

## Running Head: Damage Measurement in Childhood-Onset Lupus

### Title: Measuring Disease Damage and its Severity in Childhood-Onset Systemic Lupus Erythematosus

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## ABSTRACT

**Objectives:** To describe the frequency and types of disease damage occurring with childhood-onset systemic lupus erythematosus (cSLE) as measured by the 41-item Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), and to assess the SDI's ability to reflect damage severity.

**Methods:** Information for the SDI was prospectively collected from 1,048 cSLE patients. For a subset of 559 patients physician-rated damage severity measured by visual analog scale (MD-VAS<sub>damage</sub>) was also available. Frequency of SDI-items, and the association between SDI summary-scores and MD-VAS<sub>damage</sub> were estimated. Finally, an international consensus conference, utilizing nominal group technique, considered the SDI's capture of cSLE-associated damage and its severity.

**Results:** After a mean disease duration of 3.8 years, 44.2% (463/1048) of patients already had an SDI summary-score >0 (maximum: 14). The most common SDI items scored were proteinuria, scarring alopecia, and cognitive impairment. Although there was a moderately strong association between SDI summary-scores and MD-VAS<sub>damage</sub> ( $r_{\text{Spearman}} = 0.49$ ;  $p < 0.0001$ ) in patients with damage (SDI summary-score >0), mixed effect analysis revealed that only four SDI items, each occurring in <2% of patients overall, were significantly associated with MD-VAS<sub>damage</sub>. There was consensus among cSLE experts that the SDI in its current form is inadequate for estimating the severity of cSLE-associated damage.

**Conclusion:** Disease damage as measured by the SDI is common in cSLE, even with relatively short disease durations. Given the shortcomings of the SDI, there is a need to develop new tools to estimate the impact of cSLE-associated damage.

## **SIGNIFICANCE & INNOVATION**

- In cSLE, damage is common, and occurs most frequently in the renal, cutaneous, neuropsychiatric, and musculoskeletal organ systems.
- By design, the SDI seeks to provide an enumeration of the types of damage present in cSLE, rather than directly measuring damage severity. Despite this, the SDI summary-score is often used as a stand-alone continuous outcome measure in research.
- An international group of pediatric rheumatologists and nephrologists experienced in cSLE reached unanimous consensus that a new measure or approach is needed to better capture damage severity in cSLE.

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## INTRODUCTION

Disease activity describes theoretically reversible manifestations due to the inflammatory processes underlying systemic lupus erythematosus (SLE), while the term 'damage' is used to designate irreversible organ scarring or tissue degradation. However, a formal consensus definition of disease damage with SLE has not been published. Quantifying damage or measuring the severity of damage is an important consideration in gauging the overall outcome in SLE, particularly as disease-related mortality decreases (1, 2). Given the diversity of SLE-associated organ involvement, and in line with the development of disease activity indices for quantifying disease activity, a SLE damage index has been developed: the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index (SDI) (1).

Prior investigations support that the presence of SLE-associated damage that is scored by the SDI is associated with increased mortality in adults (2), and increased cumulative SLE activity in both adults and children (2-4). The developers of the SDI stressed that the index provides an enumeration of the presence or absence of damage types only, and that the SDI does not directly quantify damage severity (3). This is sensible because, for example, a patient with a small cataract and one with a debilitating stroke will both receive the same SDI summary-score of 1, provided each patient fulfills the definition of only one SDI item. Nevertheless, the SDI summary-score has been used as an independent, continuous outcome measure in statistical analyses (5).

There have been prior attempts to adapt the SDI to better measure damage severity by introducing item weightings. However, two prior attempts at item weightings using data gathered from adults with SLE did not meaningfully improve the association of SDI summary-scores with mortality, and therefore item weighting were not pursued further (2, 6). One prior

1 attempt was made to weight SDI items (based on SLEDAI item weights) in data from patients with  
2 childhood-onset SLE (cSLE); this approach did not improve prediction of damage using cumulative  
3 disease activity as a predictor, and was similarly not pursued (4).

4 In about 20% of patients with SLE the disease is diagnosed during childhood (cSLE), i.e.  
5 before 18 years of age (7). A prior international consensus process (8), focused on outcome  
6 measures in cSLE and juvenile dermatomyositis, defined a core set of variables to characterize  
7 cSLE-associated damage and its impact. Based on consensus, the agreed upon cSLE damage core  
8 set consists of the SDI as the current standard damage tool, a physician global damage  
9 assessment of damage [visual analog scale (VAS) or Likert scale], growth (height and weight),  
10 bodily development (menses, Tanner staging), and a measure of health-related quality of life.

11 The Outcome Measures in Rheumatology (OMERACT) collaborative has recently  
12 published a revised framework. The OMERACT Filter 2.0 builds on the OMERACT Filter 1.0, i.e.  
13 the use of outcome measures in rheumatology that are valid, discriminate conditions of interest,  
14 and are feasible (9). The OMERACT Filter 2.0 advocates development of core outcome  
15 measurement sets in rheumatology (10). There is new emphasis on the concept of multiple 'core  
16 areas' (death, disease impact, resource use, and disease manifestations) which may be addressed  
17 by these core outcome sets. Finally, the need to explicitly consider "perspective" is stressed, as  
18 well as the "context" in which an outcome measure will be used. The aspect of perspective  
19 (patient, physician, and/or society) and context appear particularly important when capturing  
20 damage severity. While the previously developed cSLE damage core set (8) touches on at least  
21 two of the OMERACT core areas for construct measurement, stand-alone use of the SDI is still  
22 commonplace when quantifying the amount of damage in clinical studies of both SLE and cSLE.

1           Based on the above, we sought to critically appraise the SDI when used in cSLE by: 1)  
2 delineating the frequency of SDI damage items in a large composite cohort under consideration  
3 of disease duration; 2) comparing the SDI summary-score to a physician global assessment of  
4 damage severity; and 3) to explore the possible impact of SDI item weightings to better capture  
5 damage severity as rated by the treating physician using statistical techniques. Subsequently, our  
6 findings and analyses were presented at a consensus conference held in April 2017, where an  
7 international panel of cSLE experts was asked to advise on approaches to measure damage  
8 severity in cSLE.

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## MATERIAL & METHODS

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### Patients

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Longitudinal data from large, prospective cohorts of cSLE were reanalyzed. These were the United Kingdom Juvenile-onset SLE Cohort Study (UK, n= 350) (1), the cSLE cohort followed at Cincinnati Children’s Hospital Medical Center (CCHMC, n= 139), and an international cohort (n= 559) assembled in Latin America, Australia, Asia, and various European countries by the Pediatric Rheumatology International Trials Organization (PRINTO) (8). The final composite study cohort included 1,048 patients. General demographic data were recorded, though ethnic/racial data were not collected for the PRINTO dataset due to legal restrictions. Approval was given by the Cincinnati Children’s Hospital Medical Center Institutional Review Board for this secondary analysis. Training had been provided for the completion of the SDI and other disease measures of all cohorts considered in this study. All physicians completing instruments were experienced in the care of children with cSLE.



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**Damage measures and scales**

***Systemic Lupus International Collaborating Clinics / American College of Rheumatology***

***Damage Index.*** Developed through a consensus process focused on adults with SLE, the SDI quantifies irreversible damage according to specific item definitions (1). The SDI captures damage in patients since their diagnosis with SLE, irrespective of whether damage is due to the SLE process itself, its treatment, or a co-morbid condition. Damage captured in the SDI is considered non-reversible if any given item has been present for at least 6 months continuously, or immediately for some events associated with acute organ damage, e.g. myocardial infarct (1).

The 41 items included in the SDI were selected based on experience with adult-onset SLE, with items mostly scored as being either present or absent. While there is no overall weighting system, some six SDI items (stroke, myocardial infarct, tissue loss, bowel infarct, avascular necrosis, or malignancy) can be scored twice, if two qualifying events occur at least 6 months apart from each other. The SDI item ‘end stage renal disease’ is always given a score of 3 when present for at least 6 months continuously. Scoring is cumulative: once an item qualifies for scoring in the SDI, that item is always scored moving forward, even if it subsequently resolves or is corrected (2). The SDI-summary-score is the simple sum of the item scores; thus a summary-score of 0 is assigned to patients who have *never* met criteria for any listed damage item.

***Visual analog scale of disease damage severity.*** Treating physicians contributing data to the PRINTO cohort rated damage severity on a 10-cm VAS (MD-VAS<sub>damage</sub>) for their patients. The

1 following anchor statements were included at each end of the 10-cm scale: 0, no damage; 10,  
2 very severe damage. This rating was done either prior to or after completing the SDI.

3

#### 4 **Statistical analyses**

5 Descriptive analyses included frequencies for categorical variables as well as means and  
6 standard deviations for numerical variables. Comparison of numerical demographic features and  
7 SDI summary-scores between cohorts was done by a fixed effect model, with differences of post-  
8 hoc means between groups corrected for multiple comparisons using the Tukey's method.  
9 Damage item frequency was calculated based upon the SDI score at the last follow-up visit  
10 available for each patient and, per SDI instructions, included all SDI item ever scored for a given  
11 patient. Contingency table analysis compared item frequencies between groups of patients  
12 (CCHMC, UK, PRINTO). Significant differences between item frequencies were based on chi-  
13 square analyses or Fisher exact testing, where appropriate. Given variation in disease duration,  
14 for purposes of statistical comparison of item frequency between cohorts, only patient SDI scores  
15 with total disease durations of 4.5 years or less were considered. The 4.5 year cut-off reflects the  
16 70<sup>th</sup> percentile of follow-up in the cohort with the shortest follow-up (PRINTO).

17 To assess the relationship of SDI summary-scores to physician-perceived severity of  
18 damage (MD-VAS<sub>damage</sub>), we calculated the Spearman correlation coefficients from patient visits  
19 with available data. Correlation with MD-VAS<sub>damage</sub> was then separately assessed only for patient  
20 visits with known damage (SDI scores > 0). This was done to capture damage severity, which  
21 seems relevant only with the presence of some damage (SDI summary-score >0). To evaluate the  
22 effect of multiple comparisons, correlations were also calculated separately using only the first,

1 and then last visit for each patient. Finally, individual damage items (present vs. absent) were  
2 assessed for their associations with the MD-VAS<sub>damage</sub> ratings using logistic regression models and  
3 the GEE method in computation. Computations were performed using SAS 9.3 (Cary, NC) or  
4 EXCEL (version 2013, Redmond, WA).

5

## 6 **Consensus Conference**

7 From April 23<sup>rd</sup> through 25<sup>th</sup> 2017, an international consensus conference of physicians  
8 with expertise in cSLE was held in Cincinnati, Ohio. The expert group consisted of thirteen  
9 physicians (10 pediatric rheumatologists and 3 pediatric nephrologists) with profound experience  
10 in the care of cSLE. Guided by an experienced moderator (BMF), nominal group technique was  
11 used to facilitate discussion and consensus formation. Consensus was defined a-priori as  $\geq 75\%$   
12 agreement among participating experts. Prior to opening discussion, results of the analyses (see  
13 below) and a review of relevant literature were presented

14

15

## **RESULTS**

### 16 **Patients**

17 As expected, most patients included in this study were female (82.9%), without significant  
18 gender differences between cohorts. While UK and CCHMC cohort data were collected after  
19 2006, the PRINTO cohort data were completed by 2004. There were significant racial differences  
20 present between the UK and CCHMC cohorts. Patient age at diagnosis and mean total disease  
21 duration were significantly higher in the CCHMC cohort when compared to the other datasets

1 (CCHMC vs other cohorts; mean age: 13.9 years vs. 12 years;  $p < 0.0001$ , mean duration: 5.15 years  
2 vs. 3.5-3.8 years;  $p < 0.0001$ ). Additional details are shown in **Table 1**.

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#### 4 **Overall disease damage as measured by the SDI**

5       Among the 1,048 patients, a total of 585 (55.8%) lacked disease damage (SDI summary-  
6 score = 0) at the time of the last follow-up, which occurred, on average, 3.8 years post diagnosis  
7 with cSLE (**Table 1**). The proportion of patients without damage at last follow-up was highest in  
8 the UK cohort (77.7%). Mean SDI summary-scores significantly differed between the UK and  
9 PRINTO cohorts, and PRINTO and CCHMC cohorts, but not between the CCHMC and UK cohorts  
10 (**Table 1**). Overall, the mean SDI summary-score increased incrementally and closely related to  
11 increasing disease duration (**Figure 1, Panel 1**).

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#### 13 **Common and less common types of disease damage with cSLE**

14       The frequency of SDI items at the final follow-up visit in each cohort is summarized in  
15 **Table 2**. The three most commonly encountered SDI items were long-standing nephrotic-range  
16 proteinuria, scarring alopecia, and chronic cognitive impairment in all three cohorts. Irrespective  
17 of disease duration, the four most commonly damaged organ systems were the neuropsychiatric,  
18 kidney, skin, and musculoskeletal (**Figure 1, Panel 2**). There were four SDI items that were present  
19 in fewer than three patients ( $3/1,048 = 0.3\%$ ): angina, myocardial infarction, mesenteric  
20 insufficiency, and tendon rupture. An additional 12 SDI items were present in  $< 1\%$  of the study  
21 population. No patient had the SDI item pulmonary infarction scored. (**Table 2**).

22

## 1 Relationship between physician-rated damage severity and SDI summary-scores

2 Ratings of MD-VAS<sub>damage</sub> were available for 1,793 of a total of 1820 patient visits with SDI  
3 scores. Of these, 1,245 (69.4%) were without damage (SDI summary-score = 0), and 548 (30.5%)  
4 with some damage (SDI summary-score > 0).

5 Damage-free (SDI summary-score=0) patients are expected to have a MD-VAS<sub>damage</sub> of 0.  
6 However, physicians considered 24.2% (301/1245) of “damage-free” patients as having some  
7 damage (MD-VAS<sub>damage</sub> >0). As shown in **Figure 2, Panel 1**, with SDI summary-scores of 0, MD-  
8 VAS<sub>damage</sub> ratings were <1 in 94% of the visits.

9 **Figure 2, Panel 2** provides an overview of the MD-VAS<sub>damage</sub> and SDI summary scores  
10 throughout the range of observed values. Only 5.7% (31/548) of patients with SDI summary-  
11 scores of >0 were considered “damage-free” by their treating physician (MD-VAS<sub>damage</sub>=0).

12 The correlation between SDI summary-score and MD-VAS<sub>damage</sub> overall was strong  
13 ( $r_{\text{spearman}} 0.71$ ;  $p < 0.0001$ ), though when narrowed to include only visits with some damage (SDI  
14 >0) the correlation was only moderate ( $r_{\text{spearman}} 0.496$ ;  $p < 0.0001$ ). Correlations were similar when  
15 considering only the first, or last visit for each patient, ranging from 0.66-0.72 for all SDI scores,  
16 versus 0.45-0.54 for only those visits with SDI summary scores >0.

17 In exploratory analysis using mixed effect modeling, we aimed at identifying SDI-items  
18 that importantly influence physician-rated damage severity. This analysis revealed that only four  
19 of the 41 SDI items were significantly associated with the MD-VAS<sub>damage</sub>. They were the SDI items  
20 pulmonary fibrosis, shrinking lung syndrome, chronic pericarditis, and extensive cutaneous scar.  
21 Of note, all of these SDI-items had an overall frequency of <2% in the composite study cohort.

22

1 **Consensus Conference**

2 Neither the SDI nor the proposed pediatric adaptation of the SDI (11) were considered  
3 adequate to measure damage severity in cSLE. There was consensus (100%) that a separate  
4 measure or approach to capture damage severity of cSLE was needed, and that the OMERACT  
5 Filter 2.0 framework should be used for its development (83% agreement). Consensus was  
6 reached around a definition of cSLE-associated damage and damage severity as a first step  
7 toward improving measurement of damage-related constructs.

8 Damage associated with cSLE was defined as *“Impairment of anatomy or physiology that  
9 may be associated with scarring, may accumulate, and is not completely reversible. Damage may  
10 be caused by disease, adverse effects of medication, or associated comorbidity. In children this  
11 may lead to stunted cognitive, and physical development”* (83% consensus).

12 Based on consensus (77% agreement) damage severity was defined as follows: *“Severity  
13 of damage is measured by the organs involved, and the extent of anatomical and physiological  
14 derangement as judged by the expected impact on mortality, degree of support required, activity  
15 limitation, restriction in social participation, and patient-centered quality of life.”*

16

17 **DISCUSSION**

18 We examined the patterns and severity of disease damage in a large composite cohort of  
19 cSLE patients with the goal to appraise the ability of the SDI to capture disease damage and its  
20 severity. Based on detailed statistical analysis and expert consensus, the SDI was considered in  
21 inadequate for quantifying the impact of disease damage in cSLE.

1           Although cSLE damage patterns have previously been described in detail (4, 7, 12), our  
2 analyses seem unique given the number of cSLE patients included, and the analysis of physician  
3 global assessments of damage severity. Damage patterns were largely similar across disease  
4 cohorts, with SDI-items in the neuropsychiatric, renal, musculoskeletal and skin systems most  
5 frequently encountered. Dissimilarities in damage patterns were identified for the frequency of  
6 chronic muscle atrophy or muscle weakness across cohorts. Reasons for these differences are  
7 unknown but could include differences in access to and use of medications, as well as differences  
8 in the relevant healthcare systems and demographics. Unfortunately, insufficient longitudinal  
9 data were available to identify the driving factors for the observed differences. Only two patients  
10 in our cohort encountered malignancies (type unknown), and this observation is in line with the  
11 malignancy risk based on an earlier epidemiological study in cSLE (13), supporting the  
12 representativeness of this composite cohort. Further, the rarity of most SDI items in our cohort  
13 in line with prior studies in adults (14).

14           Both SDI organ domain scores and total SDI summary-scores increased with disease  
15 duration. Indeed, SDI summary-scores were closely correlated with disease duration. This  
16 supports our prior research where disease duration and cumulative disease activity were closely  
17 correlated with each other, but the cumulative burden of disease activity with cSLE was the  
18 better predictor of SDI summary-scores in a smaller cSLE cohort (4). A close relationship between  
19 damage accrual as measured by the SDI and disease duration supports the construct validity of  
20 the SDI for measuring damage.

21           The SDI-summary-score is the simple sum of its mostly un-weighted SDI-item scores. Thus  
22 one might expect that a higher score corresponds to more severe damage, especially because

1 there are seven “high-impact” items that receive an additional score (myocardial infarction,  
2 stroke, end-stage renal disease, avascular necrosis, malignancy, significant tissue loss, and  
3 gastrointestinal infarction/resection) if occurring repeatedly. While true item weightings have  
4 been incorporated in other scales used for cSLE and SLE (4, 15), our findings imply that more  
5 sophisticated item weightings will not improve the ability of the SDI to capture cSLE-associated  
6 damage severity. This is because there were only statistically significant associations between  
7 the MD-VAS Damage summary score and a few, rarely-endorsed, SDI items. This observation is  
8 similar to that of earlier studies using other statistical approaches, which also found little value  
9 in item weightings to improve the SDI’s ability to reflect damage severity, or mortality (2, 4, 6).

10 Although disease damage accumulated with cSLE was substantial, many of the SDI-items  
11 were rarely scored. Indeed, nearly half of SDI items were encountered in <1% of cSLE patients.  
12 Although it might be tempting to eliminate items with extremely low prevalence to improve the  
13 feasibility of the scale when used in cSLE, we do not think this is advisable as item reduction will  
14 not improve the construct validity of the SDI, nor its ability to capture damage severity. Further,  
15 SLE and cSLE are highly heterogeneous in their phenotypes and certain SDI items, such as  
16 myocardial infarctions, are known to occur more commonly with higher age and longer disease  
17 durations than those captured by our study. There is also broad agreement that the inclusion of  
18 rarely scored items is warranted when estimating damage with other multi-system diseases such  
19 as inflammatory immune-mediated myositis and vasculitis, respectively (16, 17).

20 If the SDI was a good measure of cSLE-associated damage severity, children with SDI  
21 summary-scores of 0 (best possible value) should consistently have an MD-VAS<sub>damage</sub> rating of 0  
22 (best possible value). However, over 20% of children without cSLE-associated damage received a



1 MD-VAS<sub>damage</sub> >0. While the exact reasons for this observation are unknown, this could simply be  
2 a reflection of so-called “end-scale aversion”: it has been recognized that raters tend to fail to  
3 provide the best or worse possible rating on a VAS (18, 19). Actually, almost all MD-VAS<sub>damage</sub>  
4 rating with SDI summary-scores of 0 were in the range of 0 to <1.

5 Another explanation for MD-VAS<sub>damage</sub> ratings exceeding 0 in patients without damage  
6 may be that certain pediatric specific damage is not considered in the SDI currently. Indeed, there  
7 is consensus among pediatric rheumatologists that pubertal development and growth are  
8 important aspects that deserve consideration when measuring cSLE-associated damage (8). This  
9 is reflected in the proposal of a pediatric version of the SDI (pSDI) where two items are added to  
10 the traditional SDI (11), namely reduced growth and delayed development. A problem with these  
11 cSLE-specific items might be that both items can resolve, which could be perceived to violate the  
12 concept of irreversibility of disease damage as defined by the SDI. Pediatric experts involved in  
13 the delineation of the cSLE damage core set considered this as acceptable, given the more  
14 pronounced tissue regeneration in children (8). An example to be considered is the resolution of  
15 some bone erosions in pediatrics.

16 The concept of reversibility of some damage is now clearly stated in the consensus  
17 definition of cSLE-associated damage. Notably, some of the current SDI items can also “resolve”  
18 clinically, such as nephrotic range proteinuria or seizures, but the resultant SDI item scores are  
19 maintained (2). Whether it would be more sensible to reduce the summary-score when growth  
20 and development delays have resolved or to continue considering them in a damage summary-  
21 score will need further evaluation, should the validation of the pSDI be pursued.

1 For the SDI to be considered a robust measure of cSLE-associated damage severity, one  
2 would expect a strong correlation between the SDI summary-score and the MD-VAS<sub>damage</sub> rating.  
3 However, our data suggest that this is not the case, which is in line with our prior research (6).  
4 Indeed, the lack of a strong association of damage severity with commonly encountered SDI-  
5 items likely reflects the SDI originators' caution that the index provides only an enumeration of  
6 damage items, rather than quantifying severity (1). Hence, one might suggest the use of the term  
7 "summary-count," rather than summary-score, to emphasize the distinction in future research.  
8 This may imply that it is inadvisable to present means and standard deviations of the SDI  
9 summary-score, or to use the SDI summary-score as a continuous variable in statistical models.

10 The limitation of the SDI to measure damage severity is not surprising because SDI items  
11 vary considerably in their impact on patient function, and the need for medical interventions. For  
12 example, a stroke resulting in hemiparesis will likely have greater impact on patient function than  
13 a cataract, despite the equal summary-score contribution of each item. Indeed, physician  
14 perception of damage severity is likely influenced by both the type of damage, and the resultant  
15 prognosis and/or health care utilization. This might indicate that there is a need for Likert scaling  
16 of SDI items to better capture the extent or impact of damage encountered. For example, a stroke  
17 that does not result in long-term clinical deficits would receive a lower item score than a stroke  
18 causing mild localized paresis, which in turn would be scored less than a stroke that renders the  
19 patient unable to walk or to speak.

20 Perspective is also a key factor when estimating the severity of cSLE damage. This can be  
21 exemplified by scarring alopecia, which has an extremely limited impact on mortality, but could

1 be devastating from a patient’s viewpoint. These considerations are further complicated by the  
2 known resilience of children (11).

3 The short-comings of the SDI were highlighted by deliberations of cSLE experts during the  
4 recent consensus conference. In accordance with the OMERACT Filter 2.0 (10), the importance of  
5 perspective when measuring the severity or impact of cSLE-associated damage is reflected in the  
6 newly developed provisional consensus definition of damage severity: *“as judged by the expected  
7 impact on mortality, degree of support required, activity limitation, restriction in social  
8 participation, and patient-centered quality of life.”*

9 Limitations of our study include the lack of physician damage severity ratings from all  
10 patients included in the composite cohort. Use of physician global assessments may be  
11 considered problematic in itself (20), with potential inter-rater and intra-rater variation, which  
12 we were unable to assess. Nonetheless, over 1,200 MD-VAS<sub>damage</sub> ratings were available for  
13 analysis, and VAS are widely used in medical research in general and rheumatology in particular.

14 Taken together, the analysis of a large cSLE data set confirms the construct validity of the  
15 SDI as a valid measure to “count’ damage events in children and adolescents with cSLE. The SDI  
16 in its current form is ill suited to accurately quantify the severity of cSLE-associated damage, even  
17 if item-weightings were revisited in an effort to improve the algorithm used to calculate the SDI  
18 summary-score. We propose an international effort, supported by the relevant professional  
19 organizations, to capture the severity of impact of disease damage of patients with SLE from  
20 childhood through adulthood.

21

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12

1 **FIGURE LEGENDS:**

2 **Figure 1, Panel 1**

3 The relation of SDI summary-scores and disease duration in the cohort (n=1048) is shown for patients up  
4 to 10 years since the diagnosis with cSLE. Analysis of variance supports a strong linear relationship (R-  
5 square = 0.9; p-value <0.0001)

6 **Figure 1, Panel 2**

7 The relationship of presence of damage in the nine organ domains of the SDI is shown for  
8 disease durations up to 6 years. Diabetes and malignancies were very rare and are omitted  
9 from depiction. Lines are moving averages of annual values. The most commonly damaged  
10 organ systems were the neuropsychiatric and the musculoskeletal, renal and skin

11 **Figure 2, Panel 1**

12 The relationship between physician-rated severity of damage (MD-VAS<sub>Damage</sub>) and the SDI  
13 summary-score in patients with cSLE are depicted, with focus on MD-VAS<sub>Damage</sub> ratings of 0, 1 or  
14 2. Despite SDI scores of 1 or 2, some physicians provided damage severity ratings of 0.  
15 Conversely, only 76% of patients with a SDI summary-scores of 0 received the best possible  
16 MD-VAS<sub>Damage</sub> rating.

17 **Figure 2, Panel 2**

18 The relationship between physician-rated severity of damage (MD-VAS<sub>Damage</sub>) and the SDI  
19 summary-score in patients with cSLE are depicted. With higher SDI summary-scores more  
20 commonly higher MD-VAS<sub>Damage</sub> ratings are assigned.

**Table 1: Demographics and Summary Score by Cohort**

<i>Cohort:</i>	<i>All Cohorts</i>	<i>UK (1)</i>	<i>Cincinnati (2)</i>	<i>PRINTO (3)</i>		<i>P-value</i>	
					<i>(1) vs. (2)</i>	<i>(1) vs. (3)</i>	<i>(2) vs. (3)</i>
<b>Total N:</b>	1048	350	139	559		N/A	
<b>Female (%)‡</b>	869 (82.9%)	291 (83.1%)	118 (84.9%)	460 (82.3%)			
<b>Age at Diagnosis†</b>	12.2 (3.1)	12 (3.32)	13.9 (2.82)	12 (2.95)	<0.0001	0.86	<0.0001
<b>Disease Duration†</b>	3.81 (2.98)	3.82 (3.17)	5.15 (3.75)	3.46 (2.57)	<0.0001	0.08	<0.0001
<b>SDI Summary-score†</b>	0.94 (1.56)	0.56 (1.06)	0.99 (1.59)	1.16 (1.76)	0.0006	0.0001	0.30
<b>Patient N (%) with SDI summary-score = 0‡</b>	585 (55.8%)	272 (77.7%)	80 (58.5%)	233 (41.7%)		<0.0001	

† Listed values are Mean (Standard Deviation). P-values are from post-hoc analysis using fixed effect models and correcting for the

Tukey's method and only listed if p-value are <0.1. N/A: Not applicable. ‡ Listed values are Frequency (in %); P-values are from Chi square

tests and only listed if p-values are <0.1



**Table 2. Comparison of SDI Item Frequency by Cohort\*\***

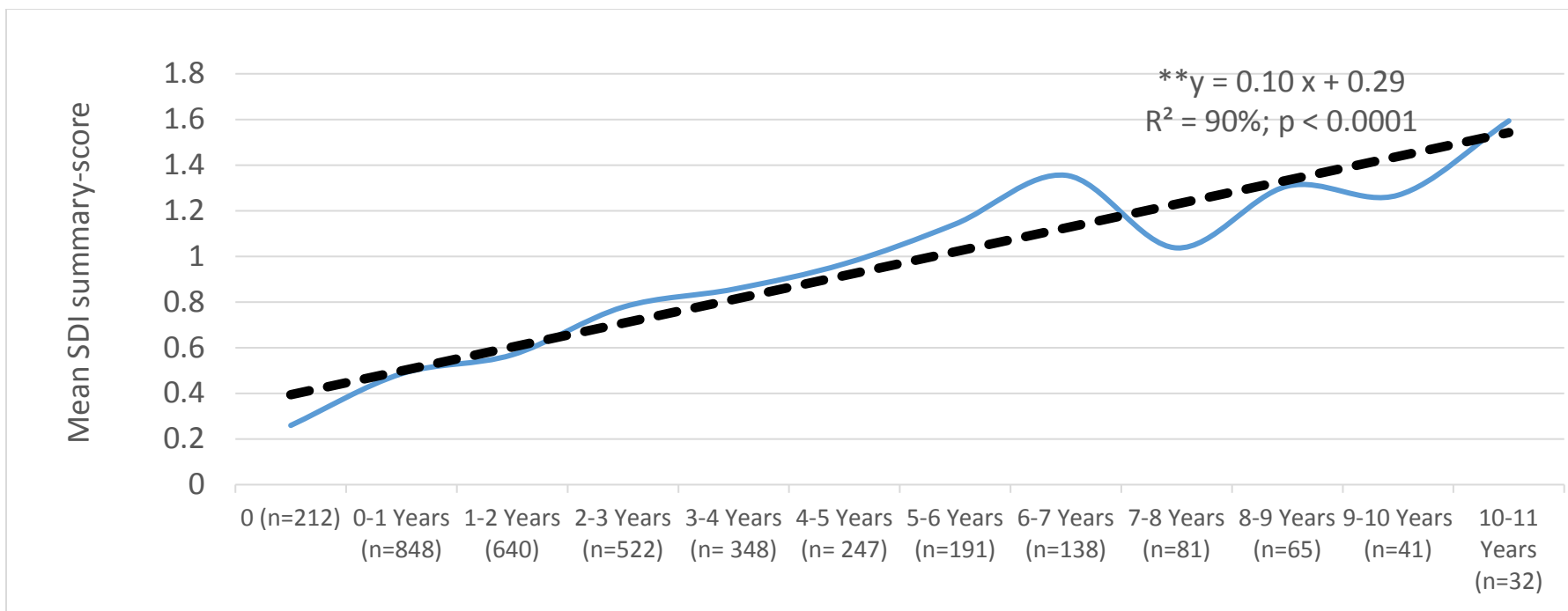
	<i>Overall</i>	<i>UK</i>	<i>CCHMC</i>	<i>PRINTO</i>	<i>P-value</i>
<b><u>Ocular</u></b>					
Cataracts	4.2	2	6.5	5	0.38
Retinal change	1.7	1.1	0.7	2.3	0.24
<b><u>Neuropsychiatric</u></b>					
Cognitive impairment	8.4	3.4	12.2	10.7	0.0004*
Seizures requiring therapy	3.9	2.3	2.2	5.4	0.09*
Cerebrovascular accident	2.9/ 0.4	2 / -	3.6/ 1.4	3.4/0.4	0.014 <sup>†</sup>
Cranial/peripheral neuropathy	2.4	2.3	0.7	2.9	0.33 <sup>†</sup>
Transverse myelitis	0.4	0.3	0.7	0.4	0.29 <sup>†</sup>
<b><u>Renal</u></b>					
Estimated GFR <sub>‡</sub> < 50%	3.6	1.1	4.3	5	0.034*
Proteinuria ≥ 3.5 gm/day	9.6	4.3	10.8	12.7	0.0038*
End-stage renal disease	1.3	0.6	3.6	1.3	0.14 <sup>†</sup>
<b><u>Pulmonary</u></b>					
Pulmonary hypertension	0.4	0.9	0.7	0	0.41 <sup>†</sup>
Pleural fibrosis	1.3	0.3	0	2.3	0.18 <sup>†</sup>
Shrinking lung	0.8	0.3	0	1.3	0.82 <sup>†</sup>
Pulmonary fibrosis	0.9	0.6	0.7	1.3	0.6 <sup>†</sup>
Pulmonary infarction	0	0	0	0	-
<b><u>Cardiovascular</u></b>					
Angina/artery bypass	0.1	0	0	0.2	1 <sup>†</sup>
Myocardial infarction	0.1/ 0.1	0/ -	0/ -	0.2/ 0.2	-
Cardiomyopathy	0.9	0.3	0.7	1.3	0.21 <sup>†</sup>
Valvular disease	0.9	0.9	0	1.1	0.75 <sup>†</sup>
Pericarditis/pericardectomy	1.6	0.9	0.7	2.3	0.91 <sup>†</sup>

	<i>Overall</i>	<i>UK</i>	<i>CCHMC</i>	<i>PRINTO</i>	<i>P-value</i>
<b><u>Peripheral vascular</u></b>					
Claudication for 6 months	0.3	0	0	0.5	0.67 <sup>†</sup>
Minor tissue loss	2.4/ -	0.9/ -	1.4/ -	3.6/-	0.28 <sup>†</sup>
Significant tissue loss ever	0.7/0.3	0.3/ -	0.7/ 0.7	0.9/0.4	0.11 <sup>†</sup>
Venous thrombus swelling, ulcer/stasis	2.5	1.7	0.7	3.4	0.81 <sup>†</sup>
<b><u>Gastro Intestinal -</u></b>					
Bowel infarction or resection	1.3/ 0.3	1.1	1.4/ 0.7	1.4/0.4	0.88 <sup>†</sup>
Mesenteric insufficiency	0.1	0.3	0	0	0.63 <sup>†</sup>
Peritonitis	0.2	0	0	0.4	0.63 <sup>†</sup>
Stricture/upper GI tract surgery ever	0.4	0.6	0	0.4	1 <sup>†</sup>
Pancreatic insufficiency	0.5	0.3	0	0.7	1 <sup>†</sup>
<b><u>Musculoskeletal</u></b>					
Muscle atrophy/weakness	7.9	4	3.6	11.4	0.0056
Deforming/erosive arthritis	4.7	2.9	3.6	6.3	0.19
Osteoporosis with fracture	2.6	1.4	2.2	3.4	0.39 <sup>†</sup>
Avascular necrosis	2.7/1.0	0.6/ -	10.8/ 5	2/0.4	0.055 <sup>†</sup>
Osteomyelitis	0.4	0	0.7	0.5	0.63 <sup>†</sup>
Ruptured tendons	0.1	0.3	0	0	0.41 <sup>†</sup>
<b><u>Skin</u></b>					
Scarring chronic alopecia	9.1	11.7	6.5	8.2	0.06
Extensive scar/panniculum	1.7	1.4	1.4	2	0.82 <sup>†</sup>
Skin ulceration for 6 months	2.7	1.7	0	4.1	0.27
<b><u>Premature gonadal failure</u></b>					
	2	0.6	0.7	3.2	0.24 <sup>†</sup>
<b><u>Diabetes</u></b>					
	0.9	1.1	1.4	0.5	1 <sup>†</sup>
<b><u>Malignancy</u></b>					
	0.2	0.3	0.7	0	-

\*\*\* Values are % of patients with SDI item score of 1 / 2, or for ESRD a score of 3; ‡glomerular filtration rate; \*P-values are from logistic models after adjusting for disease duration; † p-values are from Fisher's exact test.

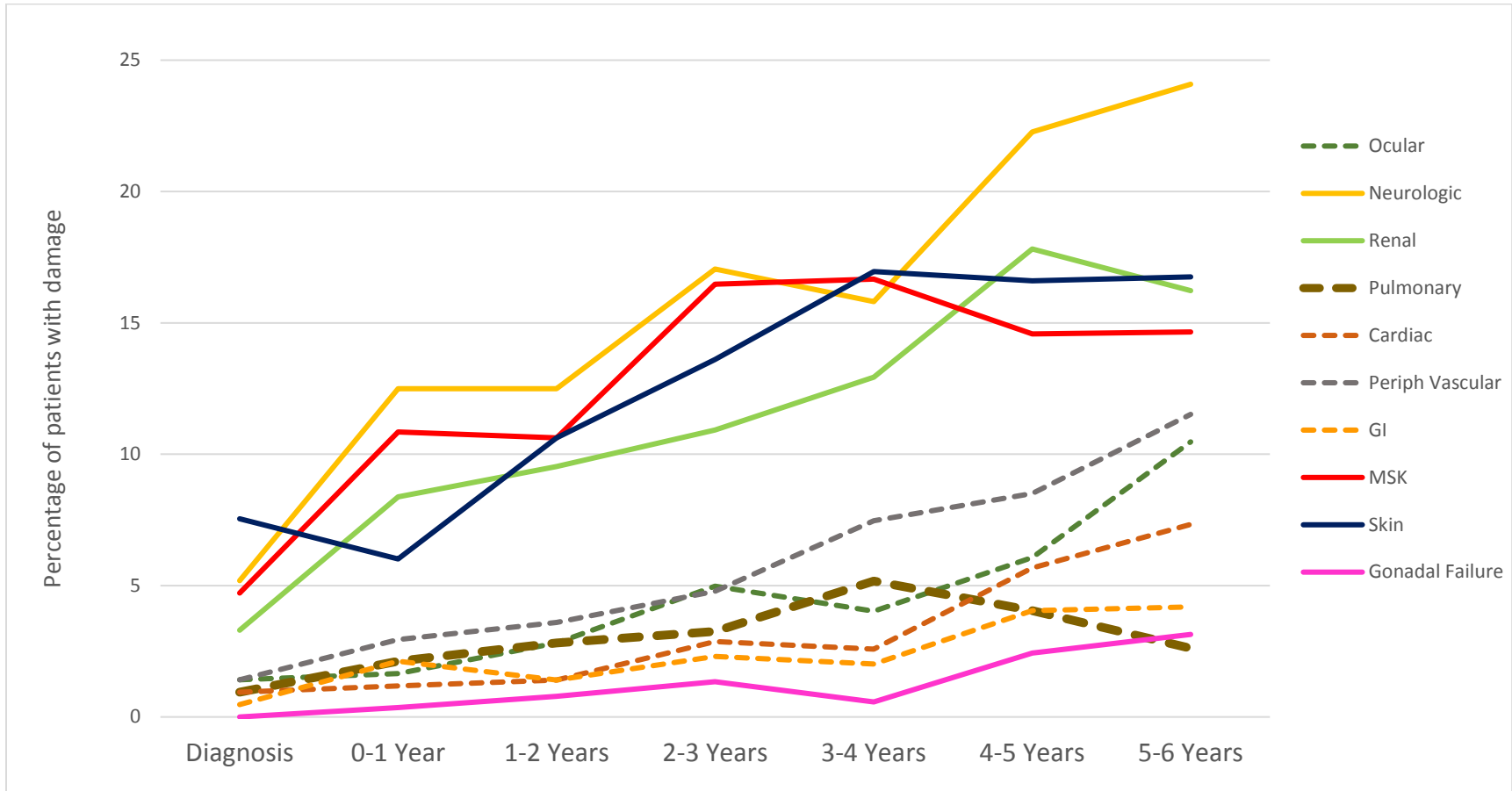
Figure 1: Damage accumulation over time

Panel 1: Observed SDI summary-scores by disease duration for up to 10 years



\*\* Function of linear trendline including information about model fit ( $R^2$ )

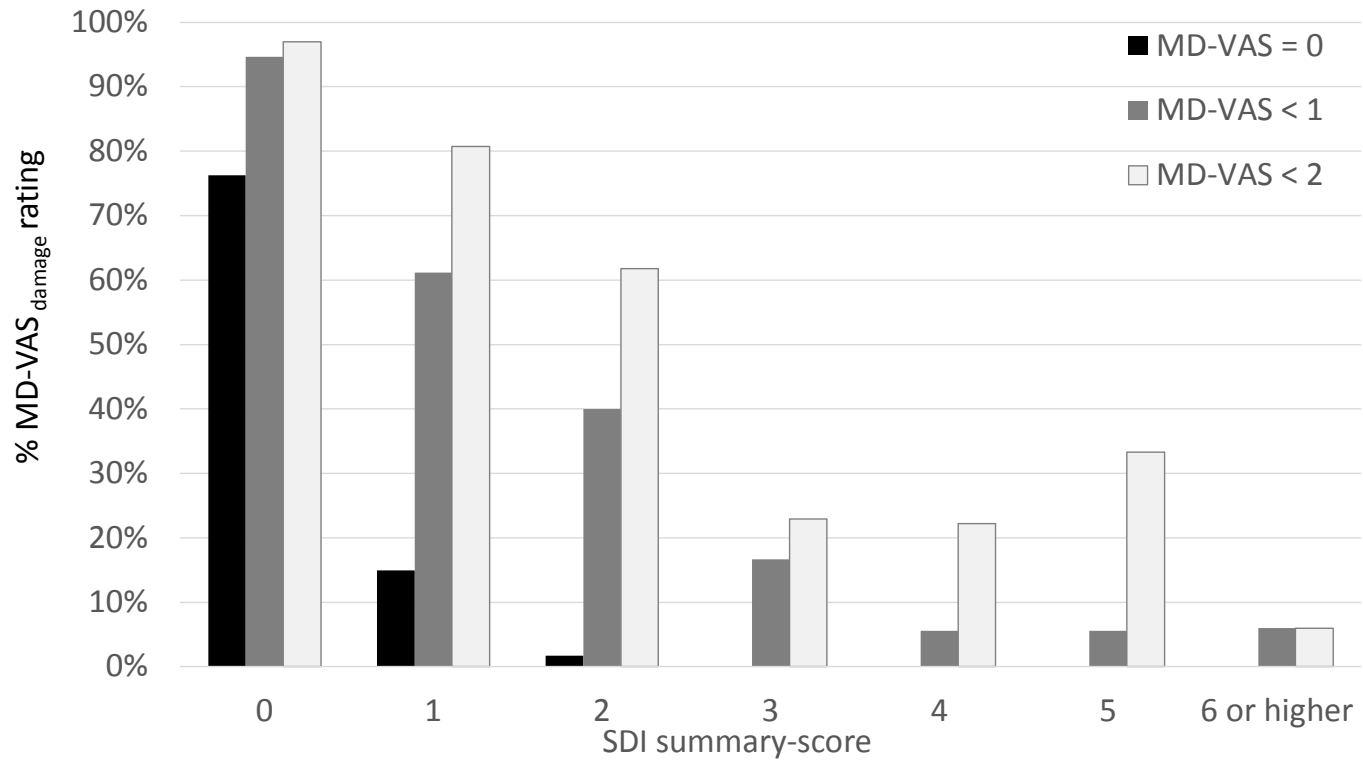
**Panel 2: Observed SDI organ system involvement by disease duration for up to 6 years\***



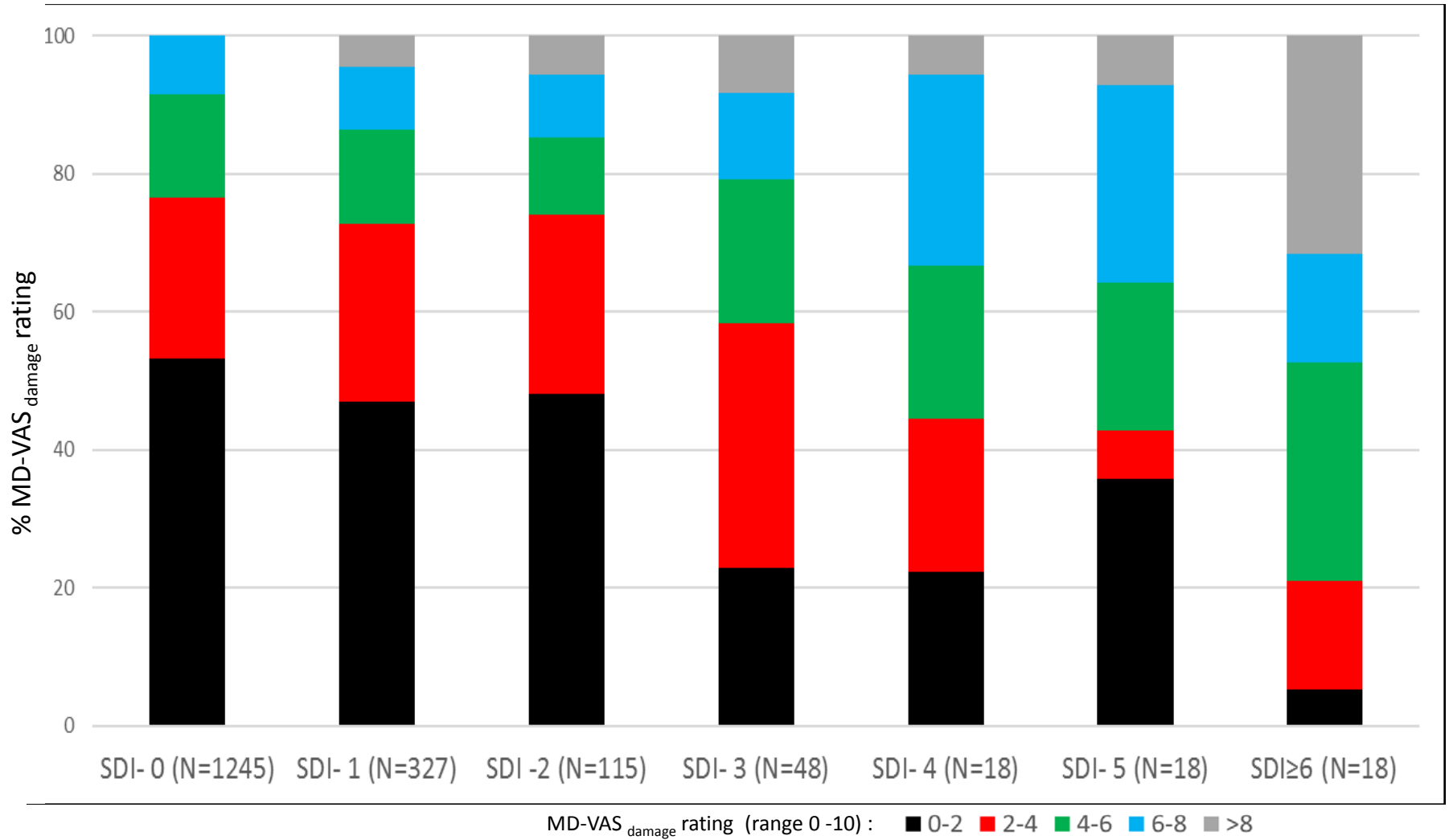
\* Malignancies and diabetes was present in < 0.4% of the composite cohort and both SDI organ systems are excluded from the figure`

Figure 2: SDI summary-scores and physician rating of perceived damage severity in cSLE.

Panel 1: MD-VAS<sub>Damage</sub> ratings of up to 2 (range 0 -10)



Panel 2: MD-VAS<sub>Damage</sub> ratings for SDI scores up to 12



OLD FIGURE or A

