The Mirage of Stability: Challenges of Predicting Disease Activity Over Time in Systemic Lupus Erythematosus (SLE)

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Background

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with complex aetiology and varying clinical presentations, from mild mucocutaneous symptoms to systemic and multiorgan inflammation and tissue damage[1]
- SLE is typically characterised by periods of exacerbation (known as flares) and remission
- The most commonly used outcome measure to describe long-term disease activity is the Annual Mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (AMS) score

Methods

- A targeted literature review was conducted for predictive equations based on large databases with long follow-up in North America
- The predictive equations were used to estimate the AMS
- Disease activity trajectories were simulated using each equation for representative patient profiles
- Resulting AMS trajectories were reviewed by clinical and health economics experts during an advisory board to assess alignment with clinical plausibility, clinical expectations, and applicability in cost-effectiveness models (CEMs)

Objective

- To compare published predictive equations using AMS, assess their clinical face validity, and explore their suitability for CEMs

Results

Four sources of predictive equations were identified:

NICE TA397[2] (John Hopkins Cohort)	Watson et al. 2015[3] (John Hopkins Cohort)
Longitudinal data from patients from the John Hopkins Lupus Cohort Minimum follow-up: 24 months Data extracted in 2010 1,282 patients	Longitudinal data from patients from the John Hopkins Lupus Cohort Minimum follow-up: 24 months Data extracted in 2010 1,354 patients
Clarke et al. 2021[4] (SLICC Inception Cohort)	**Touma et al. 2024[5] (Toronto Lupus Cohort)**
SLICC Inception Cohort enrolled patients fulfilling ACR Classification Criteria for SLE within 15 months of diagnoses from 1999-2011 Annual follow-up through April 2020 1,697 patients	Data from the Toronto Lupus Cohort between 1997-2020 Mean follow-up: 10.5 years 1,255 patients

Comparison of each source:

	NICE TA397	Watson et al. 2015	Clarke et al. 2021	Touma et al. 2024
Long follow-up	✓	✓	✓	✓
Detailed regression	✗	✓	✓	✓
Recent data	✗	✗	✓	✓
Includes flares	✗	✗	✗	✓
Disease activity score used	SLEDAI	SLEDAI	SLEDAI	SLEDAI-2K
Used in previous submissions	✓	✗	✗	✗

Covariates and estimated coefficients used in each predictive equation:

	NICE TA397	Watson et al. 2015	Clarke et al. 2021	Touma et al. 2024
Constant	2.0577	1.491	5.762	1.4724
AMS	-0.4163	-0.460	-0.755	-0.3972
Cumulative AMS[a]	✗	✗	✗	0.0712
Male gender	-0.0991	-0.080	-0.207	✗
Black	0.3524	0.383	0.126	0.0073
Asian	✗	✗	✗	0.1724
Other	✗	✗	✗	0.2496
Age at diagnosis	✗	✗	✗	-0.0155
Log of age	-0.3586	-0.2414	-1.134	✗
Log of SLE duration	✗	✗	✗	-0.0877
Renal involvement	✗	-0.3014	0.627	✗
Increased DNA binding	✗	0.2759	0.939	✗
Low complement	✗	0.4838	0.775	✗
Haematological involvement	✗	0.1043	-0.025	✗
Anaemia	✗	0.1521	0.144	✗
Hypertension	✗	✗	✗	0.1359
Antimalarials	✗	✗	✗	-0.1529
Immunosuppressants	✗	✗	✗	0.1337
Sigma ui[b]	0.4093	0.3864	✗	✗

[a] lifetime average AMS; [b] the standard deviation of the patient-specific random error term (mean=0)

The following equation was used to predict the change in annual average SLEDAI score from the previous year to the next:

$$AMS_t = AMS_{t-1} + \beta X_t$$

Where β is the vector of coefficients, and X is the vector of covariates.

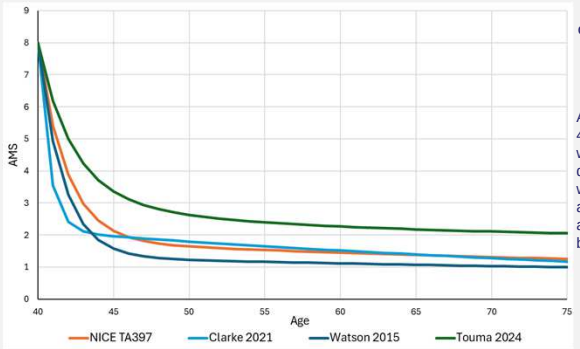

Figure 1

Assuming a 40-year-old white female, diagnosed with SLE at age 35, with an AMS of 8 at baseline

- All equations produced similar AMS trajectories **(Figure 1)**: a steep decline in the first 3-5 years, and a plateau around year 10 with mild disease
- Differences were minor and related to the speed of decline and the plateau level

- Experts noted that, while these patterns may be reasonable at the population level, **they do not reflect individual variability, the relapsing-remitting nature of SLE, or the role of flares**
  - The up-and-down nature of disease activity has been previously shown[6]
  - They considered it possible that the **long-term reduced disease activity is due to the effect of organ damage**
- The inclusion of age as a covariate was also questioned, as it is estimated from a limited time period, and therefore **the full effect of age could not be estimated**
- The experts believed the direction of the coefficients and most of the coefficients included in each of the four existing models make sense
  - **For annual mean SLEDAI, when the disease activity is high, the drop after treatment will also be larger**
- **Extrapolation for lifetime (i.e. beyond 20 years) for CEMs was questioned** due to a significantly shorter follow-up

Conclusions

- Existing predictive equations of AMS offer a consistent but simplified view of SLE disease activity progression
- Expert feedback highlighted the importance of clinical plausibility and their ability to capture key features of SLE that influence long-term treatment value
- Further research should focus on developing improved predictive equations designed to better capture aspects of SLE natural history that affect long-term outcomes, with a specific focus on their inclusion into CEMs

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Abbreviations

ACR, American College of Rheumatology; AMS, Annual Mean Systemic Lupus Erythematosus Disease Activity Index; CEM, cost-effectiveness model; NICE, National Institute for Health Care and Excellence; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; TA, technology appraisal

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