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Evaluating the construct of damage in systemic lupus erythematosus

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ABSTRACT

Objective. The Systemic Lupus International Collaborating Clinics, American College of Rheumatology and Lupus Foundation of America are developing a revised SLE Damage Index (SDI). Shifts in the concept of damage in SLE have occurred with new insights into disease manifestations, diagnostics, and therapy. We evaluated contemporary constructs in SLE damage to inform development of the revised SDI.

Methods. We conducted a 3-part qualitative study of international SLE experts. Facilitated small groups evaluated the construct underlying the concept of damage in SLE. A consensus meeting using nominal group technique was conducted to achieve agreement on aspects of the conceptual framework and scope of the revised damage index. The framework was finally reviewed and agreed upon by the entire group.

Results. Fifty participants from 13 countries were included. Eight thematic clusters underlying the construct of SLE damage were purpose, items, weighting, reversibility, impact, timeframe, attribution, and perspective. The revised SDI will be a discriminative index to measure morbidity in SLE, independent of activity or impact on the patient, and should be related to mortality. The SDI is primarily intended for research purposes and should take a life course approach. Damage can occur before a diagnosis of SLE but should be attributable to SLE. Damage to an organ is irreversible but the functional consequences on that organ may improve over time through physiological adaptation or treatment.

Conclusion. We identified shifts in the paradigm of SLE damage and developed a unifying conceptual framework. These data form the groundwork for the next phases of SDI development.

Significance and Innovations.

We have developed a contemporary and expanded conceptual framework for damage in SLE that integrates purpose, items, weighting, reversibility, impact, timeframe, attribution, and perspective.

Damage is a health state related to organ structure and function. The degree of reduced organ function relates to physiologic impairment.

Damage can occur before a diagnosis of SLE but should be attributable to SLE. Damage to an organ is irreversible but the functional consequences on that organ may improve over time through physiological adaptation or treatment.

This theory informed framework is an important first step as the SLICC, LFA and ACR revise the lupus Damage Index.

Systemic lupus erythematosus (SLE) is characterized by autoantibody formation and inflammation of target organs. Disease activity, treatment, comorbidities, concurrent illnesses, and aging may result in organ dysfunction and damage. Among patients who survive more than 10 years, the cause of death is usually multifactorial and not limited to active SLE. The Systemic Lupus International Collaborating Clinics (SLICC), American College of Rheumatology (ACR) Damage Index (SDI) was developed as a measure of morbidity, distinct from disease activity, health status, and mortality.(1) This global damage index describes the total of the measurable damage that has occurred from any mechanism, regardless of attribution. Originally, damage was defined as 'non-reversible change, not related to inflammation, occurring since the diagnosis of lupus, ascertained by clinical assessment and present for at least 6-months unless otherwise stated.'(1) Damage may be a consequence of disease activity, therapy, intercurrent illness or an indirectly related event (Figure 1). Comprised of an additive point system of 41 items(2), the SDI enumerates the accumulation of damage that has occurred since the diagnosis of SLE in 12 systems. To be scored, most items must be present for at least 6 months, and in some domains, repeat episodes occurring at least 6 months apart score an additional point.

The SDI has served the lupus research community for over 20 years with demonstrable reliability(3), validity(2); is associated with reduced quality of life, increased mortality; and has been a secondary endpoint in trials.(4, 5) However, shifts in the concept of damage in SLE have occurred, with new insights into disease manifestations, diagnostic modalities, and therapy.(6) Studies have demonstrated that additional factors contribute to damage accrual including sex, age, race/ethnicity, lower income/education, medical coverage/access to care, place of residency, baseline damage, medications, hypertension, and antiphospholipid antibodies.(6-8) Additional issues suggesting the benefit of revision of the SDI include the fact that despite the total possible SDI ranging from 0 to 45, the majority of SLE patients with organ damage have scores of 0-3(2, 4, 9, 10), indicating the full range of the index is not being utilised .(11) Others have questioned the applicability of the SDI in pediatric SLE.(5, 12, 13) As a result of these issues, the SLICC, Lupus Foundation of America (LFA) and the ACR have embarked on a collaborative effort to develop a revised Damage Index. Using a measurement science

(clinimetric) approach, the steps to developing an index include defining the construct to be measured, item generation, item reduction, item weighting and threshold identification, refinement and validation.(14, 15) This rigourous methodologic approach has been succesfully applied across rheumatic diseases.(16, 17)

The objective of this first phase of index development was to evaluate the current concept of damage in SLE. By establishing a contemporary definition of disease damage we aim to develop the conceptual framework, i.e. a model representing the relationships between the factors and the construct to be measured, as the basis for the delopment of a revised SLE Damage Index.(18)

MATERIAL AND METHODS

Study design. We conducted a cross-sectional qualitative study using a content analytic approach to evaluate the current construct underlying the concept of damage in SLE. A consensus meeting using nominal group technique (NGT)(19) was conducted to achieve agreement on aspects of the conceptual framework and scope of the revised damage index.

Sample. Stakeholders were purposively sampled to participate in a face-to-face meeting. Stakeholders included international adult and pediatric SLE experts (physicians, nurses), members of the partner organizations (SLICC, LFA and ACR), SLE researchers/coordinators, methodologists, and trainees. There is no consensus on the approriate sample size for a belief elicitation study.(20) Using central limit theorum, a minimum sample size of 30 is required to assume a normal distribution to the mean values of summarized data. This conservative approach provides a more robust sample size than usually recommended for content analytic studies.(21, 22)

Facilitated small groups. Participants met as a large group in a room with rectangular tables arranged in an open 'U' with a large computer screen at the open end of the 'U' formation.(23)

They were presented lectures on the historical concept of damage in SLE, development of the SDI, pediatric considerations in SLE damage assessment, and methodology of index development. The participants broke-out into 6 facilitated small groups of 5-8 people, ensuring that a specific geographic region was not overrepresented in each group. The facilitated small groups designated a note taker and reporter. Using a standardized template of open-ended questions, the facilitated small groups were asked: What are we measuring? What is damage in SLE? What are controversial aspects of defining damage?

Using a round-robin, semi-structured approach, two facilitators asked the reporters to share their findings with the larger group. The facilitators used probes (can you tell us more about that?) to encourage elaboration on comments. Note takers recorded comments at the level of each facilitated small group, while the facilitators transcribed comments at the large group level.

Analysis. Participant characteristics were summarized using descriptive statistics. Hsieh and Shannon's qualitative content analytic approach was used to analyze the facilitated small group data.(24) Independently, 2 reviewers read all the facilitated small group and large group notes repeatedly to achieve immersion and obtain a sense of the whole data set.(21, 25) The notes were re-read word by word to derive codes by first highlighting the exact words from the text that appear to capture key thoughts or concepts. The reviewers made notes of the initial analysis and created labels for codes that are reflective of the thoughts. The codes were organized into meaningful clusters. The results of the 2 independent analyses were compared. Disagreements were resolved by discussion and consensus. Conceptual links amongst the themes were used to develop an analytical thematic schema. A directed acyclic graph model was used to illustrate a unifying conceptual framework. Descriptive statistics were used to summarize the data.

Consensus meeting. A purposively sampled expert panel (n=9) was presented the original conceptual framework, the thematic clusters and conceptual framework for damage in SLE at a

virtual meeting. In round robin fashion, the panelists were presented thematic clusters one at a time. Using NGT, the panelists were asked to deliberate on each cluster. No interactive discussion occurred. After each panelist had the opportunity to speak, serial discussion was led by the moderator for clarification of points made. For each round of discussion, the first person to speak was different than in the previous round. All panelists had the opportunity to speak first and avoid the potential effect of strong personalities. All participants had an opportunity to contribute.(19) One week later, a second virtual NGT meeting was conducted to review and achieve consensus on the constructs and characteristics of the new conceptual framework underlying damage in SLE.

Research Triangulation. Consensus on the thematic clusters and conceptual framework were presented back to the entire group for review. This research triangulation enhances the credibility of the findings and ensures the analysis reflects the full breadth and depth of the data.(26)

RESULTS

Sample. There were fifty participants, 27 (54%) female, 23 (46% male); from 13 countries across Europe, North America, South America, Asia and Australia.

Thematic Clusters. Eight thematic clusters emerged regarding facets underlying the construct of damage in SLE: purpose, items, weighting, reversibility, impact, timeframe, attribution, and perspective.

Purpose. There was agreement that the SDI should measure morbidity in SLE, independent of disease activity or severity. It should be a discriminative index(27), primarily used for research purposes, and applicable for use in trials. The SDI could secondarily be an evaluative index(27) with the ability to predict mortality and better detect change over time if measured over an adequate period of follow-up. In the context of clinical trials, it was commented that trials of 6-12 month duration rarely demonstrate progression, with only open label extensions studies

over multiple years showing change. The current SDI does not detect change in short term studies, and so the revised SDI should only be used in short term studies if there are parts of the index that can reflect damage more quickly. Third, the existing SDI has also been used for covariate adjustment in regression analyses. Some experts expressed the view that the SDI should be applicable to clinical practice and could be used as an educational tool. The index should be feasible containing items that are accessible. Experts opined the current SDI is not always scored accurately. The revised index should have clear scoring instructions.

Consensus was achieved that the revised SDI should primarily be a discriminative index, meant for research purposes. Items under consideration to comprise the index should not be restricted at this phase of development, but items should be medically acceptable and feasible.

Items. Some items in the damage index were thought to be redundant, infrequently observed or inconsequential. Some experts called for the index to be simplified. Conversely, participants suggested adding new items such as obstetrical complications, thyroid disease, striae, sicca syndrome, infertility in men, inability to work and hyperlipidemia. Contemporary definitions are required for items such as pulmonary arterial hypertension, interstitial lung disease, renal impairment, osteoporotic fracture, cardiomyopathy, and stroke. For example, persistent proteinuria below the nephrotic range is predictive of a poor renal and overall prognosis.(28-32) From a pediatric viewpoint the SDI is missing items (e.g. growth restriction, delayed sexual maturation).(5) Compared to adults, some items occur infrequently in pediatric patients (e.g. pulmonary infarction) whereas other items occur more frequently (proteinuria, scarring alopecia, cognitive impairment, and muscle atrophy/weakness).(5)

Consensus was achieved to consider a broader range of potential items and evaluate contemporary definitions of items.

Weighting. Some participants suggested that the weighting of items should be re-evaluated. Perspective may influence weighting, for example pediatric versus adult, or patient versus

health provider. Weighting could be influenced by whether or not a given organ damage type has the propensity to clinically improve. Within a domain, related items may be weighted differently. Impact of damage items and weighting may vary by age and sex. Others suggested weighting does not improve the index, as this has been tested before.(12, 33) Some opined the prognostic importance of individual items is not reflected in the scores such that a cataract is weighted similarly as myocardial infarction. The relative weights of items may be different across age groups. Definitions of items may require an age adjustment.

Consensus was achieved to consider item weighting in the revised SDI and evaluate if weighting confers added value.

Reversibility. The notion of damage reversibility was proposed. Examples of delayed puberty, growth, and proteinuria, which later normalizes were discussed.(5) Similarly, renal transplant or cataract surgery would confer normalisation of function. The consensus opinion was that damage is not reversible but can improve or be surgically corrected. The expert view was that once damage is scored, the damage score should not improve even if function normalizes.

Impact. Some participants commented that the concept of damage should incorporate processes which have an impact on the patient, including quality of life, functional impairment, disability, psychosocial impact, and cost. Impact is also related to the life plan, e.g., avascular necrosis of the femoral head may impact a runner differently than a pianist. The relationship between damage and impacts on the patient are influenced by patient characteristics (e.g., occupation, age), patient preferences, intercurrent life events (e.g. Covid-19) and environmental factors (e.g. socio-economic status, urban/rural). Higher damage scores are associated with 10-year cumulative costs that are 9-fold higher than those with lower damage scores.(34)

However, experts agreed that including quality of life, functional impairment, disability, psychosocial impact, and cost into one damage measure is too large a scope. The experts came

to consensus that impact on the patient is an important but separate concept. It should not be incorporated in the damage index; but warrants separate measures.

Time frame. Participants questioned the time frame of 6-months that an item needs to be present to score in the index. Some experts felt that the 6-month threshold is arbitrary and based on clinical gestalt, and questioned if the 6-month interval should it be the same for all items. For example, in some patients 3-months of proteinuria can cause damage while others can have 3 years of inflammatory proteinuria without damage. The greater regenerative potential in children means that the 6-month item definitions may not always be relevant for long-term damage in that age-group.(13) The relationship of an item recurrence over time was considered. For example, nephron loss can occur with aging, with each episode of nephritis or with ongoing nephritis. Over time, each nephritis episode can compound the resultant damage.(35)

Consensus was achieved that time could be specified in the item definition. If possible, a consistent default time could be considered in the index as multiple time definitions may be impractical to implement.

***Attribution*.** In the original SDI, items occuring before a diagnosis were not included. For items occurring after the diagnosis of SLE, no attribution was deemed necessary. Some proposed that early events such as coronary artery disease on imaging or transient ischemic attacks should be considered. This may enhance the progression of the score over time reflecting the evaluative purpose of the instrument. Recent Danish registry data have demonstrated that co-morbidities are increased before SLE diagnosis.(36) Events occurring before a formal diagnosis of SLE were discussed, e.g. atherosclerotic events, splenectomy for immune thrombocytopenic purpura that subsequently evolved to SLE, placenta-mediated complications in pregnancies or antiphospholipid syndrome-related events (stroke, pulmonary embolism) prior to SLE diagnosis.(37) Using the date from the first SLE attributable symptom, as is done in systemic sclerosis trials, was proposed.

Experts commented that if we include items occurring *before* a diagnosis of SLE, some limits to what should be included were discussed. There were conflicting opinions on whether to attribute to SLE or not. Some felt attribution remains unnecessary. Others suggested that any damage prior to a diagnosis of SLE should have some 'walls' e.g., a time period or be attributable to a process linked to SLE. Some opined that an item should only be included if the physician considers that it is related to lupus.

The expert panel came to agreement that if damage occurs prior to a diagnosis of SLE, it should be attributable to SLE. Damage occurring after a diagnosis of SLE may be attributable to wider factors and attribution to SLE is not required.

Perspective. There has been no assessment of the SDI and individual damage items from both the patient and physician perspective. It is also possible that damage impact will be affected by the individual's age such as cataract at 30 years of age compared to the same pathology occurring at 65 years of age or older. The impact of damage on children may be perceived differently by pediatric patients and their parents rather than providers. It would be ideal to use the same SDI in children as they grow up to be adults. The revised index should take a life-course approach. There was agreement that the index should reflect the provider perspective as items such as avascular necrosis and osteoporosis are based on physician diagnosis. Patients and parents will likely value items differently than providers. For example, among pediatric patients, having good friends, being happy most days and achieving goals are deemed more important than being able to do desired activities.(38) Among patients and parents, medication side effects and pain were deemed more important than active joint count and disability score.(39) Conversely, physicians have the expertise to diagnose organ dysfunction and its physiologic consequences.

Consensus was achieved that the revised SDI will be developed from the physician perspective primarily and take a life course approach. Complementary indices could be developed to capture the impact of damage from the patient perspective.

Conceptual framework. Based on facilitated small group discussions, the NGT expert panel discussed the eight thematic clusters and came to consensus on a unifying contemporary conceptual framework of damage in SLE and scope of the revised Damage Index. Tables 1, 2, and Figure 2. The expert panel agreed on the concepts underlying the revised damage index moving forward. The SDI is a measure of morbidity in SLE, independent of disease activity or impact on the patient, but related to mortality. It is an evaluative index primarily intended for research purposes and should take a life course approach. Damage can occur before a diagnosis of SLE, but if so, it should be attributable to SLE. Damage to an organ is irreversible but the functional consequences on that organ may improve over time through physiological adaptation or treatment. The concept of damage is comprised of a number of different constructs, all of which are determinants of damage. Damage can impact the patient, is influenced by individual patient characteristics, patient preferences and environmental factors. This unifying conceptual framework and scope of the new index was reviewed by and supported by the entire group. The entire group also agreed that damage can be accrued prior to the diagnosis of SLE but did not come to agreement on how to operationalize this for a new damage index. In contrast, experts agreed that impact on the patient was beyond the scope of one damage index and warrant separate indices. Similarly, a damage index weighted from the patient perspective and/or a damage index for use in administrative data are warranted, as separate endeavours. Some individuals expressed concerns regarding differential weighting of items.

DISCUSSION

We have developed a contemporary and expanded conceptual framework for damage in SLE that integrates purpose, items, weighting, reversibility, impact, timeframe, attribution, and perspective. Damage is a health state related to organ structure and function. The degree of reduced organ function relates to physiologic impairment. Damage can occur before a diagnosis of SLE but should be attributable to SLE. Damage to an organ is irreversible but the functional consequences on that organ may improve over time through physiological adaptation or treatment. The revised SDI will be an discriminative index(27) to measure morbidity in SLE, independent of activity or impact on the patient, but related to mortality. The SDI is primarily intended for research purposes and should take a life course approach. As it is not feasible for

one index to encompass the whole framework, consensus was achieved on the scope of the revised index. This theory-informed framework is an important first step as the SLICC, LFA and ACR revise the lupus Damage Index.

The original purpose of the SDI, to measure morbidity in SLE, distinct from disease activity continues to hold true. There is agreement that damage is the result of cumulative insults. Consensus was achieved that the damage index is primarily a discriminative index, meant for research purposes, applicable across the life span. This purpose should be balanced by items that are medically acceptable and feasible. However, the index may be secondarily used in general clinical practice, as an educational tool or as an evaluative index. For its wider use in the community, trade-offs between technological advancement versus feasibility will need to be considered. These trade-offs may have implications for sensitivity and specificity. Further, these trade-offs will have implications for use of the new index in emerging nations where access to healthcare is subject to significant financial strictures. The consensus opinion was not to restrict potential items at this phase. Once the primary index is developed, a simplified index for wide-spread use could be explored.

Areas that require further investigation in the next phases in damage index development include item weighting and attribution. The weighting of items was a concept with conflicting opinions. In the SDI items are weighted equally, with the exception of end stage renal disease which confers 3-times the weight, and some items that can be double counted if they recur. Development of SLE classification criteria found that experts weigh disease manifestations, autoantibodies and complement proteins differentially.(19, 40-42) However, another study reported the ability to detect the relationship between the score and mortality was not enhanced by the use of a weighted score.(33) Furthermore, in a study using Rasch analysis, a weighted SDI was more difficult to apply and did not improve the index.(12) Moving forward, data driven methods will be needed to ascertain if differentially weighted items confer added value.

A second area of additional discussion related to time and attribution. The question of attribution may be difficult. Might for example, a cataract be due to steroid treatment, concomitant diabetes or related to one or both parents having cataracts i.e. genetics? Experts agreed to remove time from the construct. Originally, the requirement for an item to be present for 6-months was intended to differentiate damage from inflammation. It is now proposed that a time constraint could be added to the definition of each item. In that context, there may however be a need for a default time-period for simplicity and exceptions to this being defined based on best evidence. Experts agreed with the concept that damage does not have to occur after the diagnosis of SLE in order to be scored. The time of diagnosis of SLE can be confounded by access to care or by the use of alternative, but related, diagnoses such as undifferentiated autoimmune rheumatic disease, pre-lupus etc. Experts agreed that damage can be accrued prior to the diagnosis of SLE but in this specific context, damage should be attributable to SLE. Further work is needed into how to operationalize the time when an item occurs and its relation to diagnosis of SLE. Next steps may include operationalizing attribution on an item-by-item basis or using a broad criterion such as including damage items occurring after the first SLE manifestation regardless of attribution. These future deliberations will need to be balanced against adding undue complexity to the index.

Impact on the patient, including health-related quality of life, functional impairment, disability, psychosocial impact, and cost were all thought to be part of the conceptual framework of damage in SLE. However, the experts agreed that including these concepts was beyond the scope of a single damage index. There was also substantial interest in the applicability of the SDI to pediatric SLE patients and was considered across many of the thematic clusters. The purpose of the SDI in pediatrics should be the same as in adult patients. However different items and/or definitions may need to be incorporated. The weighting of items and impact on pediatric patients may be different than among adults and warrants further evaluation. An innovative solution is to consider a ‘network of measures’ that encompass a variety of perspectives and concepts, particularly when trying to measure a complex construct such as damage.

Strengths of this study are the contribution of international SLE experts and use of both qualitative and consensus methods. This study design explores a complex and nuanced phenomenon; and facilitates contribution from all the participants rather than an individual expert, in a formalized manner.(23, 43) This methodology allows for the incorporation of a spectrum of experience and knowledge. It stimulates constructive debate, while reducing the potential bias of an influential opinion, and is best suited for topics where there is insufficient evidence.(23, 25) Our triangulation of the content analysis from facilitated small groups, presentation of the results for review to the expert panel and then back to the whole group supports the validity of our findings.

In summary, we have identified shifts in the paradigm of damage in SLE and developed a unifying conceptual framework. These data form the groundwork for the next phases of damage index development.

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Table 1. Comparison of characteristics of the original SLICC/ACR Damage Index, facilitated small group concepts and final consensus.

Characteristic	Original SDI	Facilitated small Group Concepts	Nominal Group Consensus
Purpose	Discriminative index	Discriminative index Evaluative index	Discriminative index
Items	NA	Redundant Inconsequential Infrequent Pediatric, Obstetric Comorbidity	Contemporary definitions Consider new items
	Ascertained by clinical assessment	Ascertained by imaging, diagnostic testing, patient reported outcomes	Define the method of assessment for each item
Weighting	No weighting	Consider weighting by perspective, age, ability to improve	Consider weighting Evaluate added value
Reversibility	Non-reversible change, not related to inflammation	Some damage items may be reversible	Damage to an organ is irreversible but the functional consequences on that organ may improve over time through physiological adaptation or treatment Do not lose points for improvement
Impact	NA	Disability HR-QoL Cost Duration of damage are part of the concept of damage	Effect on the patient (HR-QoL, cost, disability) is a separate but related concept
Time Frame	Items are present for at least 6 months unless otherwise stated	Less time More time	Specify time in item definition

	Occurring since the diagnosis of lupus	Damage may occur before SLE diagnosis	Can accrue damage before diagnosis
Attribution	Damage may result from SLE Atherosclerosis Hypercoagulability Therapy for SLE Other comorbid conditions Not attributable to SLE disease activity Duration of treatment Disability	Pre-clinical events Pregnancy events	In established SLE, attribution of damage items is not required Damage items occurring before SLE diagnosis should be attributable to SLE
Perspective	Physicians treating adult patients	Physicians Adult patients Pediatric patients Parents of pediatric patients	Physician perspective primarily, life course approach Develop other indices for patient perspective

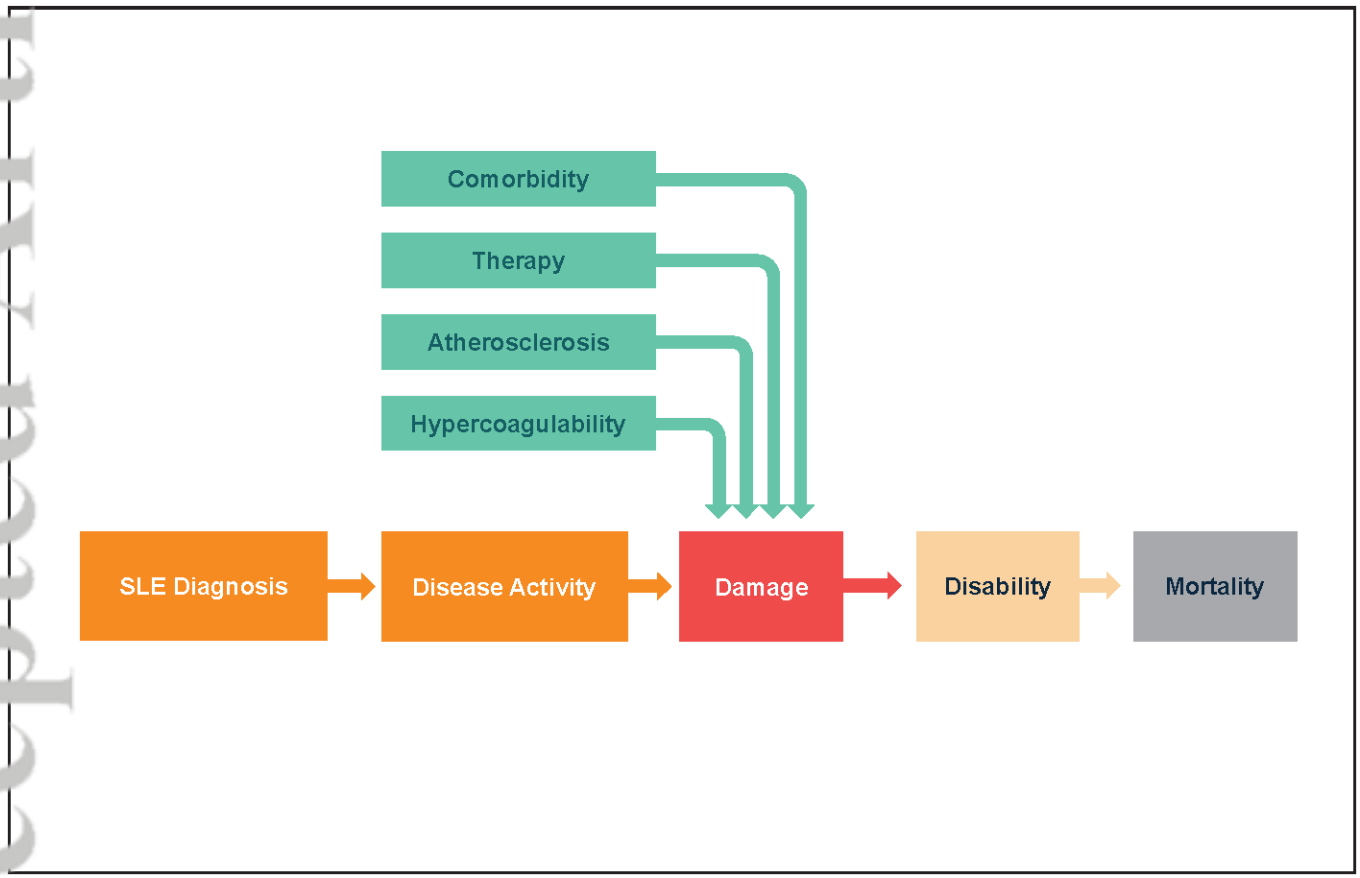
HR-QoL Health Related Quality of Life

Table 2. Synthesis of original and revised construct underpinning the SDI

SDI	Construct
Original SDI	Non-reversible change, not related to inflammation, occurring since the diagnosis of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Damage may be a consequence of disease activity, therapy, intercurrent illness or an unrelated event
New SDI	The SDI is a measure of morbidity in SLE, independent of disease activity or impact on the patient, but related to mortality. It is an evaluative index primarily intended for research purposes and should take a life course approach. Damage can occur before a diagnosis of SLE, but if so, it should be attributable to SLE. Damage to an organ is irreversible but the functional consequences on that organ may improve over time through physiological adaptation or treatment.

Figure 1. Original conceptual framework of damage in SLE

Figure 2. Contemporary conceptual framework of damage in SLE.
Note: This expanded conceptual framework specifically delineates impacts on the patient (quality of life, functional impairment, disability, psychosocial impact, and cost) that may have previously been included under the term morbidity, as well as other determinants of damage (age, race). This illustration clearly demonstrates many facets that comprise damage in SLE and visually assists in clearly demarcating what is both within and beyond the scope of a new damage index. The other facets of damage may be captured with other measures, together forming a network of related indices.



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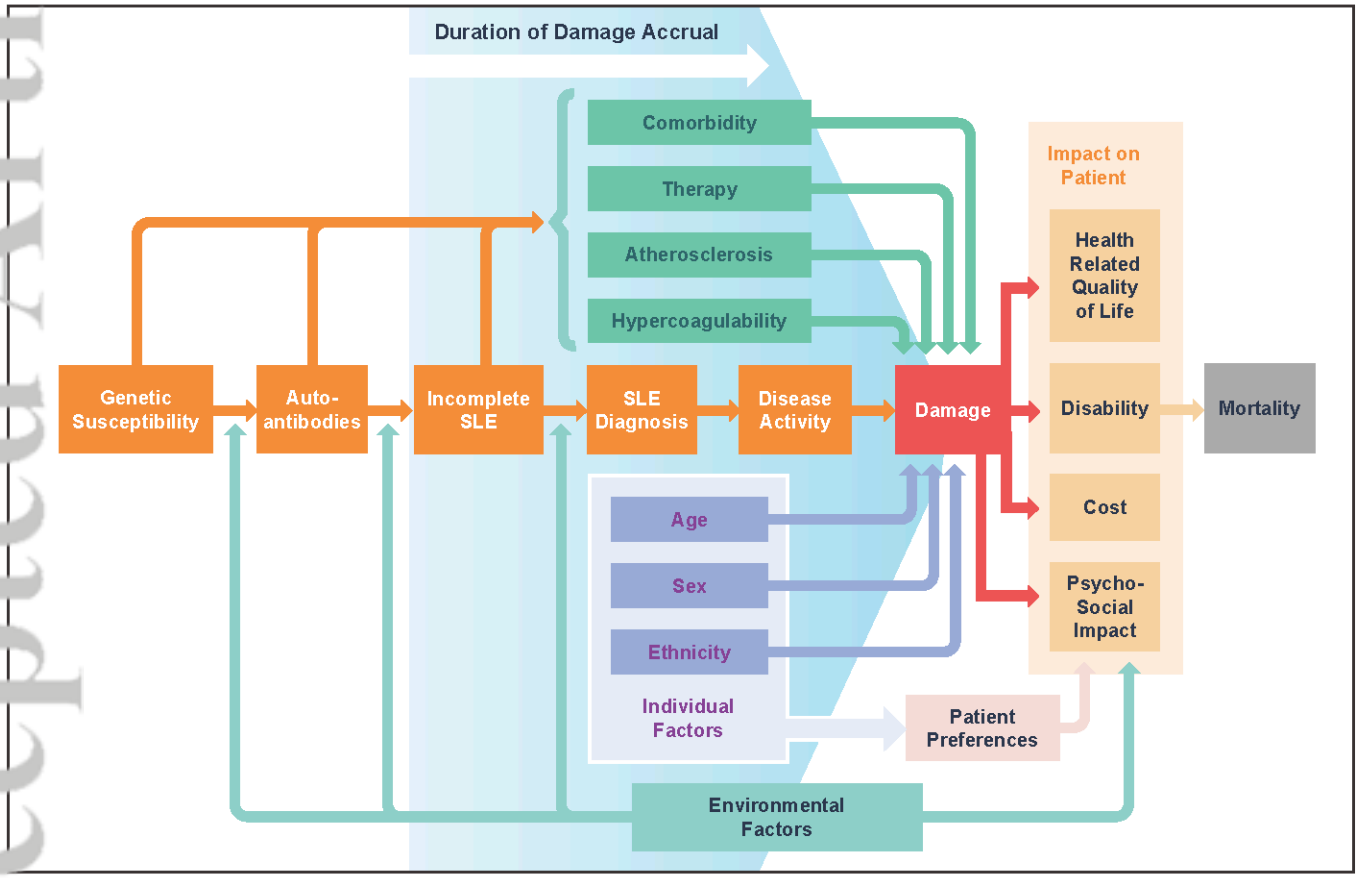

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