Systemic Lupus Erythematosus Disease Activity Score

Subjects: Rheumatology

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Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that affects multiple organ systems and manifests in a relapsing–remitting pattern. Consequently, it is paramount for rheumatologists to assess disease activity, identify flare-ups, and establish treatment goals for patients with SLE. In 2019, the Systemic Lupus Erythematosus Disease Activity Score (SLE-DAS) was introduced as a novel tool for measuring disease activity. This tool refines the parameters of the established SLE Disease Activity Index 2000 (SLEDAI-2K) to enhance the assessment process.

systemic lupus erythematosus SLE-DAS SLE

1. Introduction to Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a complex, chronic systemic autoimmune disease characterized by the production of autoantibodies against a variety of self-antigens. It can affect multiple bodily systems and organs, including the kidneys, skin, brain, heart, lungs, hematologic system, and musculoskeletal system, leading to widespread inflammation and tissue damage.

Globally, the incidence of newly diagnosed cases of systemic lupus erythematosus (SLE) is estimated at 5.14 per 100,000 person-years, ranging from 1.4 to 15.13, leading to approximately 400,000 new individuals affected by SLE each year. Additionally, the global prevalence of SLE is estimated at 43.7 per 100,000 persons, varying from 15.87 to 108.92, corresponding to approximately 3.41 million people currently living with the disease [1]. The variation in incidence and prevalence can be attributed to differences in population genetics, environmental factors, socioeconomic status, the availability of healthcare, and the comprehensiveness of healthcare records [2].

SLE predominantly affects women, with a female-to-male ratio of 9:1 [1]. The female predominance is even higher during peak childbearing ages. The pathophysiological mechanisms responsible for sexual dimorphism in SLE are still unclear, but cytokine pathways and genetics have been proposed to explain this sexual dimorphism [3].

2. Challenges in the Management of SLE

One of the main features of SLE is its unpredictable course, with periods of low or no disease activity (relapsing) alternating with periods of high disease activity (flares). Flares can cause damage to the affected organs and impair the quality of life of patients. In addition, most patients initially present with mild disease activity but may

progress to moderate and severe conditions over time [4][5]. Thus, there is a need to measure disease activity to allow clinicians to identify flares early, potentially mitigating organ damage and improving patient outcomes.

While there have been significant improvements in the long-term outcomes for patients with SLE over the past decades, the persistence of increased morbidity and mortality, particularly among young individuals, remains a concern [6]. A meta-analysis of 15 reports involving a total of 26,101 patients with SLE and 4640 deaths revealed that the all-cause standardized mortality ratio (SMR) significantly increased 2.6-fold in patients with SLE. Specifically, the risks of mortality were significantly increased for deaths attributed to renal disease (SMR 4.69, 95% CI 2.36–9.33), cardiovascular disease (SMR 2.25, 95% CI 1.30–3.89), and infection (SMR 4.98, 95% CI 3.88–6.40) [7]. Regular monitoring of disease activity helps in assessing the risk and extent of organ damage, which is critical for tailoring treatment plans.

Recently, there is growing interest in applying the treat-to-target (T2T) approach to SLE treatment, similar to its successful implementation in other rheumatic diseases like rheumatoid arthritis and ankylosing spondylitis. Rheumatologists are considering the adoption of the T2T strategy for SLE treatment. Central to the T2T strategy is the ability to define specific treatment goals and precisely measure disease activity, which are crucial for guiding therapeutic decisions. This approach enables early detection of disease flares and continuous monitoring of treatment efficacy, ensuring timely adjustments to meet set targets. However, further discussions and investigations are needed before T2T can be fully integrated into clinical practice for SLE [8].

3. Measurement of Disease Activity in SLE

As outlined above, measuring disease activity in SLE is fundamental to effectively managing this complex autoimmune disease. However, there is still a lack of a single definition or measure of disease activity. This variability in measurement tools reflects the diverse manifestations and complexities of SLE. Consequently, the choice of an assessment tool often depends on the specific clinical context and the aspects of the disease that need to be monitored.

Various tools have been developed to assess disease activity and organ damage in patients with SLE [9]. These tools include the British Isles Lupus Assessment Group Index (BILAG) [10], the European Consensus Lupus Activity Measurements (ECLAM) [11], the SLICC/ACR Damage Index (SDI) [12], the SLE Disease Activity Index 2000 (SLEDAI-2K) [13], the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI [14], the Systemic Lupus Erythematosus Disease Activity Score (SLE-DAS) [15], and Easy-BILAG [16]. They capture different aspects of disease activity, such as clinical signs and symptoms, laboratory test results, organ involvement, patient-reported outcomes, and physician assessments.

Among these assessment tools, SLEDAI-2K is commonly used in both clinical practice and basic SLE research. Notably, SLE-DAS, a relatively recent addition, was developed by expanding upon the elements in SLEDAI-2K [15].

4. Development and Characteristics of SLE-DAS

SLE-DAS, introduced by Jesus et al. in 2019, is an enhancement to the widely used SLEDAI-2K. This index was developed with two representative longitudinal cohorts of Caucasian patients, comprising 324 individuals in the derivation cohort and 196 in the external validation cohort. It has shown good construct validity and a higher discriminative power for detecting clinically meaningful changes in SLE disease activity compared to its predecessor, SLEDAI-2K. The correlation coefficients between SLE-DAS and SLEDAI-2K were significant in both the derivation and the external validation cohorts at the last follow-up visit (both at r = 0.94). In addition, the predictive value of SLE-DAS in assessing damage accrual over follow-up was better than that of SLEDAI-2K, further demonstrating its criterion validity [15].

One of the key modifications of SLE-DAS is the inclusion of several critical items in evaluating disease activity. These additions include cardiac/pulmonary involvement, gastrointestinal issues, sterile peritonitis, and hemolytic anemia. The index also employs continuous measures for conditions including arthritis, proteinuria, thrombocytopenia, and leucopenia. However, SLE-DAS excludes items including urinary casts, hematuria, pyuria, and fever. Consequently, SLE-DAS comprises a 17-item assessment, a modification from the original 24-item format of SLEDAI-2K [15].

5. Comparison of SLE-DAS and Other SLE Activity Indices

Jesus et al. showed a strong correlation between both SLE-DAS and SLEDAI-2K scores with the Physician Global Assessment (PGA) [15]. When using score changes (Δ) in SLE-DAS of ≥ 1.72 and SLEDAI-2K of ≥ 4 as indicators of clinically meaningful improvement, the researchers found the sensitivity was 82.1% and the specificity was 96.9% for ΔSLE-DAS ≥ 1.72. In contrast, for ΔSLEDAI-2K ≥ 4, the sensitivity was significantly lower at 44.8%, and the specificity remained high at 96.5%. This suggests that SLE-DAS performed better in detecting clinically meaningful changes in SLE compared to SLEDAI-2K. An important factor contributing to this difference is the use of continuous measures for arthritis, proteinuria, thrombocytopenia, and leucopenia in SLE-DAS, which offers a great advantage over the categorical classification of these factors in SLEDAI-2K.

Saraiva et al. investigated flare-ups in 442 patients with SLE who initially presented with low disease activity. These flare-ups were identified based on expert-consensus definitions during follow-up visits. The researchers used various indices for classifying these flare-ups, including the SLE-DAS (Δ ≥ 1.72), classic-SELENA Flare Index (c-SFI), revised-SFI (r-SFI), and SLEDAI-2K (Δ ≥ 4). The study revealed that the sensitivities for detecting SLE flare-ups were 97.1% for SLE-DAS, 88.4% for both c-SFI and r-SFI, and 56.5% for SLEDAI-2K. For specificities, the results were 97.3% for SLE-DAS, 98.1% for c-SFI, 96.8% for r-SFI, and a notably high 99.2% for SLEDAI-2K. Among these four measurements, SLE-DAS exhibited the best discriminative ability in identifying flares, as determined through receiver operating characteristic curve analysis [17].

However, Leosuthamas et al. evaluated the performance of five SLE disease activity indices in a study of 27 patients with active SLE [18]. These indices included the SLE-DAS (Δ ≥ 1.72), SLEDAI-2K responder index-50 (SRI-50), the BILAG-based Composite Lupus Assessment (BICLA), SLE responder index-4 (SRI-4), and a variant replacing SLEDAI-2K with SRI-50 in SRI-4 (denoted as SRI-4(50)). The researchers found no significant

differences between these indices when assessing clinical improvement based on PGA and lupus-related medication in patients with SLE. However, the study's relatively small sample size was a limitation.

Despite its utility, the scoring process of BILAG is complex and time-consuming, often requiring specialized training for evaluators. To address this, the Easy-BILAG was developed, building upon BILAG-2004, to provide a more rapid and accurate evaluation across all SLE clinical settings [16]. Easy-BILAG is a single-page document that uses color-coding to indicate disease activity in nine domains. The domains are mucocutaneous, musculoskeletal, cardiorespiratory, neuropsychiatric, hematological, gastrointestinal, ophthalmic, constitutional, and renal. For each domain, Easy-BILAG scores the clinical items as not present, improving, same, worse, or new. Rare manifestations are scored, only when necessary, on a second page. Moreover, Easy-BILAG contains many constitutional items including fever, weight loss, anorexia, lymphadenopathy, and splenomegaly that are more detailed than the SLE-DAS. Furthermore, its sub-classification for individual items is also more detailed. For instance, while SLE-DAS only considers swollen joints, Easy-BILAG also accounts for inflammatory joints in addition to swollen joints.

6. The Association of SLE-DAS with Health-Related Quality of Life (HRQoL)

Traditionally, the evaluation of disease activity and organ damage in SLE relies on physician assessment. However, there has been a growing recognition of the importance of patient-reported outcomes, particularly regarding the impact of SLE on quality of life (QoL) [19]. Although tools like the Medical Outcomes Study Short Form (SF-36) can be used for assessing HRQoL in patients with SLE, there are several instruments developed specifically for HRQoL in patients with SLE, such as the Lupus Quality of Life (LupusQoL) questionnaire, the SLE-specific Quality of Life (SLEQoL) questionnaire, and the SLE Quality of Life (L-QoL) questionnaire [20]. There are domains that are common to these questionnaires and also those unique to each questionnaire to address specific aspects of life affected by SLE.

7. SLE-DAS as a Predictor for Hospitalization Risk in SLE

In a prospective cohort study involving 326 Taiwanese patients with SLE, individuals categorized as having moderate or severe disease activity according to SLE-DAS were associated with a significantly higher risk of hospital admissions. This increased risk was significant for both SLE-specific and all-cause hospital admissions. In contrast, when the SLEDAI-2K index was used for classification, there was no significant correlation with SLE-specific hospitalizations and only a marginal association with all-cause admissions [21]. Similarly, Wang et al. showed that patients classified with moderate or severe activity by the SLE-DAS had more frequent hospitalizations for both overall and SLE-related issues. Conversely, the moderate or severe activity classification by SLEDAI-2K was only significantly associated with an increase in overall hospital admission rates for patients with SLE [22]. This difference may be explained by the inclusion of cardiac or pulmonary involvement of SLE in SLE-DAS compared to SLEDAI-2K.

8. Assessing SLE Disease Activity during Pregnancy Using SLE-DAS

Pregnancy introduces maternal physiological changes in patients with SLE, complicating disease activity assessments. Symptoms like edema, proteinuria, or hypertension might be attributed to either normal pregnancy changes or lupus flares. Buyon et al. introduced a modified version of SLEDAI-2K, termed the SLE-pregnancy disease activity index (SLEPDAI) [23]. However, SLEPDAI has not yet been fully validated, and further studies are needed to confirm its reliability and accuracy.

Larosa et al. evaluated SLE-DAS and SLEPDAI in the first trimester to predict maternal flare-ups and obstetric complications in the second and third trimesters among a cohort of 158 pregnant women with SLE. A high correlation between SLE-DAS and SLEPDAI in the first trimester was observed ($\rho = 0.97$, $p < 0.01$). Both SLE-DAS and SLEPDAI were found to be predictive of maternal flares associated with adverse pregnancy outcomes (APOs), including fetal and neonatal mortality, premature delivery before 37 weeks due to placental insufficiency, and birth of infants small for their gestational age. Moreover, the SLE-DAS model performed slightly better than SLEPDAI model, as assessed by the area under the receiver operating characteristic curve and goodness-of-fit analysis [24]. While both SLEPDAI and SLE-DAS are simple and effective in predicting maternal flares and adverse pregnancy outcomes, SLE-DAS might be favored for its potential ease of use and detailed continuous assessment capabilities, which are important in the dynamic context of managing SLE during pregnancy.

9. SLE-DAS as a Treatment Target for SLE

The treat-to-target (T2T) strategy has emerged as a proposed approach for SLE management, with low disease activity (LDA) or remission status as the predefined targets. The lupus low disease activity state (LLDAS) framework, introduced in 2016 [25], mandates not only a SLEDAI-2K score of ≤ 4 but also the absence of new disease activity in major organ systems, a SELENA-SLEDAI PGA score (ranging from 0–3) of ≤ 1, low doses of steroids, and stable use of immunosuppressive or biological agents. Achieving LLDAS has been associated with a significant reduction in organ damage risks and, most importantly, a lower mortality risk [26][27]. Consequently, many clinical trials have adopted LLDAS as a pivotal outcome measurement [28][29].

However, measuring LLDAS in routine clinical settings can be challenging. Abdelhady et al. showed a good agreement between SLEDAI-2K-derived LLDAS and SLE-DAS in a study of 117 patients with SLE [30]. Assunção et al. found that SLE-DAS LDA (defined as SLE-DAS ≤ 2.48 and a daily prednisone dose or its equivalent ≤ 7.5 mg) correlated well with SLEDAI-2K-derived LLDAS in a study involving 774 patients with SLE, with 300 in the derivation cohort and 474 in the validation cohort [31]. They found that a small proportion of patients exhibiting active lupus arthritis (1.03%), skin rashes (1.37%), and mucosal ulcers (0.34%) still qualified for LLDAS. However, none with these symptoms were classified as SLE-DAS LDA subgroups. This suggests that SLE-DAS LDA might offer a more apparent target in T2T strategies. In addition, Cunha et al. noted that 7.5% of patients with SLE meeting the LLDAS criteria did not achieve SLE-DAS LDA, with a higher SLE-DAS score at baseline predicting

potential flare-ups [32]. The comparative value of SLE-DAS LDA and LLDAS in predicting SLE flare-ups remains to be elucidated.

10. Conclusions

The advent of the SLE-DAS and its disease activity classification presents a potentially invaluable tool for rheumatologists, particularly for its utility in effectively assessing clinical responses, predicting hospitalizations, and guiding treatment objectives in patients with SLE. As efforts continue to refine disease activity measures, tools like SLE-DAS become pivotal in enhancing the management of SLE. While further research and comparative studies are essential to fully establish its superiority and applicability, the current evidence underscores the promise and relevance of SLE-DAS in contemporary clinical practice. Ultimately, this tool is expected to contribute to improved patient outcomes.

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