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ORIGINAL ARTICLE

Homocysteine levels are independently associated with damage accrual in systemic lupus erythematosus patients from a Latin-American cohort

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Abstract

Objective To determine the impact of homocysteine levels on damage accrual in systemic lupus erythematosus (SLE) patients.

Methods This longitudinal study was conducted in consecutive patients seen every 6 months at our Rheumatology Department since 2012. Patients with available homocysteine levels and who had at least one subsequent visit were included. Univariable and multivariable Cox regression models were done to determine if homocysteine levels were predictive of damage accrual as per the SLICC Damage Index (SDI). The multivariable model was adjusted for pertinent variables (age at diagnosis, gender, socioeconomic status, disease duration, disease activity (SLEDAI), Framingham score, antimalarial and immunosuppressive drug use, average daily dose, and exposure time to prednisone (PDN)).

Results One hundred forty-five patients were included; their mean (SD) age at diagnosis was 43.70 (12.09) years, 136 (93.8%) were female, and nearly all were Mestizo. At baseline, disease duration was 7.55 (6.73) years; patients were followed for 3.54 (1.27) years. The SLEDAI was 5.60 (4.34), and the SDI 0.97 (1.35). The average daily PDN dose was 7.30 (5.78) mg/day and the time of PDN exposure was 7.36 (6.73) years. Mean homocysteine levels were 10.07 (3.71) μmol/L. The highest tertile of homocysteine levels predicted new damage accrual in the univariable and multivariable models [HR 1.78 (95% CI, 1.042–3.039); $p = 0.035$ and HR 2.045 (95% CI, 1.077–3.883); $p = 0.029$, respectively]. Increased levels (> 15 μmol/L) were found in 12 (8.3%) patients; 75 (51.7%) patients increased ≥ 1 SDI point.

Conclusion In SLE patients, homocysteine levels predicted damage accrual independently of other well-known risk factors for such occurrence.

Keywords Damage accrual · Homocysteine · Systemic lupus erythematosus

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Introduction

Overall, systemic lupus erythematosus (SLE) patients have a 5–6-fold increased risk of premature coronary heart disease. This excess risk is especially pronounced in younger women where it may be > 50-fold [1]. In the general population, hyperhomocysteinemia is associated with increased risk of cardiovascular disease, which has also been the case for women with SLE from the Toronto Risk Factor Study of coronary heart disease [2]. Most of the studies that have investigated the relationship between SLE and homocysteine (Hcy) levels have focused on cardiovascular diseases [3–6], while others have focused on active renal disease [7, 8] and cutaneous lupus erythematosus [9].

Hcy is a non-essential, sulfur-containing, non-proteinogenic amino acid which is synthetized by transmethylation of the essential, diet-derived amino acid methionine [10]. Hcy level concentration in fasting plasma is maintained by homeostasis (5–15 μmol/L) under physiological conditions [11]. Hcy mainly exerts cellular toxicity on the vascular system by three different mechanisms: protein homocysteinylation and Hcy-thiolactone formation, reduction of methylation, and oxidative/nitrosative stress [12]. Hyperhomocysteinemia adversely affects the endothelium, is prothrombotic, decreases nitric oxide availability, and stimulates foam cell formation; all suggesting that Hcy is proatherogenic [13, 14]. Recent studies have demonstrated the possible role of Hcy on the activation of the immune system and the induction of the expression of proinflammatory molecules. Therefore, a possible role for this molecule in the pathogenesis of autoimmune diseases, such as SLE, is now being considered [15, 16].

SLE is characterized by disease flares and damage accrual [17]. The improved longevity of SLE patients translates into a situation in which these patients are accruing more organ damage; such damage has been demonstrated to affect lupus patients' quality of life and their survival [18]. The role of Hcy as a predictor of damage in SLE has not been evaluated previously. We have now conducted such a study to determine the impact of Hcy levels on damage accrual in a primarily Mestizo SLE patient population taken into consideration other well-known risk factors that may also impact on damage in this condition.

Methods

We studied SLE patients from the Guillermo Almenara Irigoyen Hospital of the Peruvian Social Security Administration. Data from the Almenara Lupus Cohort [19], which started in January 2012, have been previously reported. For this study, the cut-off point was June 2017. In summary, all SLE patients presenting to the outpatient rheumatology department of this hospital were invited to participate in this study; all patients met the 1997 American College of Rheumatology (ACR) criteria [20] at enrollment.

The constitution of this cohort had been approved by the hospital's institutional review board (IRB). Patients who signed the informed consent were recruited into this cohort and followed every 6 months with a protocol which included an interview, medical records review, physical examination (performed by a trained rheumatologist), and laboratory tests. For this study, patients with a Hcy baseline measure and at least one subsequent visit were included. The demographic data included were gender, age at diagnosis, and socioeconomic status by the Graffar's method [21]. Clinical variables included were disease activity (ascertained with the Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K) [22]), disease damage (ascertained with the System Lupus International Collaborating Clinics (SLICC)/ACR damage index (SDI) [23]), disease duration at baseline, and the Framingham score as a composite variable of cardiovascular risk. Therapeutic variables included were glucocorticoid (as prednisone (PDN)) intake, reported as current dose and time of exposure, antimalarial and immunosuppressive drugs use at baseline reported as current, past, or never. The primary endpoint was defined as the incidence of new damage accrual defined as an increase in at least one point in the SDI during the follow-up. Plasma total Hcy levels were measured by ACL Rochem Biocare analyzer by immunoluminiscence; the reagent used was from HemosIL®, Werfen, Barcelona, Spain. This method has a very good concordance with the measurements obtained by high-pressure liquid chromatography (99.9%). All measurements were performed in a single laboratory, certified by the American College of Pathologists and the International Society of Thrombosis and Haemostasis. Hyperhomocysteinemia was defined as Hcy > 15 μmol/L [2, 24]. Also, we have evaluated several cut-off points of hyperhomocysteinemia suggested by different investigators [3, 5, 25], establishing their sensitivity and specificity, respectively.

Statistical analyses

Values for categorical variables are given as numbers (percentages) and values for continuous variables are given as means and standard deviations (SD). Mean values of Hcy were compared among those patients with and without damage using the Student's *t* test.

Kaplan-Meier plots and the log rank test were performed to evaluate the effect of time on the occurrence of damage accrual according to tertiles of Hcy levels. We calculated the optimal cut-off value of Hcy for a higher likelihood of developing new damage using the corresponding receiver–operating characteristic (ROC) curve.

Univariable and multivariable Cox regression models were performed to determine the impact of Hcy levels (divided into

tertiles) on the risk of new damage. Multivariable analyses were adjusted for age at diagnosis, disease duration, gender, socioeconomic status, SLEDAI, Framingham score, inmunosuppressive drug use, antimalarials use, current dose, and time of exposure to PDN and SDI. As Hcy is expected to increase the cardiovascular damage, the Framingham score was included in the model to adjust for the traditional cardiovascular risk factors. In alternative analyses, Hcy levels were considered as a continuous variable, in order to further analyze their predictive value. Results are expressed as hazard ratios (HR).

In order to evaluate if Hcy correlated with any metabolic or clinical variable that could be explaining its impact on damage, Pearson correlations were performed with several metabolic and clinical variables (C-reactive protein, erythrocyte sedimentation rate, triglycerides, total, HDL and LDL cholesterol, body mass index, Framingham score, hemoglobin, SLEDAI, creatinine levels). Bonferroni's correction for multiple correlations was performed.

A p value (two-sided) < 0.05 was considered significant in all analyses. All statistical analyses were performed using SPSS v. 21.0 (IBM, Chicago, IL).

Results

One hundred forty-five patients were included in these analyses; these patients were similar to the rest of the patients in the cohort in terms of gender, ethnicity, age at diagnosis, disease duration, SLEDAI, and SDI at baseline. One hundred thirty-six (93.8%) were female and almost all were Mestizo (mixed Amerindian and European ancestry). Their mean (SD) age at diagnosis was 43.70 (12.09) years. Their disease duration was 7.55 (6.73) years. At baseline, Hcy levels were 10.07 (3.71) μmol/L, the SLEDAI was 5.6 (4.34), and the SDI 0.97 (1.35). The average daily dose of PDN was 7.30 (5.78) mg/d and the time of exposure to PDN was 7.36 (6.73) years. Patients were followed for 3.54 (1.27) years, and 75 (51.7%) increased at least one point in the SDI. Other patients' characteristics are shown in Table 1. For those patients in whom the SDI increased, the mean (SD) value of Hcy was 10.99 (4.30) μmol/L; it was 9.10 (2.66) μmol/L for those in whom the SDI did not increase; $p = 0.002$ (Fig. 1).

Kaplan-Meier plots of the event-free proportion between the low (T1 ≤ 8 μmol/L), medium (T2: > 8–10.5 μmol/L), and high (T3 > 10.5 μmol/L) Hcy tertiles who were followed for the occurrence of new damage ($p = 0.035$) are shown in Fig. 2. In those with Hcy higher than 10.5 μmol/L, damage accrual–free survival was 83.0% in the first year, 71.8% in the second year, and 47.2% in the third year. The highest tertile of homocysteine levels predicted new damage accrual in the univariable and multivariable models [HR 1.780 (95% CI: 1.042–3.039); $p = 0.035$ and HR 2.045 (95% CI: 1.077–3.883); $p = 0.029$, respectively] and they are shown in Table 2.

Table 1 Systemic lupus erythematosus patients studied ($n = 145$)

Characteristics	
Age at diagnosis, years, mean (SD)	43.70 (12.09)
Disease duration, years	7.55 (6.73)
Female gender, *n* (%)	136 (93.8)
Disease duration, years, mean (SD)	7.55 (6.73)
Socioeconomic status, *n* (%)	
High	29 (20.0)
Medium	61 (42.1)
Low	55 (37.9)
Homocysteine levels, mean μmol/L (SD)	10.07 (3.71)
SLEDAI, mean (SD)	5.6 (4.34)
SDI, mean (SD)	0.97 (1.35)
PDN current dose, mg/day, mean (SD)	7.30 (5.78)
PDN time of exposure, years, mean (SD)	7.36 (6.73)
Antimalarial use, *n* (%)	
Never	13 (9.0)
Past	22 (15.2)
Current	110 (75.9)
Immunosuppressive drugs use (*N* (%))	
Never	39 (26.9)
Past	39 (26.9)
Current	67 (46.2)
Duration of follow-up, years, mean (SD)	3.53 (1.26)

PDN prednisone, *SDI* SLICC/ACR damage index, *SLEDAI* systemic lupus erythematosus disease activity index, *N* number, *SD* standard deviation

Twelve (8.3) patients had levels of Hcy > 15 μmol/L; this cut-off provided a sensitivity of 20% and a specificity of 98.6%. The corresponding ROC is depicted in Fig. 3 being the area under the curve of 0.616. Other Hcy cut-off points and their corresponding sensitivity and specificity values are shown in Table 3. In the alternative analysis, in which Hcy levels were examined as a continuous variable, Hcy predicted new damage accrual in the univariable and multivariable model [HR 1.083 (95% CI: 1.029–1.139); $p = 0.002$ and HR 1.099 (95% CI: 1.031–1.171); $p = 0.004$, respectively] (supplementary Table 1). When evaluating the correlation between Hcy and several clinical and metabolic markers, only creatinine levels remained associated after adjusting for multiple comparisons (data not shown). When we examined the impact of Hcy per domain of the SDI, we could not find, any specific associations (data not shown).

Discussion

Utilizing the baseline data from a primarily Mestizo SLE cohort, we have examined whether Hcy levels can predict damage accrual independently of other well-known risk factors; indeed, we

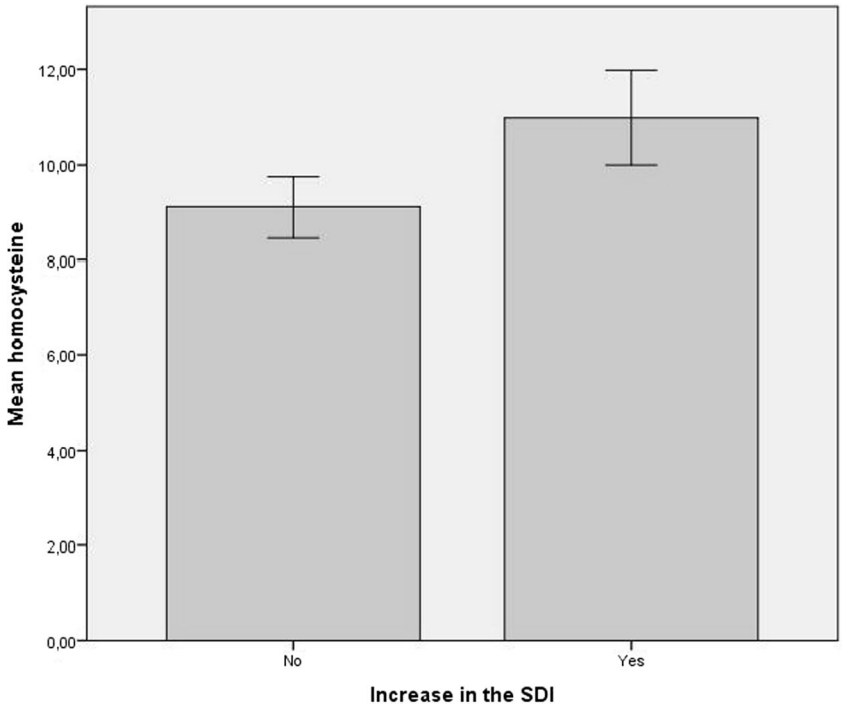

Fig. 1 Homocysteine values according to changes in the SDI over time. *Horizontal lines reflect 95% confidence intervals, $p = 0.002$

found that to be the case. The prevalence of hyperhomocysteinemia has been estimated to be 5% in the general population and 13 to 47% among patients with symptomatic atherosclerotic vascular disease from the general population [26]. We found hyperhomocysteinemia defined as > 15 μmol/L in 8.3% of our SLE patients; using this cut-off point, the percentages are similar to those previously reported in the literature [2, 24]. However, this value does not have optimal sensitivity and specificity (20% and 98.6%, respectively). The cut-off points used by other investigators have parameters with sensitivities varying between 20.0 and 66.7% and specificities varying from 58.4 to 98.6% (Table 3). For this reason, the cut-off point for Hcy that we have used in the present study should be evaluated in larger populations.

Malinow et al. reported an elevated risk for thickening of the carotid artery intima media (OR 3.15) starting at Hcy concentrations > 10.5 μmol/L in asymptomatic adults [27]. In SLE, elevated Hcy levels have been associated with clinical cardiovascular diseases; they have also been found to be an independent risk factor for atherosclerosis progression [4, 28, 29]. Sabio et al. reported that elevated Hcy levels (≥ 15 μmol/L), body mass index, and daily PDN dose were independently associated with an increased risk of hypertension in 99 (23%) women with SLE [24]. McMahon et al. found that two traditional cardiac risk factors (age ≥ 48 years and diabetes), and four proinflammatory biomarkers (one of them Hcy levels ≥ 12 μmol/L), had overall better predictive value for the presence, progression, or acquisition of carotid artery plaque in SLE patients than did any

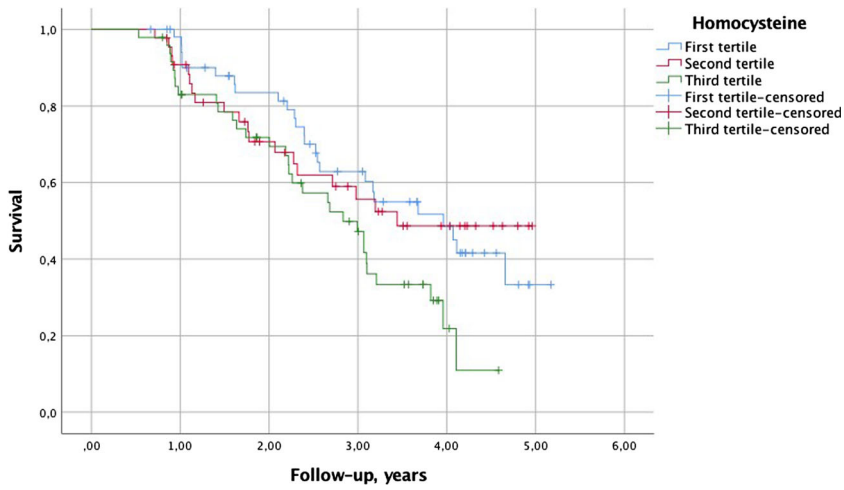

Fig. 2 Kaplan-Meier curve of the probability of damage accrual–free survival in SLE patients using stratified homocysteine levels ($p = 0.035$)

Table 2 Homocysteine levels by tertiles as predictor of damage accrual in SLE (univariable and multivariable analyses)

Variables	Univariable analyses			Multivariable analyses		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age at diagnosis, years	1035	(1.015–1.055)	< 0.001	0.991	[0.949–1.034]	0.673
Disease duration, years	1.030	(1.001–1.061)	0.044	1.032	[0.962–1.108]	0.374
Gender (female)	0.757	(0.305–1.877)	0.547	0.773	[0.233–2.559]	0.673
Socioeconomic status						
High	Ref.			Ref.		
Medium status	1.300	(0.701–2.409)	0.405	1.999	[0.815–4.904]	0.130
Low status	1.274	(0.757–2.145)	0.362	2.051	[0.622–6.767]	0.238
Educational level, years	0.940	(0.879–1.004)	0.067	0.869	[0.759–0.996]	0.043
Homocysteine						
Low tertile	*Ref.*			*Ref.*		
Medium tertile	*1.042*	*[0.574–1.893]*	*0.892*	*1.154*	*[0.600–2.219]*	*0.668*
High tertile	*1.780*	*[1.042–3.039]*	*0.035*	*2.045*	*[1.077–3.883]*	*0.029*
SLEDAI,	1.034	(0.982–1.088)	0.201	1.035	[0.976–1.098]	0.254
Immunosuppressives use						
Never	Ref.			Ref.		
Past	0.803	(0.408–1.581)	0.526	0.904	[0.421–1.938]	0.795
Current	1.372	(0.808–2.328)	0.242	1.663	[0.911–3.036]	0.098
Hydroxychloroquine use						
Never	Ref.			Ref.		
Past	1.011	(0.451–2.270)	0.978	0.960	[0.336–2.740]	0.939
Current	0.570	(0.296–1.098)	0.093	0.711	[0.319–1.584]	0.404
Prednisone current dose (mg/d)	1.004	(0.969–1.042)	0.811	0.998	[0.955–1.044]	0.940
Time of exposure to prednisone, years	1.022	(0.992–1.054)	0.152	0.991	[0.936–1.050]	0.768
Framingham score	1.068	[1.031–1.107]	< 0.001	1.067	[0.990–1.151]	0.092
SDI	1.082	(0.920–1.272)	0.341	0.877	[0.704–1.093]	0.244

SDI SLICC/ACR damage index, *SLEDAI* systemic lupus erythematosus disease activity index

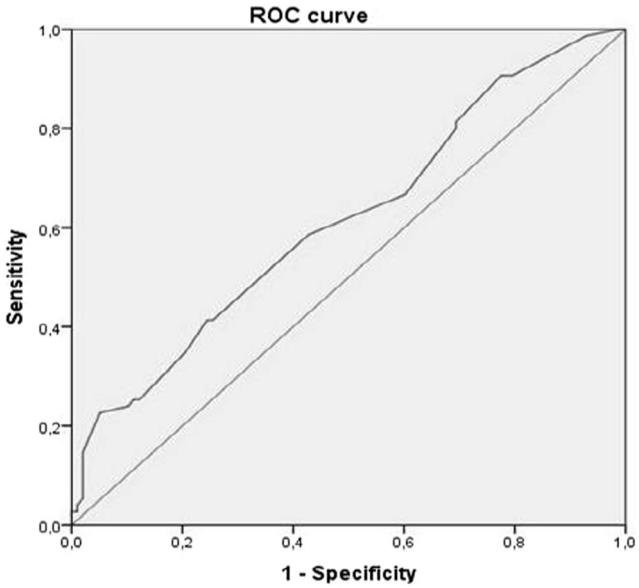

Fig. 3 Receiver–operating characteristic (ROC) curve of Hcy levels as predictor of damage in SLE

individual biomarker or traditional risk factor [30]. Studies in lupus, however, have not been limited to vascular and atherosclerosis disease; Catejon et al., for example, reported significantly higher Hcy serum levels (17.36 ± 5.50 μmol/L), uric acid and inflammatory biomarkers such as interleukin (IL)-8, sICAM-1, or complement molecules in 15 SLE patients with metabolic syndrome [31]. Petri et al. found Hcy levels to be strongly associated with renal disorder, low glomerular

Table 3 Cut-off value of plasma homocysteine levels as predictor of damage in SLE

	N	%	Sensitivity	Specificity
> 10 μmol/L	49	33.8	58.7%	74.3%
> 11 μmol/L	41	28.3	41.3%	97.1%
> 12 μmol/L	26	17.9	34.7%	97.1%
> 13 μmol/L	19	13.1	24.0%	97.1%
> 14 μmol/L	16	11.0	22.7%	98.6%
> 15 μmol/L	12	8.3	20.0%	98.6%

filtration rate, and proteinuria in a study comprising 829 SLE patients [7]. Likewise, Moroni et al. found higher Hcy levels in patients with active renal disease than in patients in complete remission (16.8 ± 7.2 versus 11.8 ± 3.7 μmol/L) and in patients with antiphospholipid antibodies (aPL) than in aPL negative patients (14.5 ± 5.8 versus 11.8 ± 4 μmol/L) [8]. Finally, Bonciani et al. found hyperhomocysteinemia in patients with different chronic and subacute cutaneous lupus erythematosus manifestations [9]. These studies, taken together, provide evidence for the deleterious effect of Hcy, and its possible role as a predictor of poor outcomes in SLE.

The accrual of damage can be explained because Hcy is able to induce chemokine and chemokine receptor expression in human vascular cells and monocytes, including IL-1β, IL-6, IL-8, IL-12, IL-18, IL-1 receptor antagonist, C-reactive protein, adhesion molecules, and metalloproteinases [14, 15, 32–34]. In addition, it has been found that hyperhomocysteinemia increases the number of splenic B cells, elevates the level of plasma immunoglobulin G, and increases atherosclerotic lesion formation [35]; this could be potentiated in SLE patients because of a possible higher sensitivity to the toxic effect of Hcy and its metabolites on the lupus vasculature [24] with levels of anti-N-Hcy-albumin antibodies significantly higher and are largely determined by Hcy, C-reactive protein and the disease duration [36].

Our mean value of Hcy was higher in those patients in whom their SDI increased which is comparable to the results of Sabio et al. who found a median value of Hcy of 12 (8–15) μmol/L in 19 (21.6%) SLE patients that increased ≥ 1 SDI point [37]. We found that Hcy levels > 10.5 μmol/L were associated with a 78% increase in the probability of damage accrual in the univariable analysis and 98% in the multivariable analysis. Furthermore, Kaplan-Meier analysis revealed that the probability of damage accrual–free survival decreased with higher Hcy tertile levels in our SLE patients. The Framingham Risk Score includes traditional cardiac risk factors, but it has limited usefulness in patients with SLE who, overall, are relatively young [38]. When we included it in the analyses, Hcy levels remained associated with new damage. This could reflect a putative role for Hcy in inflammatory-associated disease progression and damage accrual [15]. As has been reported by others, patients with damage are more likely to develop further damage over time and are also at higher risk of future mortality [39]. Additionally, it will take more years of follow-up to address the most important question, which is if we keep Hcy levels down, would we be able to reduce the most important coronary events and slow or prevent more renal damage and other disease manifestations [40]?

Our study has some limitations. First, this cohort is relatively small, and ethnically homogeneous, so whether Hcy levels impact on damage accrual in patients from other ethnic/racial groups cannot be stated. Second, antimalarials were not shown to have a protective effect but the total time of antimalarial use could not be estimated from the available data; likewise, steroids were not shown to be deleterious which was probably due to the fact that we were unable to estimate its cumulative dose. Third, we could not determine which one of the domains and elements of the SDI was most impacted which is probably due to the small number of specific events as a result of a relatively short follow-up time. Fourth, ours is not an inception cohort; thus, it did not allow us to evaluate the impact and interaction of some variables at disease onset and over the course of the disease. Fifth, as we could not fully match or adjust for a proinflammatory status, we cannot be sure if Hcy levels per se are responsible for the increased damage observed, or if Hcy levels are rather a surrogated marker of a proinflammatory status. Nevertheless, our study has some important strengths. It is the first longitudinal study to determine the impact of Hcy levels on damage accrual in a primarily Mestizo SLE patient population. Thus, we consider relevant to report these data which should prompt the conduct of longitudinal studies with a larger number of patients in order to confirm our findings.

In conclusion, we describe for the first-time Hcy levels to be a contributing factor to new damage occurrence in SLE patients, independently of age at diagnosis, gender, disease duration, socioeconomic status, disease activity, use of PDN, antimalarials, and immunosuppressive drugs at baseline. These associations should be further explored in longitudinal studies to determine their temporal relationship.

Author contributions All authors were involved in drafting or critically revising this manuscript for important intellectual content, and all authors approved the final version to be published. Drs. Paola A. Zeña Huancas and Manuel F. Ugarte-Gil have full access to all the study's data and take responsibility for their integrity and the accuracy of the analyses performed.

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Compliance with ethical standards

Disclosures None.

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