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High disease activity status suggests more severe disease and damage accrual in systemic lupus erythematosus

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ABSTRACT

Objective Disease severity in SLE is an important concept related to disease activity, treatment burden and prognosis. We set out to evaluate if high disease activity status (HDAS), based on ever attainment of a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) disease activity score of ≥10, is an indicator for disease severity in SLE.

Methods Using prospectively collected data, we assessed the association of HDAS with sociodemographic and disease characteristics and adverse clinical outcomes using logistic regression or generalised estimating equations.

Results Of 286 patients with SLE, who were observed for a median (range) of 5.1 years (1–10.8 years), 43.7% experienced HDAS at least once during the observational period. Autoantibody positivity, particularly anti-dsDNA and anti-Sm positivity, were associated with increased likelihood of HDAS. Age ≥45 years at diagnosis was associated with reduced likelihood of HDAS (p=0.002). Patients with HDAS had higher Physician Global Assessment score (>1: OR 8.1, p<0.001) and were more likely to meet criteria for flare (mild/moderate flare: OR 4.4, p<0.001; severe flare: OR 17.2, p<0.001) at the time of experiencing HDAS. They were also more likely to have overall higher disease activity, as defined by time-adjusted mean SLEDAI-2K score in the highest quartile (OR 11.7, 95% CI 5.1 to 26.6; p>0.001), higher corticosteroid exposure (corticosteroid dose in highest quartile: OR 7.7, 95% CI 3.9 to 15.3; p<0.001) and damage accrual (OR 2.3, 95% CI 1.3 to 3.9; p=0.003) when compared with non-HDAS patients.

Conclusions HDAS is associated with more severe disease, as measured by higher disease activity across time, corticosteroid exposure and damage accrual. The occurrence of HDAS may be a useful prognostic marker in the management of SLE.

Key messages

What is already known about this subject?

- Identification of patients with SLE with severe disease, in terms of higher overall disease activity and greater likelihood of damage accrual, is important in order to facilitate timely intervention and to guide therapeutic strategies.
- Previously, higher baseline disease activity exemplified by a Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) cut-off ≥10 has been shown to predict better responses to belimumab and atacicept in patients in clinical trials.

What does this study add?

- We used the SLEDAI-2K ≥10 to define high disease activity status (HDAS) and analysed clinical associations of HDAS in a longitudinal SLE registry.
- We found that patients who ever experienced HDAS had increased likelihood of adverse longitudinal outcomes including higher time-adjusted disease activity, flare, corticosteroid exposure and damage accrual.

How might this impact on clinical practice or future developments?

- HDAS is a pragmatic, simple-to-use prognostic indicator that may be useful in identifying more severe patients, as shown by the increased overall disease activity, treatment burden and poorer long-term prognosis.

INTRODUCTION

SLE is a relapsing–remitting, systemic autoimmune disease that is heterogeneous in its presentation and natural history.[1] The heterogeneity of SLE presents challenges for its diagnosis and management, as well as the evaluation of potential new treatments.[2 3] Despite some improvements in the survival of patients with SLE over recent decades, the increased mortality and morbidity experienced by patients with SLE when compared with the general population is a major concern for healthcare providers.[4–7]

Several studies have identified a number of non-reversible prognostic factors that are associated with increased mortality in SLE such as gender, damage accrual and non-European ethnicity.[4 6 8–11] However, early identification of patients destined for a more severe disease course in order to facilitate more timely intervention and to guide therapeutic strategies could have

Table 1 Differences in baseline patient characteristics by HDAS

Baseline parameter	Descriptive statistics		Association of parameter with ever meeting HDAS definition* OR (95% CI; p value)
	Never experienced HDAS (n=161)	At least one occurrence of HDAS (n=125)	
Sociodemographic characteristics			
Sex			
Female	140 (87.0)	106 (84.8)	1
Male	21 (13.0)	19 (15.2)	1.2 (0.6 to 2.3; 0.602)
Ethnicity			
Caucasian	90 (55.9)	60 (48.0)	1
Asian	57 (35.4)	57 (45.6)	1.5 (0.9 to 2.5; 0.106)
Other/missing	14 (8.7)	8 (6.4)	0.9 (0.3 to 2.2; 0.745)
Disease characteristics			
Age at diagnosis (years)			
<18	4 (19.1)	6 (31.6)	1
≥18 to <45	7 (33.3)	7 (36.8)	0.5 (0.3 to 1.1; 0.088)
≥45	10 (47.6)	6 (31.6)	0.3 (0.1 to 0.6; 0.002)
Time since diagnosis of SLE (years)			
≤5	96 (59.6)	63 (50.4)	1
>5	65 (40.4)	62 (49.6)	1.5 (0.9 to 2.3; 0.120)
ACR diagnostic criteria			Per ACR criterion met:
Median no of criteria met at enrolment	4 (2–9)	5 (3–9)	1.7 (1.4 to 2.0; <0.001)
Specific criteria met:			
ANA	154 (95.7)	122 (97.6)	1.8 (0.5 to 7.3; 0.381)
Arthritis (non-erosive)	110 (68.3)	86 (68.8)	1.02 (0.6 to 1.7; 0.931)
Discoid rash	16 (9.9)	15 (12.0)	1.2 (0.6 to 2.6; 0.578)
Haematological disorder	75 (46.6)	71 (56.8)	1.5 (0.1 to 0.9; 0.087)
Immunological disorders	118 (73.3)	113 (90.4)	3.4 (1.7 to 6.8; <0.001)
Malar rash	66 (41.0)	57 (45.6)	1.2 (0.8 to 1.9; 0.435)
Neurological disorder	6 (3.7)	14 (11.2)	3.3 (1.2 to 8.7; 0.019)
Oral ulcers	56 (34.8)	48 (38.4)	1.2 (0.7 to 1.9; 0.528)
Photosensitivity	58 (36.0)	39 (31.2)	0.8 (0.5 to 1.3; 0.393)
Renal disorder	37 (23.0)	71 (56.8)	4.4 (2.6 to 7.3; <0.001)
Serositis	41 (25.5)	53 (42.4)	2.2 (1.3 to 3.6; 0.003)
Autoantibody positivity†			
ANA	118 (73.3)	119 (95.2)	7.2 (3.0 to 17.6; <0.001)
Anti-dsDNA	87 (54.0)	112 (89.6)	7.3 (3.8 to 14.1; <0.001)
Anti-La	30 (18.6)	36 (28.8)	1.8 (1.0 to 3.1; 0.044)
Anti-RNP	28 (17.4)	38 (30.4)	2.1 (1.2 to 3.6; 0.010)
Anti-Ro	57 (35.4)	64 (51.2)	1.9 (1.2 to 3.1; 0.008)
Anti-Sm	12 (7.5)	30 (24.0)	3.9 (1.9 to 8.0; <0.001)
Anti-phospholipid antibodies	61 (37.9)	60 (48.0)	1.5 (0.9 to 2.4; 0.087)
Anti-beta2-GPI	17 (10.6)	18 (14.4)	1.4 (0.7 to 2.9; 0.327)
Anti-cardiolipin	56 (34.8)	54 (43.2)	1.4 (0.9 to 2.3; 0.147)
Lupus anticoagulant	13 (8.1)	15 (12.0)	1.6 (0.7 to 3.4; 0.271)
Other serology			

Continued

Table 1 Continued

Baseline parameter	Descriptive statistics: Never experienced HDAS (n=161)	Descriptive statistics: At least one occurrence of HDAS (n=125)	Association of parameter with ever meeting HDAS definition* OR (95% CI; p value)
Anti-neutrophil cytoplasmic antibody (any)	12 (7.5)	17 (13.6)	2.0 (0.9 to 4.3; 0.092)
Positive direct antiglobulin test	30 (18.6)	37 (29.6)	1.8 (1.1 to 3.2; 0.031)
Rheumatoid factor	42 (26.1)	39 (31.2)	1.3 (0.8 to 2.2; 0.342)
Hypocomplementemia (low C3 or C4)	66 (41.0)	82 (65.6)	2.7 (1.7 to 4.5; <0.001)

*Reference group for OR is the absence of the parameter where the reference group is not specified.
†Limited to autoantibodies with a prevalence of ≥10%. Note that if we adjust for anti-dsDNA autoantibody positivity when assessing the association of other autoantibodies with HDAS, only anti-dsDNA and anti-Sm remain associated with increased odds of experiencing HDAS (data not shown).
ACR, American College of Rheumatology; HDAS, high disease activity state, SLEDAI-2K ≥10.

considerable benefit. In clinical trials and other studies, baseline disease activity, typically defined using the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) score,[12] has often been used as a means of identifying patients with more active disease at enrolment.[13–17] Recently, a SLEDAI-2K disease activity score of ≥10 has also been shown to predict responses to treatment with belimumab[16] and atacicept,[15] suggesting that this cut-off may also identify a subgroup of patients more likely to benefit from costly biologic treatment. However, focusing only on the baseline disease activity score may miss a subset of severe patients who experience active disease at other timepoints, particularly given the relapsing–remitting nature of SLE.

In this study, we defined high disease activity status (HDAS) based on patients who ever attain a SLEDAI-2K of ≥10, and investigated the clinical associations of HDAS in a longitudinal cohort of patients with SLE to evaluate if HDAS identifies a subgroup of patients with SLE who are at risk of worse outcomes.

METHODS

Study design, setting and participants

The Monash Lupus Clinic is a specialist outpatient clinic based at Monash Medical Centre in Melbourne, Australia. As a centre of the Australian Lupus Registry and Biobank,[18] the clinic prospectively collects data including sociodemographic details, pathology and treatment information and SLE-specific disease activity and damage assessments. To be enrolled, patients must meet the American College of Rheumatology (ACR)[19] or the Systemic Lupus International Collaborating Clinics (SLICC)[20] SLE Classification Criteria. The current study was limited to patients who had been followed for at least 1 year between April 2007 and February 2018, and had sufficient data available to

Table 2 Disease characteristics by HDAS status at each visit

Disease parameter	Descriptive statistics by HDAS visit status: Non-HDAS visit (n=4939)	Descriptive statistics by HDAS visit status: HDAS visit (n=741)	Association of being in HDAS with disease parameter: OR‡ (95% CI; p value)
PGA in highest quartile (PGA >1)	459 (9.3)	421 (56.8)	8.1 (6.1 to 10.8; <0.001)
SFI flare status			
Mild/moderate flare	771 (15.6)	307 (41.4)	4.4 (3.5 to 5.4; <0.001)
Severe flare	171 (3.5)	290 (39.1)	17.2 (13.6 to 21.6; <0.001)
Immunomodulatory medications being taken at time of visit*			
Hydroxychloroquine	4235 (85.8)	642 (86.6)	1.0 (0.8 to 1.2; 0.963)
Immunosuppressant†	3094 (62.6)	597 (80.6)	0.9 (0.8 to 1.0; 0.083)
Prednisolone	2962 (60.0)	651 (87.9)	1.3 (1.1 to 1.5; 0.003)
Prednisolone dose >7.5 mg/day	1114 (22.6)	508 (68.6)	2.5 (2.0 to 3.1; <0.001)

*Restricted to medications taken by ≥10% of patients.
†Including methotrexate, azathioprine, 6-mercaptopurine, leflunomide, cyclophosphamide and mycophenolate.
‡OR calculated using penalised maximum-likelihood logistic regression. Interpret OR with caution given rareness of event.
HDAS, high disease activity state; PGA, Physician Global Assessment; SFI, SELENA flare index.

Table 3 Frequency of SLEDAI disease manifestations at each HDAS visit

SLEDAI manifestations	Non-HDAS visit (n=4939) Column %	HDAS visit (n=741) Column %
Manifestations with a weighting of 8		
Seizure	0.00	0.40
Psychosis	<0.1	1.20
Organic brain syndrome	0.00	2.60
Visual disturbance	<0.1	1.40
Cranial nerve disorder	0.20	1.40
Lupus headache	0.00	1.40
Stroke/CVA	0.00	0.00
Vasculitis	0.04	8.60
At least one 8-point manifestation	0.30	15.90
Manifestations with a weighting of 4		
Arthritis	5.10	15.80
Myositis	0.20	2.60
Urinary casts	0.10	3.90
Haematuria	1.70	53.60
Proteinuria	16.50	75.60
Pyuria	0.70	33.50
Manifestations with a weighting of 2		
Rash	11.80	34.70
Alopecia	3.70	11.90
Mucosal ulcers	2.50	8.10
Pleurisy	1.20	5.40
Pericarditis	0.20	1.40
Low complement	56.60	86.90
Increased DNA binding	54.50	84.50
Manifestations with a weighting of 1		
Thrombocytopenia	2.10	2.30
Leucopenia	4.90	4.10
Fever	0.10	1.60

CVA, cerebrovascular accident; HDAS, high disease activity status; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

determine if they had ever experienced HDAS. All participants provided written informed consent for their participation.

Sociodemographic variables

Demographic details (date of birth, sex, ethnicity) were captured at enrolment. Ethnicity was captured in line with the Australian Bureau of Statistics Australian Standard Classification of Cultural and Ethnic Groups.[21]

SLE-related clinical variables

Diagnostic assessments and autoantibody positivity were assessed at enrolment. Date of diagnosis refers to when the diagnosis of SLE was confirmed by a specialist. At each visit, SLE disease activity was measured using the SLEDAI-2K,[12] the Physician Global Assessment (PGA) (0–3) and the SELENA flare index (SFI).[22] A time-adjusted mean SLEDAI (AMS)[23] was calculated as an overall measure of disease activity over the observation period. SLEDAI-2K manifestations occurring during the observation period were also classified by body system. Accrual of damage since the onset of SLE or during the observation period was measured using the SLICC/ACR Damage Index (SDI).[24] Time-adjusted mean and cumulative drug doses for glucocorticoid and other immunomodulatory medications were calculated in a similar manner to the AMS calculation.[23]

High disease activity status

HDAS is defined when a patient experienced disease activity, measured by SLEDAI-2K score ≥10 on at least one occasion during the observation period.

Statistical methods

All analyses were carried out using StataSE V.14.2 (StataCorp, College Station, TX, USA).

Descriptive statistics were used to describe the characteristics of patients categorised by HDAS. Bivariate tests (eg, Mann-Whitney U test) were used for simple bivariate comparisons. Logistic regression was used to assess the association of baseline patient characteristics with HDAS and the association of experiencing HDAS with longitudinal outcomes. Generalised estimating equations (GEEs) based on an exchangeable correlation matrix and using robust SE estimation was used to assess the association of being in HDAS with particular disease characteristics at the time of experiencing HDAS. Penalised maximum-likelihood logistic regression was used instead of GEE where a disease characteristic was rare (frequency ≤2%).

The likelihood ratio test was used to confirm that the association of any continuous exposure or confounding variables with the log odds of the outcome variable was sufficiently linear for the variable to be modelled as a continuous variable. Missing data were excluded from the analyses. Most variables had a low level of missing data. The major source of missing data was missing data for SLEDAI-2K calculation (16.4% of SLEDAI-2K assessments overall). A p value 0.05 was set as the threshold for statistical significance.

RESULTS

Patients

Of 347 patients with SLE on whom data were available, 286 (82.4%) met the criteria for inclusion in the analysis (followed for at least 1 year and had sufficient data to determine if they ever met the criteria for HDAS). Of the patients excluded from the analysis, the majority (60; 98.4%) were excluded because they had been followed for <1 year. The patients included in the analysis were followed for a median of 5.1 years (range, 1–10.8 years).

Table 4 Association of SLEDAI-2K manifestation with HDAS after exclusion from SLEDAI calculation†

SLEDAI manifestations	Non-HDAS visit with adjustment n/total (%)	HDAS visit with adjustment n/total (%)	OR (95% CI; p value)*
Manifestations with a weighting of 8			
Seizure	1/4940 (0.02)	2/740 (0.27)	*
Psychosis	7/4946 (0.14)	3/734 (0.41)	2.9 (0.6 to 10.4; 0.125)
Organic brain syndrome	12/4951 (0.24)	7/729 (0.96)	4.0 (1.5 to 10.0; 0.004)
Visual disturbance	9/4948 (0.18)	2/732 (0.27)	1.5 (0.2 to 5.8; 0.604)
Cranial nerve disorder	16/4955 (0.32)	3/725 (0.41)	1.3 (0.3 to 3.8; 0.71)
Lupus headache	10/4949 (0.2)	0/731 (0)	*
Stroke/CVA	0/4949 (0)	0/741 (0)	*
Vasculitis	46/4985 (0.92)	20/695 (2.88)	3.2 (1.8 to 5.3; <0.001)
Manifestations with a weighting of 4			
Arthritis	312/5521 (5.94)	57/429 (13.29)	1.4 (1.0 to 1.8; 0.035)
Myositis	16/4955 (0.32)	11/725 (1.52)	4.7 (2.1 to 10.1; <0.001)
Urinary casts	9/4948 (0.18)	27/732 (3.69)	28.7 (13.3 to 71.5; <0.001)
Haematuria	266/5205 (5.11)	217/475 (45.68)	65.1 (50.6 to 84.7; <0.001)
Proteinuria	1112/5368 (20.72)	262/312 (83.97)	5.4 (4.4 to 6.6; <0.001)
Pyuria	96/5035 (1.91)	185/645 (28.68)	19.2 (14.8 to 25; <0.001)
Manifestations with a weighting of 2			
Rash	682/5166 (17.2)	159/541 (30.93)	2.1 (1.7 to 2.6; <0.001)
Alopecia	211/5150 (4.1)	60/530 (11.32)	2.1 (1.5 to 2.8; <0.001)
Mucosal ulcers	136/5075 (2.68)	46/605 (7.6)	2.4 (1.7 to 3.4; <0.001)
Pleurisy	64/5003 (4.87)	33/677 (4.87)	3.6 (2.3 to 5.5; <0.001)
Pericarditis	10/4949 (0.2)	9/731 (1.23)	6.1 (2.4 to 15.1; <0.001)
Low complement	2964/5166 (57.38)	474/514 (92.22)	3.5 (2.8 to 4.5; <0.001)
Increased DNA binding	2852/5166 (55.2)	465/514 (90.47)	3.2 (2.6 to 4.0; <0.001)
Manifestations with a weighting of 1			
Thrombocytopenia	105/5044 (2.08)	15/636 (2.36)	1.0 (0.5 to 1.6; 0.867)
Leucopenia	246/5185 (4.74)	28/495 (5.66)	0.8 (0.5 to 1.1; 0.16)
Fever	8/4947 (0.16)	11/733 (1.5)	9.3 (3.8 to 24.1; <0.001)

*Too few data points to calculate OR.
†In this analysis, the SLEDAI-2K score was re-calculated based on all SLEDAI manifestations excluding the current SLEDAI-2K manifestation being investigated. Consequently, the total number of HDAS and non-HDAS visits may differ between SLEDAI manifestations.
CVA, cerebrovascular accident; HDAS, high disease activity status; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

High disease activity status

A total of 125 patients (43.7 %) had HDAS during the observation period. Over three quarters of HDAS patients (76.8%) experienced HDAS at multiple visits. Among patients experiencing at least one occasion of HDAS, the median number of HDAS visits experienced was 3 (range, 1–53).

The first HDAS visit was experienced a median of 3.6 months after enrolment (range, 0–8.9 years). Only a third (33.6%) of HDAS patients experienced HDAS at their baseline visit. Compared with patients who never experienced HDAS, HDAS patients were followed for a longer duration (median of 5.8 vs 4.6 years, p<0.001) and had a higher number of patient visits during the observation period (median of 27 vs 14 visits, p<0.001).

An alternative definition of severe disease based on the presence of major organ involvement (at least one of renal, neurological, cardiovascular or respiratory system involvement) and requirement treatment with >7.5 mg/day corticosteroids or immunosuppressants has been proposed and used in the Lupus erythematosus Cost of Illness in Europe (LUCIE) study[25 26] We found that almost all (92%) of HDAS patients of our cohort would fulfil this definition assessing the criteria over the course of the observation period. This is in contrast to only 54% of the patients labelled as severe in the LUCIE study who had SLEDAI ≥10 and hence fulfil the definition of HDAS at baseline. HDAS is a simpler measure to communicate regarding disease severity and compares well to other definitions of disease severity.

Table 5 Association of HDAS with longitudinal SLE outcomes

Longitudinal parameter	Descriptive statistics by HDAS Number (column %) HDAS (n=161)	No HDAS (n=125)	Association of ever experiencing HDAS with longitudinal SLE outcome* OR (95% CI; p value)
AMS in highest quartile (AMS ≥4.3)	9 (5.6)	59 (47.2)	11.7 (5.1 to 26.6; <0.001)†
SFI flare occurrence			
No of mild/moderate flares in highest quartile (≥7)	9 (5.6)	60 (48.0)	17.3 (7.4 to 40.5; <0.001)
No of severe flares in highest quartile (≥3)	6 (3.7)	50 (40.0)	14.9 (6.0 to 36.9; <0.001)
SDI damage accrual			
Accrued damage during observation period	45 (28.0)	66 (52.8)	2.3 (1.3 to 3.9; 0.003)
Within a specific organ system			
Musculoskeletal	16 (9.9)	23 (18.4)	1.4 (0.7 to 2.9; 0.365)
Skin	8 (5.0)	18 (14.4)	2.4 (1.0 to 6.0; 0.053)
Neuropsychiatric	5 (3.1)	10 (8.0)	2.2 (0.7 to 6.8; 0.170)
Ocular	8 (5.0)	8 (6.4)	1.1 (0.4 to 3.1; 0.879)
Cardiovascular	11 (6.8)	10 (8.0)	0.8 (0.3 to 2.0; 0.617)
Renal	4 (2.5)	20 (16.0)	7.2 (2.4 to 22.0; 0.001)
Peripheral vascular	6 (3.7)	9 (7.2)	1.4 (0.4 to 4.1; 0.593)
Pulmonary	2 (1.2)	6 (4.8)	3.0 (0.6 to 15.5; 0.199)
Gastrointestinal	2 (1.2)	4 (3.2)	2.4 (0.4 to 13.6; 0.336)
Other	8 (5.0)	10 (8.0)	1.4 (0.5 to 3.7; 0.530)
Immunomodulatory drug doses: cumulative dose over observation period in highest quartile‡			
Prednisolone	14 (8.7)	57 (45.6)	7.7 (3.9 to 15.3; <0.001)
Hydroxychloroquine	31 (19.3)	40 (32.0)	0.9 (0.4 to 2.0; 0.819)
Methotrexate	35 (21.7)	31 (24.8)	1.1 (0.6 to 1.9; 0.798)
Azathioprine/6-mercaptopurine	30 (18.6)	41 (32.8)	1.7 (0.9 to 3.0; 0.076)
Mycophenolate	13 (8.1)	58 (46.4)	9.4 (4.8 to 18.5; <0.001)

*Adjusted for patient observation time. Reference category for OR: those who did not experience HDAS during the observation period.
†OR also adjusted for cumulative prednisolone dose.
‡Limited to immunomodulatory medication taken by ≥10% of patients. Cut-offs for cumulative doses within the highest quartile were prednisolone ≥13.9 g, hydroxychloroquine ≥805.7 g, methotrexate ≥44.9 mg, azathioprine/6-mercaptopurine ≥49.9 g and mycophenolate ≥889.0 g.
AMS, adjusted mean Systemic Lupus Erythematosus Disease Activity Index; HDAS, high disease activity status; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SFI, SELENA flare index.

Baseline patient characteristics and association with HDAS

Table 1 provides an overview of the association of baseline sociodemographic and clinical variables with HDAS occurring during the observation period. Patients with immunological, serositis, renal disease or neurological manifestations, as captured by historical organ involvement on ACR classification criteria at enrolment, were more likely to have at least one occurrence of HDAS during the period of observation. Patients positive for a number of autoantibodies, including anti-dsDNA autoantibodies or anti-Sm autoantibodies, were more likely to experience HDAS compared with patients not positive for these autoantibodies (table 1). Patients with low complement C3 or C4 at baseline were also more likely to experience HDAS, but there was no association with antiphospholipid antibodies. Patients diagnosed at age ≥45 years also had significantly lower odds of experiencing HDAS compared with patients diagnosed at age <18 years.

Association of HDAS with disease characteristics

Table 2 outlines the association of HDAS with disease parameters at the time of the HDAS visit. Patients with HDAS had higher PGA (PGA>1: OR 8.1, p<0.001) and were more likely to meet criteria for flare (mild/moderate flare: OR 4.4, p<0.001; severe flare: OR 17.2, p<0.001) at the time of experiencing HDAS. Patients were also more likely to be taking prednisolone at a HDAS visit compared with a non-HDAS visit (see table 2).

The clinical manifestations at the time of HDAS were varied and not restricted to manifestations that carry a heavier weight in the SLEDAI-2K scoring system. Table 3 presents the frequency of each clinical manifestation

present in non-HDAS and HDAS visits and the breadth of organ manifestations in HDAS visits was noted across most domains including ones that carried a lower weighting in the SLEDAI-2K scoring system such as arthritis and rash. After serological activity, the most common manifestations at the time of experiencing HDAS included renal manifestations (proteinuria, haematuria, pyuria), rash, arthritis, alopecia and vasculitis.

As the definition of HDAS includes variables of SLEDAI-2K, the clinical profile of patients identified using a SLEDAI-2K cut-off is influenced by the SLEDAI-2K domains involved and their weightings. We performed additional analysis to examine the strength of the associations of each clinical variable with HDAS, after removing that variable from the calculation of HDAS. Table 4 presents the OR for the association of each disease manifestation with HDAS after this exclusion. A similar distribution of the SLEDAI-2K fields spanning across different weighting categories was observed to that shown in table 3.

Association of HDAS with longitudinal outcomes

Table 5 presents the associations of experiencing HDAS at any time with longitudinal outcomes. HDAS patients were more likely to have high disease activity across the period of observation, as defined by AMS score in the highest quartile (≥4.3) after adjusting for cumulative prednisolone dose and observation time (OR 11.7, p>0.001). The median AMS was 4.1 (range, 0–13.9) in patients with any occurrence of HDAS, compared with 1.5 (range, 0–5.1) for non-HDAS patients. HDAS patients were also more likely to experience mild/moderate flares (OR 17.3, p<0.001) or severe flares (OR 14.9, p<0.001) and to accrue damage (OR 2.3, p=0.003) during the observation period. HDAS patients were particularly more likely to accrue renal damage (OR 7.2, p=0.001). HDAS patients were also more likely to be exposed to higher cumulative doses of prednisolone and mycophenolate, as demonstrated by increased odds of being in the highest quartile of medication exposure within the entire cohort (prednisolone OR 7.7, p<0.001; and mycophenolate OR 9.4, p<0.001, respectively) (see table 3). Over the period of observation, when compared with non-HDAS patients, HDAS patients were more likely to present with neuropsychiatric, renal or vasculitis disease activity (OR >10, data not shown).

Additional models were run to assess the impact of cumulative prednisolone dose and renal disease activity in explaining the association between HDAS and damage accrual and whether adjusting for patient demographics attenuated the association of HDAS with adverse outcomes. The association between HDAS and overall damage accrual remained after adjusting for renal disease activity during the observation period but disappeared after adjusting for cumulative prednisolone dose; the association between HDAS and renal damage accrual remained significant after adjusting for prednisolone (OR 5.2; 95% CI 1.60 to 17.0). Adjusting for sex and age at diagnosis with an interaction term fitted between sex and age at diagnosis did not significantly alter the associations reported in table 5.

DISCUSSION

This study demonstrated that HDAS is a useful disease severity measure that takes into account of past or current disease activity and is also associated with important adverse outcomes such as treatment burden and prognosis. While there have been several disease severity indices proposed, their definitions are generally complicated.[27–29] One of the more recently used severity indices incorporates specific organ involvement, together with the need for treatment with corticosteroids or immunosuppressants.[25 26] Our study has suggested a simple disease activity cut-off such as SLEDAI ≥10, which has been used to evaluate subsets of responders in recent SLE clinical trials,[16] can identify a population of patients with SLE who are likely to have more severe disease. HDAS attainment on even a single occasion was associated with more severe disease and worse outcomes over time, as shown by higher overall disease activity, increased likelihood of flares, higher use of prednisolone and immunosuppression, and increased damage accrual.

Disease activity measurement is already an integral part of recommendations for disease management in SLE.[30 31] While there are several validated disease activity indices available,[32 33] the SLEDAI has been widely used[32 34] and has been shown to be sensitive to change in response to patient treatment and disease course.[35] Disease activity scoring systems such as SLEDAI-2K allow for evaluation of the breadth of organ involvement, but through weighting attempt to take into account differences in implied severity of different manifestations.[12] Kasitanon *et al* reported that having a SLEDAI-2K score ≥10 at the first visit was associated with increased mortality; however, in this study the association was lost when they adjusted for patient characteristics such as sex, ethnicity and age at diagnosis.[14] Other studies of different disease activity instruments support the notion that high disease activity predicts short-term mortality.[36]

The clinical diversity of SLE presents a major challenge for clinicians in terms of providing long-term prognostic information for patients. The use of a prognostic indicator that is linked to a global disease activity measure may be a useful adjunct to routine clinical practice.[30–32 37] Here, we have shown that attainment of HDAS at any time point provides useful prognostic information, given its association with a range of disease severity measures (ie, higher AMS, flares and damage accrual), and that these associations remained after adjustment for patient demographic characteristics. In addition, we have found differences between HDAS and non-HDAS patients in terms of medication exposure, including cumulative doses of prednisolone and immunosuppressants. The association between HDAS and overall damage accrual was lost after adjusting for cumulative prednisolone dose. While

this might be consistent with reports that corticosteroid use plays a role in damage accrual, it may also be due to collinearity between disease activity and steroid use.[38 39]

Patients who experience HDAS may be a clinically distinct subgroup. These patients were more likely to be diagnosed at an early age and be positive for multiple autoantibodies. Even though HDAS patients were more likely to experience neuropsychiatric, renal and vasculitis disease activity over time, it was possible to achieve HDAS based on activity in multiple low-weighted organ manifestations, and almost all domains of SLEDAI, regardless of weight, were observed more frequently in HDAS patients.

There are some limitations of this study. These include that it was carried out in a single centre and is a retrospective study, although of prospectively collected data.

This study provides evidence suggesting any occurrence of HDAS, defined using a simple SLEDAI-2K cut-off of 10 or higher, may be a useful prognostic indicator for SLE. HDAS is easy to calculate, and provides information regarding likelihood of future disease activity, flares, medication burden and damage accrual over time. Further studies should explore the prognostic value of HDAS in different cohorts, as it has potential to be used outside the clinical trial setting in identification of patients who are at higher risk of adverse outcomes. Confirmation of the utility of HDAS in observational cohorts could provide supported for tailored intervention in this group of patients.

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Contributors All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. RK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: RK, HTN, MN, YBS, AK, OG, EM and AH. Acquisition of data: EM and AH. Analysis and interpretation of data: RK, HTN, MN, YBS, AK, OG, EM and AH.

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