

# Risk association between hypocomplementemia and the development of lupus nephritis: A single-center, case–control observational study.

Xavier Alexander Villota Acosta <sup>1</sup>, Desiré Estefanía Torres Morales <sup>1</sup>, Oswaldo Alcocer Arias <sup>1,2</sup>, Enrique Gea Izquierdo <sup>1</sup>.

1. Department of Internal Medicine, Faculty of Medicine, Pontificia Universidad Católica del Ecuador.
2. Department of Nephrology, Eugenio Espejo Specialty Hospital, Ministry of Health, Public, Quito, Ecuador.

## Abstract

**Introduction:** Systemic lupus erythematosus (SLE) activity is monitored by complement levels C3, C4, and CH50. The present study aimed to investigate the association between hypocomplementemia and the development of lupus nephropathy (LN) in patients with SLE to determine whether hypocomplementemia is a predisposing factor.

**Methods:** The present observational, case–control study was conducted at the Eugenio Espejo Hospital in Quito, Ecuador, from 2009 to 2014. Records of patients diagnosed with SLE were included. Two groups were formed: the first with lupus nephropathy and the second without lupus nephropathy. The variables included demographic and clinical data, hypocomplementemia status, C3 and C4 levels, 24-hour proteinuria, serum creatinine levels, and serum urea levels. The strength of the association between hypocomplementemia and renal involvement in patients with SLE was summarized by odds ratios (ORs) and their 95% confidence intervals (CIs).

**Results:** A total of 134 patients were included. There were 52 cases and 82 controls. Hypocomplementemia was associated with the risk of developing lupus nephritis (OR=11.1; 95% CI 4.9–25.2; P <0.05). These results were maintained with sex-adjusted models (OR=11.2; 95% CI 4.9–25.7; P <0.05) and by age and sex (OR=11.5; 95% CI 5.0–26.7; P <0.05). Patients with extremely low C3 values had a 4-fold increased risk of developing LN, whereas those with extremely low C4 values had an 8-fold increased risk.

**Conclusions:** Hypocomplementemia is strongly associated with the development of lupus nephritis in patients with SLE.

## Keywords:

Lupus nephritis, Systemic lupus erythematosus, Hypocomplementemia.

**Received:** July 19, 2025.

**Accepted:** September 11, 2025.

**Published:** September 16, 2025.

**Editor:** Dr. Franklin Mora.

### How to cite:

Villota X, Torres D, Alcocer O, Gea E. Risk association between hypocomplementemia and the development of lupus nephritis. A single-center, case-control observational study. REV SEN 2025; 14(1):10-17.

DOI: <http://doi.org/10.56867/154>

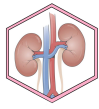
Sociedad Ecuatoriana de Nefrología, Diálisis y Trasplantes.

ISSN-L: 2953-6448



Copyright 2025, Xavier Alexander Villota Acosta, Desiré Estefanía Torres Morales, Oswaldo Alcocer Arias, Enrique Gea Izquierdo. This article is distributed under the [Creative Commons CC BY-NC-SA 4.0 Attribution License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows the use and redistribution of the article, citing the source and the original author for noncommercial purposes.

\* Correspondence author



Lupus nephropathy affects more than 50% of patients with systemic lupus erythematosus (SLE). This complication increases the mortality and morbidity of SLE, especially because of the risk of chronic kidney disease and the need for renal replacement therapy in approximately 25% of patients [1]. The prevalence of lupus nephritis is greater in African-Americans and Hispanics than in Caucasians. In general, survival in patients with SLE is approximately 95% at 5 years after diagnosis and 92% at 10 years. The appearance of lupus nephritis significantly reduces survival to 88% at 10 years after diagnosis [2]. The timely treatment of lupus nephritis and the care that must be taken to prevent end-stage renal disease requiring renal replacement therapy are the main objectives of the management of patients with SLE [3]. The monitoring of lupus patients and their various complications was highly variable; depending on each center and the experience of its professionals, but by 2010, the European League Against Rheumatism (EULAR) designed a set of recommendations for standardized follow-up [4]. Therefore, determining whether there is an association between hypocomplementemia and the development of lupus nephritis in patients diagnosed with systemic lupus erythematosus is the problem posed by this study. The objective of the present study was to determine whether hypocomplementemia is a predisposing factor for the development of LN in patients diagnosed with SLE.

## Materials and methods

### Study design

This is an observational, case-control study. The source is retrospective.

### Scenario

This study was conducted at the statistics service of the Eugenio Espejo Specialty Hospital of the Ministry of Public Health in Quito, Ecuador. The study period was from January 1, 2009, to December 31, 2014.

### Participants

The records of patients diagnosed with systemic lupus erythematosus were included in the study, according to the ACR/SLICC classification criteria, with an age greater than or equal to 18 years. Records without complement laboratory data were excluded. Two groups were formed: the first with lupus nephropathy and the second without lupus nephropathy.

### Variables

The variables included demographic and clinical data; the presence of hypocomplementemia; and the levels of C3, C4, 24-hour proteinuria, serum creatinine, and serum urea.

### Data sources/measurements

The source was indirect. The data were collected through the institutional medical records system.

### Bias

Observation and selection bias were avoided by applying participant selection criteria. The principal investigator always kept the data using a guide and records approved in the research protocol to avoid possible biases of the interviewer, information and recall. In case of doubt about the standard deviation of the data, corrections were made by in situ reviews of the anomalous data. Two researchers independently analyzed each record in duplicate, and the variables were entered into the database after verifying their agreement.

### Study size

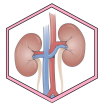
The sample was probabilistic. The population in Quito is approximately 2,679,722 people. Among the 23.87% of women of reproductive age aged 18 to 45 years, 639,649 are women. With a lupus incidence rate of 8.8 cases per 100,000 inhabitants/year, the target population with lupus is 336 possible cases. EPI Info™ (Stat Calc, Epi Info, CDC, Atlanta. Version 7.2.6 [October 2023]), with an expected frequency of the development of lupus nephropathy of 25%, a confidence limit of 5% and a level of 90% confidence, the sample size was 127 cases.

### Quantitative variables

The results of the ordinal variables are presented as frequencies and percentages. The results of the scale variables are presented as averages. Scale variables were not converted into quantitative variables.

### Statistical analysis

The strength of the association between hypocomplementemia and renal involvement in patients with SLE was summarized by odds ratios (ORs) and 95% confidence intervals (CIs), which were obtained by logistic regression, to compare the influence of the independent variable on the dependent variable. that is, hypocomplementemia on the variable lupus nephritis, both of which are dichotomous types. Logistic regression models with progressive adjustment were constructed; the first model was the crude analysis, the second was adjusted for sex, and the last was adjusted for sex and age. Finally, the models were stratified according to the type of hypocomplementemia (C3 or C4) using the same adjustment models. A  $P$  value  $< 0.05$  was considered to indicate statistical significance. The analyses were performed with the statistical package Stata v 13.



## Results

### Participants

A total of 134 patients were included, which met the expected sample size. There were 52 cases and 82 controls.

### Description of the sample

[Table 1](#) presents the characteristics of the patients analyzed, grouped by age at diagnosis of SLE. There were no differences in age or sex distribution between the groups. Laboratory tests are presented in [Table 2](#). Higher levels of proteinuria and serum creatinine were observed in the case group. With respect to histopathological diagnosis, grade IV lupus nephritis was the most prevalent (44.2%), followed by grade III lupus nephritis (21.2%) ([Figure 1](#)).

### Association

Those with lower complement levels had a greater risk of lupus nephropathy (OR = 11.06, 95% CI 4.9–25.2;  $P < 0.05$ ). Model 2 was adjusted for sex (OR=11.2 95% CI 4.9–25.7,  $P < 0.05$ ), while Model 3 was adjusted for age and sex, yielding similar results (OR=11.5 95% CI 5.0–26.7,  $P < 0.05$ ). In addition, a separate analysis was performed by complement factor, and we observed that subjects with low C3 values had a 4-fold higher risk of nephropathy, and those with predominantly low C4 values had an 8-fold higher risk. to develop nephropathy. These results were also similar between the different adjustment models.

We also analyzed the degree of association by sex; however, no effect was observed in males due to insufficient data ([Table 3](#)).

**Table 1.** Characteristics of the patients included in the study.

Characteristics	Casos (n = 52)		Controles (n = 82)		p value
<b>Sex</b> , n (%)					
Female	49	(94.2%)	72	(87.8%)	0.221
Male	3	(5.7%)	10	(12.2%)	
<b>Age</b> , n (%)					
< 20 años	11	(21.1%)	22	(26.8%)	0.186
20 a 29 años	25	(48.0%)	37	(45.1%)	
30 a 39 años	9	(17.3%)	12	(14.6%)	
40° más	7	(13.4%)	11	(13.4%)	
<b>Hemodialysis</b> , n (%)					
Yes	2	(3.8%)	2	(2.4%)	0.6409
Non	50	(96.1%)	80	(97.5%)	
<b>Hypocomplementemia</b> , n (%)					
Yes	40	(76.9%)	19	(23.1%)	0.001
Non	12	(23.0%)	63	(76.8%)	

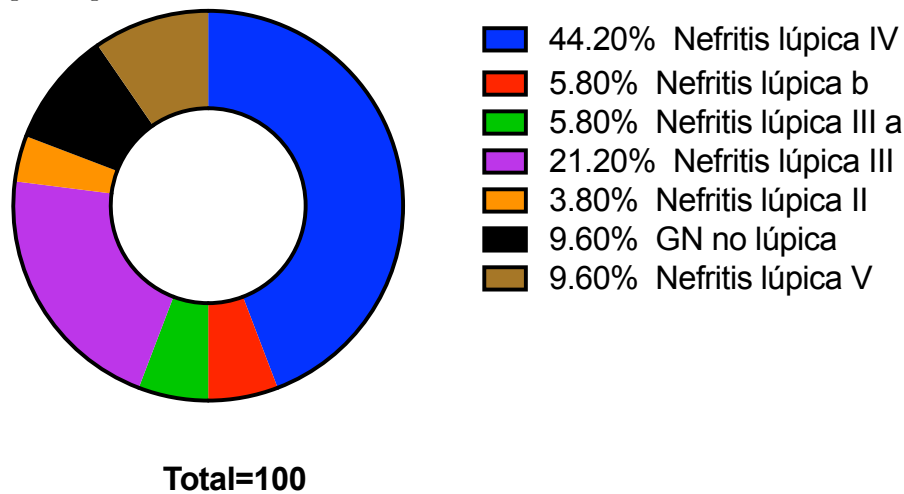
**Table 2.** Laboratory parameters.

Laboratory	Casos (n = 52)		Controles (n = 82)		p value
Mna (SD)					
Proteinuria (mg/24 hs)	2,239	± 2,010	652	± 1,048	0.033 <sup>†</sup>
Serum creatinine (mg/dl)	1.65	± 1.09	1.0	± 0.76	0.001
Urea (mg/dl)	32.4	± 18.85	23.4	± 15.76	0.028
C3 (g/L)	0.69	± 0.34	0.95	± 0.34	0.034
C4 (g/L) <sup>3</sup>	0.13	± 0.18	0.19	± 0.19	0.034

(\*) Significant at 5%

**Table 3.** Association between lupus nephropathy and hypocomplementemia according to total and type of complement.

	Model 1	Model 2	Model 3
	OR (IC 95%)	OR (IC 95%)	OR (IC 95%)
<b>Total (c3 + C4)</b>	11,06 (4,85-25,21)	11,2 (4,88-25,71)	11,54 (4,98-26,74)
<b>C3</b>	4,2 (1,87-9,49)	4,09 (1,81-9,25)	4,13 (1,82-9,37)
<b>C4</b>	8,44 (3,77-18,89)	8,57 (3,8-19,33)	8,64 (3,82-19,55)
<b>Female</b>	9,98 (4,28-23,31)	-	10,14 (4,32-23,84)

**Figure 1** . Histopathological diagnosis.

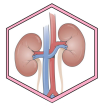
## Discussion

Lupus nephritis is a frequent complication of systemic lupus erythematosus; it affects mainly women of childbearing age, but it can be more serious if it occurs at earlier or later ages. The prevalence of this complication is approximately 50%; however, this figure depends on the ethnicity, sex, age and even the quality of life of patients with SLE, which can vary between 40% and 70% [5, 6]. Our study revealed a similar prevalence of LN: 38.8% of patients had this complication, which was detected by percutaneous renal biopsy. Similarly, it was more frequent in women (90%), of whom 46.2% were between 20 and 30 years old, findings similar to those reported in the literature. Pons-Estel et al. reported an increased risk of LN in women of reproductive age; however, in women of African-descendant ethnicity in the United States [5]. The indication for performing a renal biopsy in a patient with SLE is based on analytical findings that show an alteration of renal function, especially in the face of an unexplained deterioration of this function. A confirmed value equal to or greater than 0.5 grams of protein in 24-hour urine is the main criterion for indicating a percutaneous renal biopsy; however, the evidence of microhematuria, leukocyturia, and cylindruria also indicates a significant deterioration of renal function in patients with SLE. The criteria for repeating a renal biopsy are still controversial; however, the persistence of proteinuria is among the most reliable markers for rebiopsy of patients with SLE [1]. In the present study, 24-hour proteinuria levels of 2,239 milligrams were found in the case group and 652 milligrams in the control group, which translates into the need and indication of performing a first renal biopsy in the case group. of controls and a rebiopsy in the case group because of the persistence of proteinuria.

The main type of lupus nephropathy in this group was grade IV LN (44.2%), followed by grade III LN (21.2%). These findings differ from those of previous reports in which the prevalence of LN grades II and I were 39% and 33%, respectively [7].

Patients with LN have a risk of stage 5 chronic kidney disease of approximately 25%, which contrasts with the 2.99% of patients in this study. This could be due to adequate control and monitoring of the disease or to nonmodifiable ethnic factors, which could be the subject of further research.

Hypocomplementemia is a frequent finding and, in addition, a criterion of SLE activity; however, it is not distinguishable whether this activity is systemic or dependent and suggestive only of kidney damage by the disease in the context of the development of LN [8]. The relationship between the decrease in the 1q component of the complement system, either by genetic deficit or by the presence of autoantibodies (anti-C1q antibodies), and the predisposition and development of renal involvement in patients with SLE has been proven. High titers of anti-C1q have been associated with episodes of renal disease activity, in addition to relapses [9,10]. In this study, measurements of complement components 3 and 4 in blood revealed that 55.7% of the subjects had low complement levels, of which 53.3% had a diagnosis of LN by percutaneous renal biopsy. In general terms, when we speak of hypocomplementemia, we refer to a decrease in serum complement levels; however, advances in laboratory techniques have enabled the measurement of more of its components, as well as antibodies against it. These studies revealed that decreased complement levels are a risk factor for the development of LN, consistent with our findings. The specific measurement of certain components of the complement system, such as C1q, and its association with particular behaviors of LN could be determinants for future studies. Among the main results of the present study, we found a strong association between hypocomplementemia and the development of lupus



nephritis, with an OR of 11.1, which was statistically significant ( $P < 0.05$ ). This trend was maintained after adjusting for age, with ORs = 11.54 and 11.2, respectively. Thus, the objective of this study is met, and in addition, the hypothesis is confirmed. We did not find previous studies that have individually measured this risk association; however, Orbai et al. [8] reported that anti-C1q antibodies, anti-dsDNA antibodies, and hypocomplementemia are strongly associated with the development of renal involvement in patients with SLE (OR = 14.9; 95% CI 5.8–38.4;  $P < 0.01$ ). Although this study associates several factors, not only hypocomplementemia, as predisposing factors for the development of LN, the similarity of its findings with those of the present study is evident.

The other findings indicated that a predominantly low complement component 4 was more strongly associated with the development of LN than a lower complement component 3 was, with ORs of 8.44 and 4.2, respectively. That is, those whose c4 was lower than c3 had twice the risk of presenting a diagnosis of LN. These results differ from the findings of Ishizaqui et al. [7], who reported a risk association mainly with component 3 of the complement system and the development of LN (OR = 38.5 95% CI 4.3–345,  $P < 0.001$ ), which prompted us to clarify these results in future studies.

Monitoring disease activity by measuring immunological markers, as well as analyzing renal function, is recommended for patients with SLE at 3- to 6-month intervals, and hypocomplementemia is one of the determinants of reducing the interval between controls [1]. However, the recommendation to measure serum levels of complement is given only as a marker of disease activity, as well as a predictor of the development of LN, which, according to our findings, would be advisable for further studies to determine the ideal frequency for complement measurement in this context, in addition to recommending the routine performance of a percutaneous renal biopsy in patients with persistently low values of complement and including this as a new biopsy criterion. Renal.

In the past two decades, evidence has revealed that high titers of anti-C1q antibodies in patients with SLE are closely associated with renal involvement and can predict disease relapse in a period of approximately three months, with a strong serological association of these antibodies with anti-DNAs and hypocomplementemia as risk factors for the development of lupus nephritis [8,11,12], which suggests that future studies should analyze the findings described in the literature to be able to reproduce them in our environment.

## Conclusion

The prevalence of lupus nephritis in patients diagnosed with systemic lupus erythematosus at Eugenio Espejo Hospital was 38.8%. The age group with the highest percentage of patients with a LN diagnosis was 20-30 years, accounting for 48% of all patients. Hypocomplementemia was observed in 55.7% of the subjects. Hypocomplementemia was observed in 76.9% of the patients. There is a strong risk association between hypocomplementemia and the development of lupus nephritis in patients with SLE.

### Abbreviations

SLE: Systemic lupus erythematosus.

LN: Lupus nephritis

OR: Odds ratio

CI: Confidence Interval

EULAR: European League Against Rheumatism C1q: Complement 1q component

ACR: American College of Rheumatology

ANA: Anti-nuclear antibodies

dsDNA: Native DNA

SLICC: Systemic Lupus International Collaborating Clinics

### Supplementary information

The supplementary materials have not been provided.

### Acknowledgments

Not applicable.

### Authors' contributions

**Xavier Alexander Villota Acosta:** Conceptualization, data curation, research, visualization, original drafting.

**Desiré Estefanía Torres Morales:** Conceptualization, data curation, research, visualization, original drafting.

**Oswaldo Alcocer Arias:** Conceptualization, data curation, formal analysis, project management, software, validation, visualization, writing - review and editing.

**Enrique Gea Izquierdo:** Conceptualization, formal analysis, methodology, project management, resources, software, supervision, validation, writing - review and editing.

All the authors read and approved the final version of the manuscript.

### Financing

The study was self-financed by the authors.

### Availability of data or materials

Not applicable.

## Statements

### Approval of the ethics committee and consent to participate

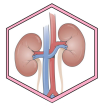
This study has a letter of exemption issued by the Bioethics Committee of the Faculty of Medicine of the Pontifical Catholic University of Ecuador.

### Consent for publication

Does not apply when specific images, radiographs or photographs of patients are not published.

### Conflicts of interest

The authors declare that they have no conflicts of interest.



### Author information

Xavier Alexander Villota Acosta  
Email: [xavialex22@gmail.com](mailto:xavialex22@gmail.com)  
<https://orcid.org/0009-0007-9379-723X>

Desiré Estefanía Torres Morales  
Email: [desiree.etm89@gmail.com](mailto:desiree.etm89@gmail.com)

<https://orcid.org/0009-0003-0531-2484>

Oswaldo Alcocer Arias  
<https://orcid.org/0009-0006-8857-1781>

Enrique Gea Izquierdo, PhD.  
<https://orcid.org/0000-0002-7123-6251>

## References

1. Ruiz Irastorza G, Espinosa G, Frutos MA, Jiménez Alonso J, Praga M, Pallarés L, Rivera F, Robles Marhuenda A, Segarra A, Quereda C; Spanish Society of Internal Medicine (SEMI); Spanish Society of Nephrology (SEN). Diagnosis and treatment of lupus nephritis. Consensus document from the systemic autoimmune disease group (GEAS) of the Spanish Society of Internal Medicine (SEMI) and Spanish Society of Nephrology (SEN). *Nephrology*. 2012; 32 Suppl 1: 1-35. English, Spanish. doi: 10.3265/Nefrologia.pre2011.Dec.11298. PID:[22293933](https://doi.org/10.3265/Nefrologia.pre2011.Dec.11298).
2. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, Karpouzas GA, Merrill JT, Wallace DJ, Yazdany J, Ramsey-Goldman R, Singh K, Khalighi M, Choi SI, Gogia M, Kafaja S, Kamgar M, Lau C, Martin WJ, Parikh S, Peng J, Rastogi A, Chen W, Grossman JM; American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)*. 2012 Jun;64(6):797-808. doi: [10.1002/acr.21664](https://doi.org/10.1002/acr.21664). PMID: 22556106; PMCID: PMC3437757.
3. Balow JE. Clinical presentation and monitoring of lupus nephritis. *Lupus*. 2005;14(1):25-30. doi: [10.1191/0961203305lu2055oa](https://doi.org/10.1191/0961203305lu2055oa). PMID: 15732284.
4. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Brey R, Cervera R, Doria A, Jayne D, Khamashta MA, Kuhn A, Gordon C, Petri M, Rekvig OP, Schneider M, Sherer Y, Shoenfeld Y, Smolen JS, Talarico R, Tincani A, van Vollenhoven RF, Ward MM, Werth VP, Carmona L. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. *Ann Rheum Dis*. 2010 Jul;69(7):1269-74. doi: [10.1136/ard.2009.117200](https://doi.org/10.1136/ard.2009.117200). Epub 2009 Nov 5. PMID: 19892750; PMCID: PMC2952401.
5. Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum*. 2010 Feb;39(4):257-68. doi: [10.1016/j.semarthrit.2008.10.007](https://doi.org/10.1016/j.semarthrit.2008.10.007). Epub 2009 Jan 10. PMID: 19136143; PMCID: PMC2813992.
6. Mohan C, Putterman C. Genetics and pathogenesis of systemic lupus erythematosus and lupus nephritis. *Nat Rev Nephrol*. 2015 Jun;11(6):329-41. doi: [10.1038/nrneph.2015.33](https://doi.org/10.1038/nrneph.2015.33). Epub 2015 Mar 31. PMID: 25825084.
7. Ishizaki J, Saito K, Nawata M, Mizuno Y, Tokunaga M, Sawamukai N, Tamura M, Hirata S, Yamaoka K, Hasegawa H, Tanaka Y. Low complements and high titer of anti-Sm antibody as predictors of histopathologically proven silent lupus nephritis without abnormal urinalysis in patients with systemic lupus erythematosus. *Rheumatology (Oxford)*. 2015 Mar;54(3):405-12. doi: [10.1093/rheumatology/keu343](https://doi.org/10.1093/rheumatology/keu343). Epub 2014 Sep 2. PMID: 25183834.
8. Orbai AM, Truedsson L, Sturfelt G, Nived O, Fang H, Alarcón GS, et al. Anti-C1q antibodies in systemic lupus erythematosus. *Lupus*. 2015 Jan;24(1):42-9. doi: [10.1177/0961203314547791](https://doi.org/10.1177/0961203314547791). Epub 2014 Aug 14. PMID: 25124676; PMCID: PMC4268323.
9. Alsuwaida A, Husain S, Al Ghonaim M, Aloudah N, Ullah A, Kfoury H. Prognostic significance of C1q deposition in serial biopsies for predicating the long-term outcome in patients with proliferative lupus nephritis. *Saudi J Kidney Dis Transpl*. 2016 Mar;27(2):305-11. doi: [10.4103/1319-2442.178547](https://doi.org/10.4103/1319-2442.178547). PMID: [26997383](https://doi.org/10.4103/1319-2442.178547).
10. Ortega LM, Schultz DR, Lenz O, Pardo V, Contreras GN. Review: Lupus nephritis: pathologic features, epidemiology and a guide to therapeutic decisions. *Lupus*. 2010 Apr;19(5):557-74. doi: [10.1177/0961203309358187](https://doi.org/10.1177/0961203309358187). Epub 2010 Jan 20. PMID: 20089610.
11. Chen Z, Wang GS, Wang GH, Li XP. Anti-C1q antibody is a valuable biological marker for prediction of renal pathological characteristics in lupus nephritis. *Clin Rheumatol*. 2012 Sep;31(9):1323-9. doi: [10.1007/s10067-012-2017-1](https://doi.org/10.1007/s10067-012-2017-1). Epub 2012 Jun 14. PMID: 22696012.



12. Stojan G, Petri M. Anti-C1q in systemic lupus erythematosus. *Lupus*. 2016 Jul;25(8):873-7. doi: [10.1177/0961203316645205](https://doi.org/10.1177/0961203316645205). PMID: 27252264; PMCID: PMC7523495.

**DOI:** Digital Object Identifier. **PMID:** PubMed Identifier.

---

## Editor's Note

The REV SEN remains neutral with respect to jurisdictional claims regarding published maps and institutional affiliations.

---