INTRODUCTION

SLE is a complex inflammatory autoimmune disease characterised by flares, damage accrual and diminished survival.\(^1\) A treat-to-target strategy has been proposed for SLE;\(^2\) however, for this approach to work, a uniform definition of the target, validated in several populations, is required.

The 2021 Definition Of Remission In SLE (DORIS) included the absence of clinical disease activity (clinical Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K)=0 and physician global assessment (PGA)<0.5), with no or minimal intake of glucocorticoids (prednisone daily dose not higher than 5mg/day) and/or remission. This approach has been proposed for SLE patients; however, for this approach to work, a uniform definition of the target, validated in several populations, is required. The 2021 DORIS includes the absence of clinical disease activity (clinical Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K)=0 and physician global assessment (PGA)<0.5), with no or minimal intake of glucocorticoids (prednisone daily dose not higher than 5mg/day) and/or remission.
immunosuppressive drugs on stable maintenance dose. However, as this target is not frequently achieved, an alternative outcome (lupus low disease activity state, LLDAS) has been proposed by the Asia Pacific Lupus Collaboration (APLC). This definition includes the following: SLEDAI-2K ≤4, which allows a low level of disease activity, without activity in major organ systems or new disease activity, PGA ≤1, prednisone daily dose not higher than 7.5 mg/day and/or immunosuppressive drugs on maintenance dose. Of note, antimalarials are allowed for both remission and LLDAS.

In Hispanic populations (from the USA and Latin America), remission and LLDAS have been evaluated in the Grupo Latino Americano De Estudio del Lupus (GLADEL) and Lupus in Minorities: NAture vs. Nurture (LUMINA) cohorts; however, in both cases, the definitions had to be somewhat modified due to the fact that same variables were just not available in these cohorts. The main missing variable in both cohorts was the PGA, a variable that allows the evaluation of some less frequent manifestations not included in the disease activity indices.

This study evaluates the impact of the original definitions of remission and LLDAS on damage accrual in a primarily Mestizo Peruvian population.

**METHODS**

The Almenara Lupus Cohort has been previously described. In short, this cohort was started in 2012 at the Rheumatology Department of the Hospital Guillermo Almenara Irigoyen in Lima, Peru. Patients who signed the informed consent were recruited and followed every 6 months. Evaluations included an interview, medical records review, physical examination and laboratory tests. In these analyses, we have included patients with at least two visits and with all the variables needed to define disease activity states.

SLE was defined using the 1997 revised American College of Rheumatology criteria. Remission and LLDAS were defined according to the 2021 DORIS and APLC definitions. Disease activity states were ascertained at each visit. Damage was ascertained with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Antimalarial use and SDI. Confounders were determined at the same visit as disease activity state, but SDI was assessed at the subsequent visit.

Alternative models including the number of years (consecutively or not) the patient was on remission or on LLDAS at the index visit were performed.

Antimalarial use and disease activity state were included as time-dependent covariables in all models. P<0.05 was considered significant in all analyses. All analyses were performed using SPSS V.27.0.

**RESULTS**

Two hundred and eighty-one patients were included, of whom 260 (92.5%) were female, with a mean (SD) age at diagnosis of 35.8 (13.3) years and a mean disease duration at baseline of 9.1 (7.0) years. Patients had a mean of 4.8 (1.9) visits and a mean follow-up of 2.7 (1.1) years. Eighty-three patients (29.5%) showed increased SDI during the follow-up. The characteristics of the patients are depicted in table 1.

Five-hundred and eighty visits (54.6%) were categorised as being on remission and 482 (45.4%) as not on remission. Based on LLDAS, 726 (68.4%) visits corresponded to LLDAS and 336 (31.6%) not on LLDAS. The proportion of the visits the patients were on remission or LLDAS is depicted in online supplemental table 1.

In the first approach, when we evaluated the impact of the disease state at a given visit on the probability of damage accrual, we found that being on remission was associated with a lower probability of damage accrual (HR=0. 456; 95% CI 0.256 to 0.826; p=0.010) (table 2, model 1); being on LLDAS (remission included) was also associated with a lower probability of damage accrual (HR=0. 503; 95% CI 0.260 to 0.975; p=0.042) (table 2).

| Table 1 | Characteristics of the patients at baseline |
|---------|------------------------------------------|
| Characteristics | n (%) or mean (SD) |
| Female gender | 260 (92.5) |
| Age at diagnosis, years | 35.8 (13.3) |
| Disease duration, years | 7.0 (3.9) |
| SLEDAI-2K | 1.4 (2.5) |
| SDI | 1.3 (1.5) |
| Prednisone daily dose, mg/day | 2.1 (3.4) |
| Antimalarial use | |
| Never | 10 (3.6) |
| Past | 19 (6.8) |
| Current | 252 (89.7) |
| Immunosuppressive drug use | |
| Never | 61 (21.7) |
| Past | 70 (24.9) |
| Current | 150 (53.4) |

SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2K.
model 2). When the three states were included (remission, LLDAS (not on remission) and active), remission was associated with a lower probability of damage accrual (HR=0.423; 95% CI 0.212 to 0.846; p=0.015) but LLDAS (not on remission) was not (HR=0.878; 95% CI 0.369 to 2.087; p=0.768) (table 2, model 3).

In the alternative approach, when we evaluated the time in years a patient was on each state, we found that the higher the number of years on remission, the lower the probability of damage accrual (HR=0.554; 95% CI 0.364 to 0.843; p=0.006) (table 3, model 1). Also, the higher the number of years on LLDAS (remission included), the lower the probability of damage accrual (HR=0.458; 95% CI 0.300 to 0.700; p=0.001) (table 3, model 2). When the three states were included, the number of years on remission (HR=0.495; 95% CI 0.316 to 0.776; p=0.002) and on LLDAS (not on remission) (HR=0.343; 95% CI 0.161 to 0.731; p=0.006) was associated with a lower the probability of damage accrual; these analyses are depicted in table 3 (model 3).

**DISCUSSION**

In this primarily Mestizo prevalent lupus cohort, remission and LLDAS were associated with less damage accrual, independent of other well-known risk factors for this endpoint; this is consistent with other reports.5 6 9 10

The rate of remission and LLDAS in this cohort was higher than the ones reported in the GLADEL and LUMINA cohorts.5 6  This could be due to the use of different definitions of remission and LLDAS (eg, in the GLADEL cohort, the analyses included complete remission (SLEDAI including serology=0) with treatment) or due to differences in treatments given the characteristics of the cohorts or the time at which patients were recruited into them (the GLADEL and LUMINA cohorts recruited patients towards the end of the 1990s and early 2000s, whereas the Almenara patients were recruited only over the last 10 years or so). Additionally, remission is less likely to be achieved early in the course of the disease,11 and the GLADEL and LUMINA cohorts included patients with a shorter disease duration. Our rates, however, are similar to those from Europe9 and Asia.12

The DORIS group has recently proposed that duration should not be included in the definition of remission5; nevertheless, a durable remission should be the ideal treatment target. Our results showed that the longer the patient remains on remission or LLDAS, the lower the probability of accruing damage, which is consistent with

### Table 2  Impact of disease activity state on damage accrual

|                      | Univariable P value | Model 1 | Model 2 | Model 3 |
|----------------------|---------------------|---------|---------|---------|
|                      | HR (95% CI) P value | HR (95% CI) P value | HR (95% CI) P value | HR (95% CI) P value |
| Not on remission     | Ref                 | Ref     | Ref     | Ref     |
| Remission            | 0.471 (0.273 to 0.815) 0.007 | 0.456 (0.252 to 0.826) 0.010 | 0.503 (0.260 to 0.975) 0.042 |
| Active               | Ref                 | Ref     | Ref     | Ref     |
| LLDAS/remission      | 0.509 (0.282 to 0.920) 0.025 | 0.503 (0.260 to 0.975) 0.042 |
| Active               | Ref                 | Ref     | Ref     | Ref     |
| LLDAS (not on remission) | 0.871 (0.374 to 2.027) 0.748 | 0.878 (0.369 to 2.087) 0.768 |
| Remission            | 0.444 (0.240 to 0.824) 0.010 | 0.423 (0.212 to 0.846) 0.015 |
| Age at diagnosis     | 1.003 (0.981 to 1.026) 0.778 | 1.016 (0.990 to 1.042) 0.238 | 1.017 (0.991 to 1.044) 0.208 | 1.017 (0.991 to 1.044) 0.204 |
| Gender, female       | 0.637 (0.213 to 1.903) 0.419 | 0.631 (0.229 to 1.738) 0.373 | 0.653 (0.226 to 1.887) 0.431 | 0.646 (0.227 to 1.835) 0.412 |
| Educational level, years | 0.936 (0.847 to 1.003) 0.189 | 0.877 (0.748 to 1.030) 0.110 | 0.889 (0.756 to 1.045) 0.155 | 0.879 (0.749 to 1.031) 0.113 |
| Socioeconomic status | Low                 | Ref     | Ref     | Ref     |
|                      | Ref                 | Ref     | Ref     | Ref     |
| High                 | 0.72 (0.418 to 2.263) 0.948 | 0.337 (0.080 to 1.423) 0.139 | 0.349 (0.090 to 1.514) 0.166 | 0.340 (0.081 to 1.432) 0.141 |
| Disease duration at baseline, years | 1.052 (1.011 to 1.095) 0.012 | 1.062 (1.017 to 1.109) 0.006 | 1.061 (1.016 to 1.108) 0.008 | 1.064 (1.018 to 1.111) 0.006 |
| Antimalarial use      | Current             | Ref     | Ref     | Ref     |
|                      | Ref                 | Ref     | Ref     | Ref     |
| Past                 | 0.983 (0.358 to 2.695) 0.973 | 0.870 (0.281 to 2.696) 0.809 | 0.921 (0.293 to 2.892) 0.888 | 0.872 (0.274 to 2.780) 0.818 |
| Never                | 1.614 (0.259 to 10.051) 0.608 | 1.629 (0.237 to 11.192) 0.620 | 1.607 (0.234 to 11.026) 0.629 | 1.601 (0.229 to 11.213) 0.635 |
| SDI                  | 1.177 (1.005 to 1.378) 0.043 | 1.044 (0.859 to 1.269) 0.668 | 1.052 (0.863 to 1.282) 0.614 | 1.038 (0.852 to 1.264) 0.711 |

Model 1: remission versus not on remission.
Model 2: LLDAS (including remission) versus active.
Model 3: remission, LLDAS (not on remission) and active.
LLDAS, lupus low disease activity state; Ref, reference; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.
diminished. Necessary in order for the risk of damage accrual to be associated with a lower probability of damage accrual. For Mestizo Latin American population.

In conclusion, being on LLDAS and/or remission is associated with a lower probability of damage accrual, but LLDAS, excluding remission, was not associated with damage accrual in the original model (definition at each visit); however, it was associated with a lower probability of damage accrual when the duration of LLDAS was taken into account. These results are consistent with data reported by other groups of investigators, including the Hopkins Lupus Cohort and the Padua Lupus Clinic.

Our study has, however, some limitations. First, as this is a prevalent cohort, we cannot exclude the impact of disease characteristics before the baseline or intake visit. Second, the relatively small sample size precludes us from making stronger conclusions. The main strength of this study is that it is the first to evaluate the impact of the 2021 DORIS definition of remission and the original APLC definition of LLDAS on damage in a primarily Mestizo Latin American population.

In conclusion, being on LLDAS and/or remission is associated with a lower probability of damage accrual. For LLDAS, a minimum duration on such a state seems to be necessary in order for the risk of damage accrual to be diminished.

### Author affiliations
1. Rheumatology, Hospital Nacional Guillermo Almenara Irigoyen, EsSalud, Lima, Peru
2. Grupo Peruano de Estudio de Enfermedades Autoinmunes Sistémicas, Universidad Científica del Sur, Lima, Peru
3. Unidad de Investigación Para La Generación y Síntesis de Evidencias en Salud, Fondo Sectorial de Investigación, Universidad San Ignacio de Loyola, Lima, Peru
4. School of Medicine, Universidad Nacional Mayor de San Marcos, Lima, Peru
5. Janssen R&D, Spring House, Pennsylvania, USA
6. Medical Affairs, Jan-Ci Argentina, Buenos Aires, Argentina
7. School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA
8. School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru

### Twitter
Manuel Francisco Ugarte-Gil @mugartegil

### Competing interests
MFU-G has full access to all of the data from the study and takes responsibility for their integrity and the accuracy of the analyses performed. CR-V has grant support from Janssen. Additionally the Almenara Lupus Cohort was partially supported by institutional grants from EsSalud (1483-GECP-ESSALUD-2013, 1733-GECP-ESSALUD-2014 and 2015 Kaelin Prize 04-IETSI-ESSALUD-2016), Pan American League of Associations for Rheumatology (PANLAR) (2015 PANLAR Prize and 2018 H Ralph Schumacher MD/JCR/PANLAR Prize), and Fundación Instituto Hipólito Unanue.

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