR: interquartile range; SD: standard deviation; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

laborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR Damage Index, SDI) (26). Social outcomes included educational level, occupational status, and officially certified disability status according to national regulations and were considered secondary exploratory outcomes.

Statistics

Continuous variables were summarised as mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]), as appropriate. Categorical variables were presented as counts and percentages. Disease duration was calculated from the recorded diagnosis date to 31 December 2025, corresponding to the end of the data-extraction period. Exploratory comparisons across Rurality Score categories used the Kruskal-Wallis test for continuous variables and the chi-square or Fisher-Freeman-Halton exact test for categorical variables, as appropriate; these p values were not adjusted for multiple comparisons. Pairwise associations among the three binary Rurality Score

components were quantified using phi coefficients, with Pearson chi-square p values reported descriptively. Multivariable regression models evaluated the association between Rurality Score and clinical and social outcomes. Logistic regression models were used for binary outcomes, including: 1. the operational severe SLE category (severe vs. mild-to-moderate disease); 2. damage at last follow-up, defined as SDI >0; and 3. social outcomes (educational level, occupational status and certified disability status). Linear regression was used to analyse SLEDAI-2K at the last visit. Primary models included age at disease onset (per 10-year increase) and sex (male vs. female) as covariates. Sensitivity analyses for the primary severe-category outcome sequentially added participating centre and disease duration. A further complete-case sensitivity analysis additionally included educational level (high-school education or higher vs lower education); patients with undeclared education were excluded. To assess dependence on the internally

derived distance threshold, distance was also modelled as a continuous exposure per 10-km increase, with and without additional adjustment for centre and disease duration. Because certified disability was observed in only 23 patients, higher-dimensional sensitivity models were not fitted for that exploratory outcome to limit over-parameterisation. Odds ratios (ORs) or regression coefficients (beta), as appropriate, with corresponding 95% confidence intervals (CIs), were reported. A two-sided p value <0.05 was considered statistically significant. Analyses used a complete-case approach and were performed in Python (Python Software Foundation).

Ethics

The study was approved by the Academic Institutional Review Board. Given the retrospective observational nature of the study and the use of anonymised data, informed consent was waived. All procedures were conducted in accordance with the Declaration of Helsinki and its later amendments.

Results

Patient characteristics

A total of 428 patients with SLE were included in the analysis. The majority were female (87.9%), and the mean age at disease onset was 37 ± 16 years. Median disease duration was 20.0 years (IQR 13.0–26.6). Disease duration differed across Rurality Score categories (Kruskal-Wallis $p=0.018$), although the pattern was not monotonic: median values were 19.0, 22.0, 13.0, and 22.6 years for scores 0, 1, 2, and 3, respectively. Overall, 141 patients (32.9%) met the operational severe category, 92 (21.5%) the moderate category and 195 (45.6%) the mild category. Based on the composite Rurality Score (range 0–3), 285 patients (66.6%) had a score of 0, 108 (25.2%) a score of 1, 28 (6.5%) a score of 2, and 7 (1.6%) a score of 3. Baseline demographic and clinical characteristics according to Rurality Score are summarised in Table I, while exploratory comparisons across score categories are reported in Supplementary Table S2. Pairwise associations among the three Rurality Score components were weak to moderate ($\phi=0.06$ for distance and low population density, 0.14 for distance and mountainous residence, and 0.33 for low population density and mountainous residence) (Supplementary Table S3), indicating partial overlap without complete redundancy.

Rurality and disease severity

The proportion of patients meeting the operational severe category differed across Rurality Score categories: 29.5% among patients with a score of 0, 35.2% with a score of 1, 57.1% with a score of 2, and 42.9% with a score of 3 (χ^2 test, $p=0.023$) (Fig. 1). In primary multivariable logistic regression analysis, each 1-point increase in Rurality Score was associated with higher odds of the severe category after adjustment for age at disease onset and sex (OR 1.35, 95% CI 1.01–1.81; $p=0.042$). Younger age at disease onset (per 10-year increase: OR 0.74, 95% CI 0.64–0.86; $p<0.001$) and male sex (male vs. female: OR 3.15, 95% CI 1.69–5.90; $p<0.001$) were also associated with the severe category (Table II).

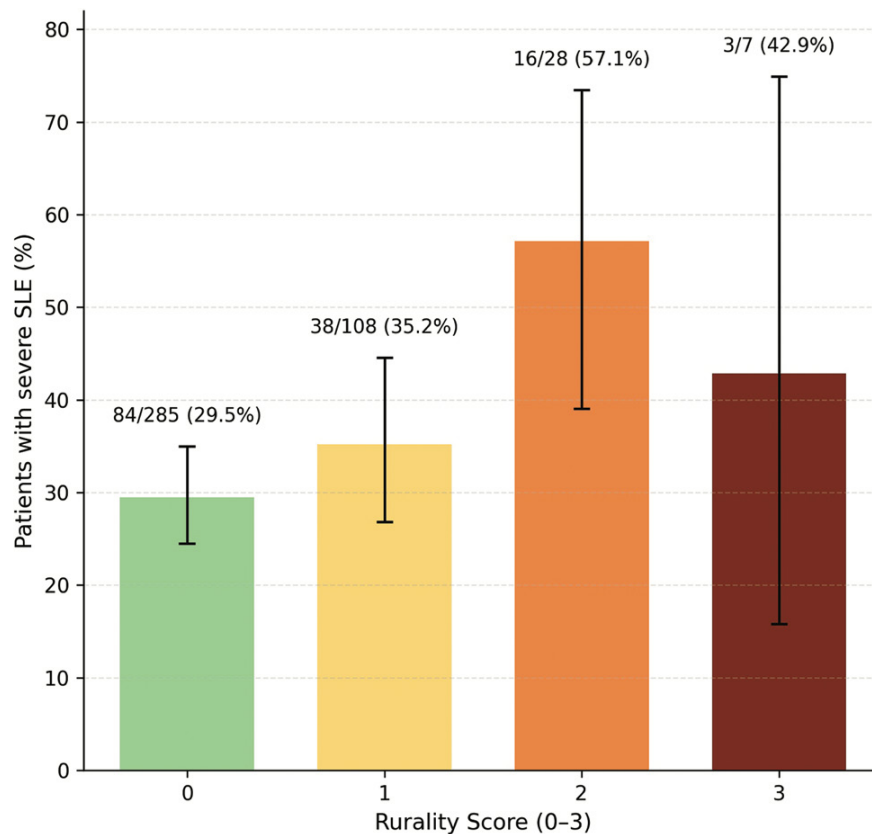


Fig. 1. Proportion of patients meeting the operational severe SLE category across Rurality Score categories.

Bars represent the proportion of patients meeting the operational severe SLE category; error bars indicate 95% confidence intervals. Values above the bars indicate n/N and the corresponding percentage.

Table II. Multivariable logistic regression analysis of factors associated with the operational severe SLE category.

Variable	Adjusted OR	95% CI	p-value
Rurality Score, per 1-point increase	1.35	1.01–1.81	0.042
Age at disease onset, per 10-year increase	0.74	0.64–0.86	<0.001
Male sex	3.15	1.69–5.90	<0.001

The operational severe SLE category was defined according to the most severe SLE-related clinical manifestation documented during the disease course, using a classification adapted from the clinical severity categories in the 2019 EULAR management recommendations (24). Rurality Score was analysed as a continuous variable.

OR: odds ratio; CI: confidence interval.

Table III. Association of Rurality Score with clinical and secondary exploratory social outcomes in multivariable regression analyses.

Outcome	Effect-estimate per 1-point increase in Rurality Score	95% CI	p-value
SLEDAI-2K at last visit	β 0.27	–0.11 to 0.66	0.16
SDI >0	OR 1.17	0.88–1.56	0.27
Certified disability	OR 1.98	1.20–3.25	0.007
Educational level	OR 0.88	0.62–1.26	0.50
Employment status	OR 0.88	0.63–1.23	0.44

All models were adjusted for age at disease onset (per 10-year increase) and sex. β denotes the regression coefficient from linear regression; Rurality Score was analysed as a continuous variable. Social-outcome models were secondary and exploratory; the certified-disability model was based on 23 events.

OR: odds ratio; CI: confidence interval.

Sensitivity analyses

Adjustment for participating centre did not attenuate the association between Rurality Score and the severe category (OR 1.48, 95% CI 1.08-2.02; $p=0.015$). After further adjustment for disease duration, the estimate remained similar (OR 1.49, 95% CI 1.09-2.03; $p=0.013$); disease duration itself was not independently associated with the severe category in this model (OR 1.01 per year, 95% CI 0.99-1.03; $p=0.46$). Among the 327 patients with non-missing education data, the age/sex-adjusted Rurality Score estimate was OR 1.29 (95% CI 0.92-1.79; $p=0.136$), whereas the model additionally including centre, disease duration and educational level yielded OR 1.51 (95% CI 1.04-2.19; $p=0.030$). Educational level was not independently associated with the severe category in that model (OR 0.81, 95% CI 0.46-1.41; $p=0.45$). When distance was analysed as a continuous exposure, no significant linear association was observed: OR 1.06 per 10-km increase (95% CI 0.97-1.16; $p=0.216$) in the age/sex-adjusted model and OR 1.07 (95% CI 0.97-1.19; $p=0.182$) after additional adjustment for centre and disease duration (Supplementary Table S4).

Rurality, disease activity at the last visit and damage

In adjusted linear regression analysis, Rurality Score was not significantly associated with disease activity at the last visit measured by the SLEDAI-2K (beta 0.27, 95% CI -0.11 to 0.66; $p=0.16$). Older age at disease onset was associated with lower SLEDAI-2K scores (beta -0.20 per 10-year increase, 95% CI -0.37 to -0.03; $p=0.023$), whereas sex was not significantly associated with disease activity at the last visit. Similarly, Rurality Score was not significantly associated with the presence of organ damage (SDI >0) after adjustment for age at disease onset and sex (OR 1.17, 95% CI 0.88-1.56; $p=0.27$) (Table III).

Rurality and social outcomes

In secondary exploratory analyses, each 1-point increase in Rurality Score was associated with higher odds of certified disability after adjustment for age

at disease onset and sex (OR 1.98, 95% CI 1.20-3.25; $p=0.007$). This estimate was based on 23 disability events and should therefore be interpreted cautiously. No significant associations were observed between Rurality Score and educational level (OR 0.88, 95% CI 0.62-1.26; $p=0.50$) or employment status (OR 0.88, 95% CI 0.63-1.23; $p=0.44$) (Table III).

Overall, a higher Rurality Score was associated with the operational severe SLE category, but not with current disease activity or cumulative organ damage. A secondary exploratory association with certified disability was also observed.

Discussion

In this regional multicentre cohort of 428 patients with SLE, a higher Rurality Score was associated with higher odds of meeting the operational severe disease category after adjustment for age at disease onset and sex (OR 1.35, 95% CI 1.01-1.81; $p=0.042$). The estimate was modest and its lower confidence bound approached the null. Importantly, however, the association was not attenuated in sensitivity analyses that additionally adjusted for participating centre and disease duration (OR 1.49, 95% CI 1.09-2.03; $p=0.013$). Because the endpoint was based on the most severe SLE-related manifestation documented at any time during the disease course, it reflects a historical clinical phenotype rather than current inflammatory activity and should not be interpreted as evidence of a causal biological effect of rural residence. The absence of an association with either SLEDAI-2K at the last visit or cumulative SDI damage is an important counterpoint to the primary finding. One possible explanation is that geographic barriers exert a greater influence earlier in the disease pathway through delayed diagnosis, reduced monitoring intensity, or disruptions in continuity of care; these mechanisms were not directly assessed in the present study. Another possibility is that rurality is associated with the probability of experiencing or having particular severe manifestations recorded, rather than with a globally more aggressive biological SLE phe-

notype. The present data cannot distinguish among these explanations, and they do not support a causal interpretation that rural residence itself produces biologically more severe lupus.

The Rurality Score was intended to capture several related but non-identical dimensions of geographic context. Pairwise associations among its components were weak to moderate (phi coefficients 0.06-0.33), with the strongest overlap between low population density and mountainous residence, supporting partial complementarity rather than complete independence. The >45-km criterion warrants particular caution because it was derived internally from the cohort distribution (mean plus one SD was 44.7 km), whereas the population-density and mountainous-municipality criteria were based on external definitions. In a sensitivity analysis, distance modelled continuously was not significantly associated with the severe category (OR 1.06 per 10 km, 95% CI 0.97-1.16), suggesting that the association observed for the composite score should not be reduced to a simple linear distance gradient. The composite score has not been externally validated and requires assessment in other territorial and healthcare settings.

These findings are consistent with a broader literature highlighting the relevance of structural, geographic and social factors in shaping healthcare access and outcomes in chronic and autoimmune diseases (10, 12, 18). Rural residence has been associated with disparities in access to healthcare and adverse outcomes across several chronic conditions (6-8). Within rheumatology, geographic barriers to specialist care and differences in healthcare utilisation have also been described among patients living in rural and remote areas (16, 17). Our study addresses several of the methodological gaps highlighted in the recent systematic review by Ohta *et al.* (19), particularly the need for multidimensional and clearly defined measures of rurality and for data from underrepresented European healthcare settings.

The association between rurality and certified disability further supports the relevance of contextual factors beyond

conventional biomedical measures. Only 23 patients had a recorded disability certification, and the highest observed proportion occurred in the score-3 group, which contained only seven patients. Although the finding may reflect social and functional dimensions of disease burden not captured by SLEDAI-2K or SDI, sparse events limit precision and preclude giving this secondary outcome the same evidential weight as the primary disease-severity analysis.

This study has several limitations. The retrospective observational design does not permit causal inference and may be affected by confounding, including socioeconomic factors, healthcare utilisation, diagnostic delay, treatment exposure and other variables not captured in the database. Participating centre differed significantly across Rurality Score categories; however, adjustment for centre did not attenuate the primary association. Although all hub-and-spoke rheumatology centres in Friuli Venezia Giulia were included, undiagnosed patients or those not referred to specialist care may have been missed. Educational level was available for 327 patients; the complete-case analyses therefore had reduced precision and should be interpreted in light of missing values. The disability analysis was based on only 23 events, so the corresponding estimate should be interpreted cautiously. Finally, the Rurality Score itself is not externally validated and the internally derived distance threshold may limit generalisability.

The study also has several strengths. To our knowledge, this is the first Italian study specifically examining the association between rurality and SLE severity. It includes a multicentre regional cohort, an understudied European setting within a coordinated public healthcare network, and an explicit multidimensional approach to rurality. Younger age at onset and male sex were associated with the operational severe category, consistent with previous literature (13, 28, 29).

In conclusion, a higher composite Rurality Score was associated with increased odds of having experienced

severe SLE manifestations during the disease course, and this association remained in sensitivity analyses accounting for participating centre and disease duration. Current disease activity and cumulative organ damage were not associated with rurality, suggesting that geographic context may capture aspects of disease burden not fully reflected by conventional clinical measures. These findings support further study of geographic context as a potential contextual determinant of SLE burden, with external validation of the Rurality Score and prospective assessment of access-to-care mechanisms.

Acknowledgements

The manuscript was prepared on behalf of the Rheumatologic Network of Friuli Venezia Giulia, Italy.

Affiliations

¹Division of Rheumatology, Department of Medicine (DMED), University of Udine, Azienda Sanitaria Universitaria del Friuli Centrale (ASUFC), Udine, Italy; ²Department of Medical, Surgical and Health Sciences, University of Trieste, Italy; ³Departmental Rheumatology Unit, Western Friuli Health Authority, Pordenone, Italy; ⁴Internal Medicine Unit, Giuliano Isontina University Health Authority, Gorizia, Italy; ⁵Rheumatology Outpatient Clinic, San Daniele District, Udine, Italy; ⁶Rheumatology Outpatient Clinic, Cividale District, Udine, Italy; ⁷Internal Medicine Unit, Central Friuli University Health Authority, Tolmezzo, Udine, Italy; ⁸Centre Hospitalier Universitaire Vaudois (CHUV), Department of Medicine and Laboratory Medicine and Pathology, Immunology and Allergy Service, University of Lausanne, Switzerland; ⁹Centre for Inflammatory Diseases, Department of Medicine, Monash University, Monash Medical Centre, Melbourne, Australia.

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