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I, Michael J Holland, hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:

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

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

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by

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ABSTRACT

Objectives: To describe the frequency and distribution of disease damage in 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 relationship to damage severity.

Methods: SDI item and summary-scores from 1,048 cSLE patients in three existing cohorts were included. In one cohort of 559 patients, treating physicians also rated damage severity, using a visual analog scale (MD-VAS_{damage}). Damage item frequency was determined, and the association between SDI scores and available MD-VAS_{damage} ratings measured. Finally, an international consensus conference, utilizing nominal group technique, considered the SDI's capture of cSLE damage severity.

Results: After a mean disease duration of 3.8 years, some damage (SDI summary-score > 0) was present in 44.2% (463/1048) of patients, with a maximum SDI summary-score of 14. The most common SDI items were: proteinuria, alopecia, cognitive impairment, and musculoskeletal atrophy. In those patients with MD-VAS_{damage} ratings and known damage (SDI > 0), there was a moderately strong association between SDI summary-scores and MD-VAS_{damage} ($r_{Spearman}$ = 0.49; p<0.0001). Mixed effect analysis revealed that only four SDI items, all occurring in <2% of patients, were significantly associated with MD-VAS_{damage}. After consideration of these results, unanimous consensus was achieved that a new instrument or approach is needed to measure cSLE damage severity.

Conclusion: Despite the relatively short mean disease duration, damage measured by the SDI was common in cSLE. Physician-perceived damage severity was not well captured by SDI summary-scores, and improved measures are needed.

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.
- After consideration of these data, and relevant literature, an international group of pediatric rheumatologists and nephrologists reached unanimous consensus that a new measure or approach is needed to better capture damage severity in cSLE.

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INTRODUCTION

Approximately 20% of systemic lupus erythematosus (SLE) cases have their onset in childhood (cSLE), i.e. before 18 years of age (1). The concept of 'damage' has been introduced to describe theoretically irreversible organ scarring or impairment seen in patients with SLE. Quantifying damage is an important consideration in gauging the overall outcome in SLE, particularly as mortality decreases (2, 3). Given the inability of a single clinical feature or laboratory test to measure damage across many organ systems, a disease damage index has been developed, the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index (SDI) (3).

The SDI tracks the presence or absence of damage items after diagnosis with SLE, and was derived from experience with adult-onset disease (3). The SDI also features a summary-score, which has been used as an independent, continuous outcome measure in statistical analyses (4). Prior investigations have shown that the presence of damage, as measured by the SDI, is associated with increased mortality in adults (2), and increased cumulative SLE activity in both adults and children (2, 5, 6). The developers of the SDI stressed that the index should be considered an enumeration of damage types only, and that it does not directly quantify damage severity (3). Notably, patients with clearly divergent damage severity may have the same SDI summary-score. For example, patients with 6-months of transient drug-induced diabetes, one area of avascular necrosis, or a small cataract would all receive the same SDI summary-score as a patient with a debilitating stroke, provided each had only one damage item.

In an attempt to adapt the SDI to better measure damage severity, earlier studies of adults with SLE explored the use of item weightings, but this did not meaningfully improve the

association of SDI scores with mortality (2,7). One prior attempt at weighting the SDI by organ system in cSLE (based on the SLEDAI-2K activity index item weightings) was also unsuccessful (6), although cSLE damage patterns have subsequently been described in greater detail (1, 8, 9).

A prior international consensus process in 2001 (10), focused on outcome measures in both cSLE and juvenile dermatomyositis, sought to define a core set of variables that could be used to capture domains relevant to cSLE damage. The resulting damage core set, adopted unanimously, included a standard damage tool (the SDI), a physician global damage assessment (VAS or Likert scale), as well as growth and development (height and weight, menses, tanner staging). The overwhelming majority of these experts (95%) also agreed that a health-related quality of life (HRQoL) assessment should be included. The perceived need for consideration of pubertal development and growth subsequently led to the development of the pediatric-specific SDI (pSDI), which adds related pediatric-specific items (8). Because of more pronounced tissue regeneration, and remaining growth potential in children, pSDI scores may decrease, though formal criteria for item resolution are not defined (8). Notably, potential issues in measuring damage severity are identical whether using the SDI or pSDI.

The Outcome Measures in Rheumatology (OMERACT) collaborative published a revised framework (OMERACT Filter 2.0) for development of core outcome measurement sets in Rheumatology (11). The filter encourages the use of measures which are valid, discriminate conditions of interest, and are feasible. It also emphasizes the concept of multiple “core areas” which may be addressed by these core outcome sets (death, disease impact, resource use, and disease manifestations). Finally, the filter also highlights the need to explicitly consider perspective, and the context in which an outcome measure is used. The aspect of perspective

(patient, physician, and/or societal cost) and context appear particularly important to damage severity, given the diverse manifestations possible in a multi-organ disease process such as cSLE.

While the previously developed cSLE damage core set (10) touches on at least two of the OMERACT core areas for construct measurement, stand-alone use of the SDI is still commonplace when gauging lupus damage in clinical studies.

In light of this reality, we sought to critically evaluate the SDI as a measure of damage severity in cSLE by: 1) further delineating the frequency of SDI damage items in a large composite cohort with consideration of disease duration; 2) comparing the SDI summary-score directly to a physician global assessment of damage severity; and 3) using statistical techniques to explore the possible impact of SDI item weightings, based on these global assessments, to better capture damage severity in cSLE. Subsequently, our findings were presented at an international consensus conference held in April 2017, in which participants were asked to consider whether a new instrument (or approach) to the measurement of damage severity in cSLE should be pursued.

MATERIAL & METHODS

Patients

In this study data from large, existing longitudinal cohorts of cSLE were analyzed. 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 1048 patients. General demographic data were considered, 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.

Damage measures and scales

Systemic Lupus International Collaborating Clinics / American College of Rheumatology Damage Index. This instrument, developed through an adult-focused consensus process, quantifies irreversible damage that has occurred since SLE was diagnosed, according to specific item definitions (3). According to the SDI, damage is considered non-reversible if any given item was present for at least 6 months continuously, or immediately for some events associated with acute organ damage, e.g. myocardial infarct (3). While there is no overall weighting system, some items can be scored twice, if two qualifying events are separated by at least 6 months (stroke, myocardial infarct, tissue loss, bowel infarct, avascular necrosis, or malignancy). 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). Therefore, an SDI 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. Physicians contributing data to the PRINTO cohort rated damage severity on a 10-cm visual analog scale (MD-VAS_{damage}). The following

anchor statements were included at each end of the 10-cm scale: 0, no damage; 10, very severe damage.

Statistical analyses

For descriptive analyses we calculated frequencies for categorical variables, as well as means, and standard deviations for numerical variables. Comparison of demographic features and SDI summary-scores between cohorts was done by least square means, and the Tukey-Kramer method was used to test for significant differences between cohorts post-hoc. Damage item frequency was calculated based upon the SDI score at the last follow up visit available for each patient, and per SDI instructions included any item ever scored. Contingency table analysis was done to compare item frequencies between groups of patients (CCHMC, UK, PRINTO). Significant differences between item frequencies were assessed using chi-square analysis or Fisher exact testing, where appropriate. Given variation in disease duration, for purposes of statistical comparison of item frequency between cohorts, only patient SDI scores with total disease durations of 4.5 years or less were considered.

To assess the relationship of SDI summary-scores to physician-perceived severity of damage, we calculated the Spearman correlation coefficient between SDI summary-scores and MD-VAS_{damage} from all patient visits within the PRINTO cohort. Correlation with MD-VAS_{damage} was then separately assessed only for patient visits with known damage (SDI scores > 0). The association between SDI and MD-VAS_{damage} in visits with known damage was examined separately to test capture of damage severity, which is most applicable only in the presence of some

damage. To evaluate the effect of multiple comparisons, correlations were also calculated separately using only the first, and then last visit for each patient. Finally, mixed effect models were used to determine the association of individual damage items with MD-VAS_{damage} ratings. .

Consensus Conference

From April 23rd through 25th 2017, an international consensus conference of physicians with expertise in cSLE was held in Cincinnati, Ohio. The group consisted of thirteen physicians (ten pediatric rheumatologists and three pediatric nephrologists), and nominal group technique was used to facilitate discussion and consensus formation. An independent moderator with experience in nominal group technique led the consensus process, and 75% agreement was selected by unanimous consent as the threshold for consensus. Results of the analyses above, as well as a review of relevant literature, were presented prior to opening discussion.

RESULTS

Patients

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

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

Overall disease damage as measured by the SDI

Among the 1048 patients, a total of 585 (55.8%) still had not acquired disease damage (SDI summary-score=0) by the time of last follow-up, which occurred at a mean of 3.8 years after diagnosis with cSLE (Table 1**).** Mean SDI summary-scores significantly differed between the UK and PRINTO cohorts (p<0.0001), and PRINTO and CCHMC cohorts (p=0.037) but not between the CCHMC and UK cohorts (p=0.14), (see Table 1). The proportion of patients without cSLE damage (SDI=0) at last follow-up was highest in the UK cohort (77.7%) (**Table 1).** Overall, the mean SDI summary score increased incrementally with increasing disease duration (**Figure 1**)

Common and less common types of disease damage with cSLE

The frequency of SDI items at the final follow-up visit in each cohort is summarized in **Table 2.** The three most commonly encountered SDI items were proteinuria, scarring alopecia, and chronic cognitive impairment. There were four SDI items that were present in fewer than three patients (3/1048 = 0.3%). These were angina, myocardial infarction, mesenteric insufficiency, and tendon rupture. None of the patients had a pulmonary infarction scored. An additional 12 SDI items were present in less than 1% of the combined cohort (**Table 2)**. When item frequency was examined separately by one-year intervals of disease duration, seven items were present in <1% of patients in every interval. These were pulmonary infarct, angina,

claudication, peritonitis, pancreatitis, osteomyelitis, and tendon rupture (data not shown). Irrespective of disease duration, the most commonly damaged organ systems were the neuropsychiatric, kidney, skin, and musculoskeletal.

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

Physician-rated damage severity (MD-VAS_{damage}) was available for 1245 patient visits. Of these, 1245/1793 (69.4%) were without damage (SDI score=0), and 548/1793 (30.5%) with damage (SDI >0), respectively. Despite being considered "damage-free" based on a SDI summary-score of 0, physicians still rated 24.2% (301/1245) of these patients as having some damage (MD-VAS_{damage}>0) (**Figure 2)**. Conversely, only 5.7% (31/548) of patients with SDI summary-scores of >0 were considered "damage-free" by their treating physician (MD-VAS_{damage}=0).

The correlation between SDI score and MD-VAS_{damage} overall was strong ($r_{spearman}$ 0.71; p<0.0001) (**Figure 2**)**,** though when narrowed to include only visits with some damage (SDI >0) the correlation was moderate ($r_{spearman}$ 0.496; p<0.0001). Correlations were similar when considering only the first, or last visit for each patient: ranging from 0.66-0.72 for all SDI scores, versus 0.45-0.54 for only those visits with SDI summary scores >0.

To further explore potential drivers of the relationship between physician-rated damage severity and SDI summary-scores, we used mixed effect analysis. This analysis revealed that only four of the 41 individual SDI items were significantly associated with the MD-VAS_{damage}. Specifically, these were pulmonary fibrosis, shrinking lung syndrome, chronic pericarditis, and

extensive cutaneous scar, all of which had an overall frequency of <2% in the composite study cohort.

Consensus Conference

Unanimous consensus was achieved that a new instrument or approach is needed for improved measurement of damage severity in cSLE. Further, 83% consensus was achieved that the OMERACT Filter 2.0 should be used for the development of such an approach. Participants then developed definitions of cSLE damage and damage severity as a first step toward improving measurement of the damage construct in cSLE. Damage within cSLE was defined as "*Impairment of anatomy or physiology that may be associated with scarring, may accumulate, and is not completely reversible. Damage may be caused by disease, adverse effects of medication, or associated comorbidity. In children this may lead to stunted cognitive, and physical development*." (83% consensus). Further, consensus (77%) was also achieved for a definition of damage severity: "*Severity of damage is measured by the organs involved, and the extent of anatomical and physiological derangement as judged by the expected impact on mortality, degree of support required, activity limitation, restriction in social participation, and patient-centered quality of life*."

DISCUSSION

We examined the pattern and severity of disease damage in a large composite cohort with cSLE. Our analyses suggest that, while the presence of damage as defined by the SDI is relatively common, most individual SDI items are rare in cSLE. The data also demonstrate no more than a moderately strong relationship between the SDI summary-score and physician perception of damage severity, in patients with known damage. Finally, there are no commonly-encountered SDI items that are significantly associated with damage severity as perceived by treating physicians.

The rarity of most SDI items in our cohort is similar to that observed in a prior study of Korean patients with primarily adult onset SLE (12), and a prior study (which included some data from the PRINTO cohort) in cSLE (8). Commonly encountered SDI items were also similar in this prior study of children, with nephrotic range proteinuria and cognitive impairment among the most commonly encountered types of damage (8).

Given that nearly half of SDI items were encountered in <1% of cSLE patients, eliminating items with extremely low prevalence might be considered in order to simplify the damage scale. If low frequency is confirmed in cohorts with longer, uniform cSLE durations, this case might be more compelling. While this subtraction could balance the previously proposed addition of items specifically relevant to childhood-onset disease in the pSDI (8), it is necessary to carefully weigh the possibility of excluding rare items with high impact (i.e. myocardial infarct, stroke), and introducing further differences from the adult SDI, against any benefit of simplification.

When SDI item scores are added to create the SDI summary-score, one might expect that a higher score (more damage items present) would also represent more severe damage. However, there was only a modest relationship between physician perception of damage severity and SDI summary-scores in those cSLE patients with damage. Further, statistically significant associations with damage severity scores were present for only a few, rarely-endorsed, SDI items. While item weightings have been incorporated in other SLE scales (13), our findings imply that item weightings will not improve the ability of the SDI to capture cSLE damage severity. This view is supported by earlier studies, which also found little value in item weightings to improve SDI measurement of damage severity (2, 6, 7).

Indeed, the lack of a strong association of damage severity with commonly encountered SDI-items likely reflects the SDI originators' caution that the index provides only an enumeration of damage items, rather than quantifying severity (3). This is in line with prior observations (7) and might suggest the use of the term "summary-count," rather than summary score, to emphasize the distinction. Hence, presenting means and standard deviations for the SDI, or even using the SDI summary-score as a continuous variable in statistical models, may be inadvisable.

This limitation is not surprising, given that various SDI items have different impacts on patient function, and the need for intervention. For example, a stroke resulting in hemiparesis will likely have greater impact than a cataract, despite the equal summary score contribution of each item. Indeed, physician perception of damage severity may vary significantly even within items. For example, consider a stroke causing mild localized paresis, versus one that renders the patient unable to walk or to speak. Perspective is also a key factor. For example, scarring alopecia might have a limited impact on mortality, but could be devastating from a patient's viewpoint.

These considerations are further complicated by the known resilience of children, who may have enhanced ability to compensate for (or even reverse) damage when compared to adults (8).

The limitations of the SDI are highlighted by the work of the recent consensus conference of cSLE experts who unanimously recommended that a new instrument, or approach, to cSLE damage severity measurement be pursued. The OMERACT Filter 2.0 (11), endorsed by the conference for development of such an instrument, is a broad guideline, which acknowledges the importance of perspective and context in the generation of new measures. The importance of perspective is also explicitly emphasized by the adopted provisional consensus definition of damage severity: "*as judged by the expected impact on mortality, degree of support required, activity limitation, restriction in social participation, and patient-centered quality of life*."

Limitations of our study include the lack of physician damage severity ratings from all patients included in the composite cohort, and variability in both component cohort and patient-specific disease durations. Use of physician global assessments is in itself problematic (14), with potential inter-rater and intra-rater variation, which we were unable to assess.

In summary, our direct comparison of the SDI to a relevant external standard of damage severity creates significant uncertainty about the usefulness of the SDI in this regard, and confirms by consensus the need for further work toward an improved measure of damage severity in cSLE.

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Table 1: Demographics and Summary Score by Cohort †

Cohort:	*All Cohorts*	*UK* *(1)*	*Cincinnati* *(2)*	*PRINTO* *(3)*	*P-value* *(1) vs. (2)*	*(1) vs. (3)*	*(2) vs. (3)*
Total N:	1048	350	139	559		N/A	
Female (%)	869 (82.9%)	291 (83.1%)	118 (84.9%)	460 (82.3%)		0.76	
Age at Diagnosis	12.2 (3.1)	12 (3.32)	13.9 (2.82)	12 (2.95)	<0.0001	0.86	<0.0001
Disease Duration	3.81 (2.98)	3.82 (3.17)	5.15 (3.75)	3.46 (2.57)	<0.0001	0.082	<0.0001
SDI Score	0.94 (1.56)	0.56 (1.06)	0.99 (1.59)	1.16 (1.76)	0.48	0.013	<0.001
Patient N (%) with SDI score = 0	585 (55.8%)	272 (77.7%)	80 (58.5%)	233 (41.7%)		<0.0001	

† Listed values are Mean (Standard Deviation) unless stated otherwise; N/A: Not applicable; P-values via least-square mean estimates, post-hoc analysis uses Tukey's estimates.

Table 2. Comparison of SDI Item Frequency by Cohort

	Overall	*UK*	*CCHMC*	*PRINTO*	*P-value**
Ocular					
Cataracts	4.2	2	6.5	5	0.38
Retinal change	1.7	1.1	0.7	2.3	0.24
Neuropsychiatric					
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†
Cranial/peripheral neuropathy	2.4	2.3	0.7	2.9	0.33†
Transverse myelitis	0.4	0.3	0.7	0.4	0.29†
Renal					
Estimated GFR < 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†
Pulmonary					
Pulmonary hypertension	0.4	0.9	0.7	0	0.41†
Pleural fibrosis	1.3	0.3	0	2.3	0.18†
Shrinking lung	0.8	0.3	0	1.3	0.82†
Pulmonary fibrosis	0.9	0.6	0.7	1.3	0.6†
Pulmonary infarct	0	0	0	0	-
Cardiovascular					
Angina/artery bypass	0.1	0	0	0.2	1†
Myocardial infarction	0.1/ 0.1	0/ -	0/ -	0.2/ 0.2	-
Cardiomyopathy	0.9	0.3	0.7	1.3	0.21†
Valvular disease	0.9	0.9	0	1.1	0.75†
Pericarditis/pericardectomy	1.6	0.9	0.7	2.3	0.91†

	Overall	*UK*	*CCHMC*	*PRINTO*	*P-value**
Peripheral vascular					
Claudication for 6 months	0.3	0	0	0.5	0.67†
Minor tissue loss	2.4/ -	0.9/ -	1.4/ -	3.6/-	0.28†
Significant tissue loss ever	0.7/0.3	0.3/ -	0.7/ 0.7	0.9/0.4	0.11†
Venous thrombus swelling, ulcer/stasis	2.5	1.7	0.7	3.4	0.81†
Gastro Intestinal -					
Bowel infarction or resection	1.3/ 0.3	1.1	1.4/ 0.7	1.4/0.4	0.88†
Mesenteric insufficiency	0.1	0.3	0	0	0.63†
Peritonitis	0.2	0	0	0.4	0.63†
Stricture/upper GI tract surgery ever	0.4	0.6	0	0.4	1†
Pancreatic insufficiency	0.5	0.3	0	0.7	1†
Musculoskeletal					
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†
Avascular necrosis	2.7/1.0	0.6/ -	10.8/ 5	2/0.4	0.055†
Osteomyelitis	0.4	0	0.7	0.5	0.63†
Ruptured tendons	0.1	0.3	0	0	0.41†
Skin					
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†
Skin ulceration for 6 months	2.7	1.7	0	4.1	0.27
Premature gonadal failure	2	0.6	0.7	3.2	0.24†
Diabetes	0.9	1.1	1.4	0.5	1†
Malignancy	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; P-values adjusted for differences in disease duration; † Denotes fisher's exact test.

Figure 1: Change in SDI Summary Score Over Time by Patient Visits

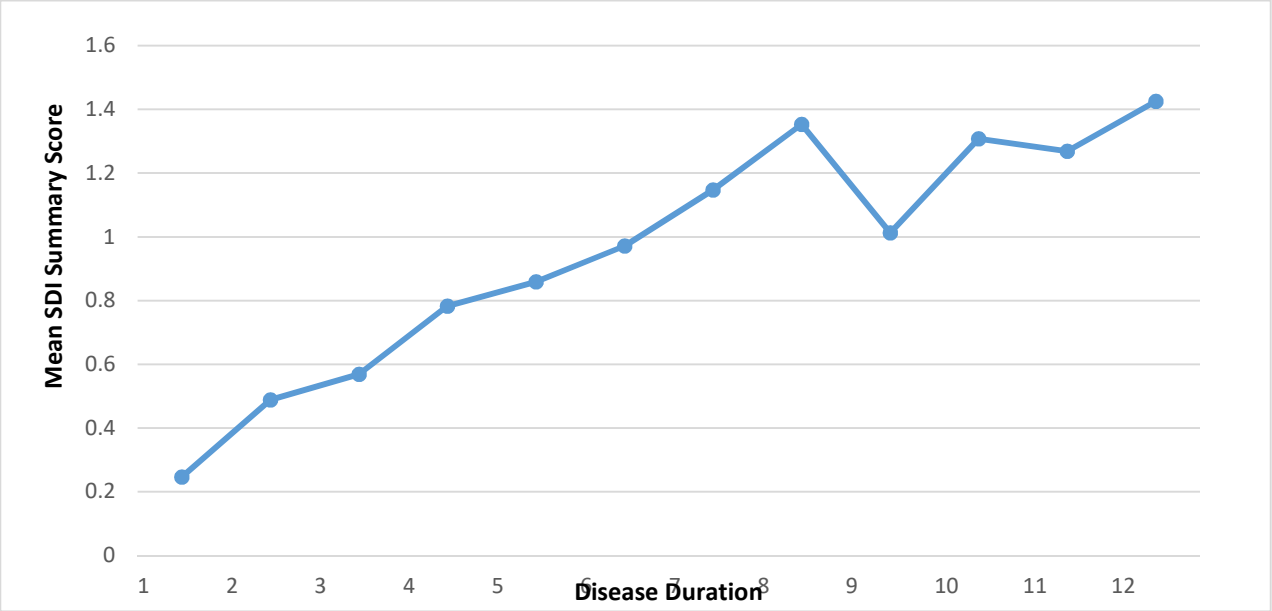

Figure 2: Variability of MD-VAS$_{Damage}$ By SDI Summary Score within the PRINTO Cohort