The Sjögren’s Syndrome Damage Index—a damage index for use in clinical trials and observational studies in primary Sjögren’s syndrome

R. J. Barry\(^1\), N. Sutcliffe\(^2\), D. A. Isenberg\(^3\), E. Price\(^4\), F. Goldblatt\(^3\), M. Adler\(^3\), A. Canavan\(^4\), J. Hamburger\(^5\), A. Richards\(^5\), M. Regan\(^6\), K. Gadsby\(^6\), S. Rigby\(^7\), A. Jones\(^8\), R. Mathew\(^8\), D. Mulherin\(^9\), A. Stevenson\(^9\), P. Nightingale\(^10\), S. Rauz\(^1\) and S. J. Bowman\(^11\)

Objective. To validate a tool for assessment of accumulated damage in patients with Primary SS (PSS).

Methods. Of the total 114 patients fulfilling American–European Consensus Group (AECG) criteria for PSS 104 were included in the study and assessed by rheumatologists at \(T\) (time) = 0 months and \(T = 12\) months. On each occasion, damage and activity data, and autoantibody status were collected. SF-36 and Profile of Fatigue and Discomfort-Sicca Symptoms Inventory (PROFAD-SSI) questionnaires were completed. Cross-sectional analysis of this data was subject to a process of expert validation by 11 ophthalmologists, 14 oral medicine specialists and 8 rheumatologists. Items were removed from the index if \(\geq 50\%\) of respondents recommended exclusion. Statistical validation was performed on remaining items. Spearman’s rank analysis was used to investigate associations between damage scores and other disease status measures and Wilcoxon matched-pair analysis to assess sensitivity to change in the damage score.

Results. Based on the expert validation, a 29-item damage score was agreed incorporating ocular, oral and systemic domains. Total damage score correlated with disease duration at study entry \((r = 0.436; P < 0.001)\), physical function as measured by SF-36 \((r = 0.250, T = 0\) months; \(r = 0.261, T = 12\) months) and activity as measured by the Sjögren’s Systemic Clinical Activity Index \((r = 0.213, T = 0\) months; \(r = 0.215, T = 12\) months). Ocular damage score correlated with the ‘eye dry’ domain of PROFAD-SSI \((r = 0.228, T = 0\) months; \(r = 0.365, T = 12\) months). Other associations not present on both assessments were considered clinically insignificant. On Wilcoxon analysis, the index was sensitive to change over 12 months \((z = –3.262; P < 0.01)\).

Conclusion. This study begins validation of a tool for collection of longitudinal damage data in PSS. We recommend further trial in both the experimental and clinical environment.

Key words: Sjögren’s syndrome, Damage measure, Clinical trials, Validation.

Introduction

Primary SS (PSS) is an immune-mediated CTD, with characteristic inflammation of the exocrine glands leading to dryness of mucosal surfaces. This most often manifests as dryness (sicca) symptoms affecting the eyes and mouth [1]. Up to 20% of patients, however, will display systemic or extra-glandular features including inflammatory arthritis, neurological, cutaneous, haematological or pulmonary involvement [2, 3]. Despite there being an \(\sim 40\)-fold increase in the risk of B-cell lymphoma in patients with PSS [4], mortality due to the disease process is otherwise rare, with most patients displaying a relatively stable and benign clinical picture [5, 6].

The natural history of CTDs is typified by periods of disease inactivity, punctuated by spontaneous ‘flares’. These ‘flares’ may show a variable resolution, either spontaneously or under the influence of a therapeutic intervention, or may persist resulting in permanent damage to the affected organ or tissue. This distinction between ‘activity’ (reversible) and ‘damage’ (irreversible) has become increasingly important in the assessment of clinical disease status [7].

In order to gauge accurately the efficacy (and thus justify the utilization) of new, and expensive biological therapies—such as anti-TNF medication that has revolutionized the treatment of severe RA—it is important to have objective measures of both disease activity and disease damage [7, 8]. Such indices have already been successfully validated and are widely employed for assessment of patients with both RA and SLE [9–13] but are only recently being developed for use in PSS [14, 15]. We have recently published an activity index for use in PSS [the Sjögren’s Systemic Clinical Activity Index (SCAI)] [14]. The analysis described in this manuscript sets out our data from the same UK cohort, in order to develop a tool for longitudinal assessment of accumulated damage in patients with PSS, for use in both experimental trials and clinical assessment.

Methods

The demographic details of the participants have previously been published [14] and are similar to other published cohorts. In brief, 114 female patients with PSS fulfilling American–European Consensus Group (AECG) criteria [16] were recruited between April 2003 and June 2005 from eight UK hospitals and data from 104 of these was deemed suitable for inclusion in the study. The multi-centre Research Ethics Committee (MREC) granted the study ethical approval and written informed consent was gained from all patients. Twenty-five patients had previously participated in studies to develop the Profile of Fatigue and Discomfort-Sicca Symptoms Inventory (PROFAD-SSI) [8, 17].

Participants were reviewed by a rheumatologist on two occasions \([T\) (time) = 0 months and \(T = 12\) months] and damage data collected. On these two occasions the BDI, PROFAD-SSI, SF-36 and SCAI were also completed for each participant.

Blood was collected for measurement of routine biochemical, haematological and immunological tests at both time-points.
A serum sample was also stored at −20°C until analysis of anti-SSA/Ro and anti-SSB/La antibody titres could be performed at the University of Birmingham Clinical Immunology Laboratories using a standard validated ELISA.

**Instrument development**

A draft damage index was derived in 2000 (based generally on the SLICC damage index as validated for SLE) and further revised by the authors of this study [7]. Damage items were grouped into ocular, oral and systemic domains. The systemic domain was further sub-classified into neurological, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, endocrine and malignancy sub-domains.

Damage data at $T = 0$ and $T = 12$ months was collected for each participant using this index. A score of 1 was allocated to each item detected on clinical examination, and no weighting of scores was applied. Damage items were deemed ‘present’ only if persistent for at least 6 months, and if the assessing clinician considered the feature directly attributable to either the pathophysiology or treatment of PSS. Cross-sectional analysis of damage accumulated at each visit was performed on this data.

Following data collection the index and preliminary cross-sectional data were sent to a cohort of experts in the fields of ophthalmology (specifically those with a specialist interest in corneal and external disease), oral medicine and rheumatology for further validation. Respondents were asked to comment on the damage summaries as presented, and in particular were asked to indicate as to which individual items were appropriate for inclusion in an index of damage for use in PSS, and which items should be excluded.

Items were subsequently removed from the damage index if exclusion was recommended by ≥50% of respondents in any of the specialty groups.

**Statistical analysis**

All statistical analyses were performed using the revised damage index scores resulting from the process of expert validation. Data was initially entered into a Microsoft Excel spreadsheet before being transferred to SPSS v15.0 [18] for further analysis.

Spearman correlation analysis was used to assess the strength of correlations between damage scores and demographic variables, SF-36 domain scores, PROFAD domain scores, BDI total score and the SCAI total score. We also evaluated the correlations between the damage scores and a modified version of the SCAI activity index (‘Modified SCAI’), which retains the ‘objective’ components but excludes a number of more ‘subjective’ symptom items (fatigue, myalgia, Raynaud’s syndrome, shortness of breath and pleuroperticardial pain), which are not scored in this version. Wilcoxon matched-pair analysis was used to assess sensitivity to change within the damage scores over the 12-month observation period.

**Results**

**Sample demographics**

Cross-sectional data was available for 104 patients. All participants were females. All except five participants were Caucasian. Median age at study entry was 56.5 yrs (range 25–82 yrs, interquartile range 52–66 yrs) and median time since diagnosis of PSS was 9 yrs (range 0–38 yrs, interquartile range 6–14.75 yrs). The median age of study participants at diagnosis of PSS was 47.5 yrs (range 18–76 yrs, interquartile range 37.25–57.75 yrs).

Anti-Ro antibodies were detected in 79% of study participants, and anti-La antibodies were present in 59%. Eighty-one percent were positive for ANAs and 59% were RF positive. Sixty-two percent of study participants had a positive labial gland biopsy, 53% had raised IgG, 3% had a paraprotein and 20% had a low complement C4 on at least one occasion during the study period.

At study entry, 58% of study participants were documented as having a mean unstimulated salivary flow rate of 0 ml/15 min, and 35% had a Schirmer-I result of 0 mm/5 min in each eye.

**Damage items**

Ocular and oral damage data were available for 87 (84%) patients at study entry, of which complete follow-up data at 12 months was available for 78 (75%). Systemic damage data were available for all 104 patients at study entry, of which complete follow-up data was available for 94 (90%). There was no statistically significant difference with regard to demographic factors between those patients lost to follow-up and those with data available for analysis at the end of the study period.

All data presented from this point onwards is based on those participants for whom complete follow-up is available at 12 months.

**Preliminary damage item frequencies**

The preliminary damage items included in the data-collection phase and their response frequencies are set out in Table 1 (oral and ocular) and Table 2 (systemic features).

Forty-four patients (56%) displayed at least one item of ocular damage at study entry (median score 0, interquartile range 0–1). 47.5 yrs (range 18–76 yrs, interquartile range 37.25–57.75 yrs).

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<table>
<thead>
<tr>
<th>Damage Domain</th>
<th>Patients with damage item at $T = 0$ months</th>
<th>Patients with damage item at $T = 12$ months</th>
<th>No. of patients with resolution of damage item over 12 months</th>
<th>No. of patients with new occurrence of damage item over 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular Domain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal scarring</td>
<td>7 (8.97)</td>
<td>9 (11.54)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Tear duct surgery* (punctal plugs or cautery)</td>
<td>27 (34.62)</td>
<td>32 (41.03)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Tear duct surgery* (punctal plugs or cautery)</td>
<td>19 (24.36)</td>
<td>24 (30.77)</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Cataract*</td>
<td>6 (7.69)</td>
<td>6 (7.69)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retinal change*</td>
<td>4 (5.13)</td>
<td>4 (5.13)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic blepharitis</td>
<td>6 (7.69)</td>
<td>7 (8.97)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Oral Domain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caries</td>
<td>27 (34.62)</td>
<td>27 (34.62)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Teeth loss</td>
<td>28 (35.90)</td>
<td>31 (39.74)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Salivary gland swelling</td>
<td>11 (14.10)</td>
<td>13 (16.67)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unstimulated salivary flow 0 ml/15 min</td>
<td>45 (57.69)</td>
<td>90 (44.10)</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Oral infection</td>
<td>9 (11.54)</td>
<td>8 (10.26)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Parotid surgery</td>
<td>8 (10.26)</td>
<td>8 (10.26)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gum disease</td>
<td>10 (12.82)</td>
<td>8 (10.26)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Oral ulceration</td>
<td>16 (20.51)</td>
<td>18 (23.08)</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>11 (14.10)</td>
<td>12 (15.38)</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*Whilst recorded as a single item in our data, a distinction should be made between punctal plugs and punctal cautery in future indices. **Item to be recorded but not scored. Items in bold removed from preliminary damage index after process of expert validation.
This had risen to 50 patients (64%) after 12 months (median score 1, interquartile range 0–1). Examining our cohort as a whole, each item of ocular damage registered an increase over the period of observation with the exception of cataract and retinal change, both of which remained constant. Some reversibility was observed in individual participants for the presence of chronic blepharitis and occurrence of a Schirmer-I test result of 0 mm/5 min bilaterally.

Sixty-one patients (78%) displayed at least one item of oral damage at study entry (median score 1, interquartile range 1–2). This had risen to 67 patients (86%) after 12 months (median score 1, interquartile range 1–2). Again, most items of oral damage increased in frequency over the observation period with the exception of parotid surgery, which remained constant, and infections and gum disease, which decreased in frequency of detection. Some reversibility was observed in individual patients for the unstimulated salivary flow rate result, presence of caries, oral ulcers and dysphonia.

Sixty-seven patients (71%) registered at least one item of systemic damage at study entry (median score 2, interquartile range 1–4). This had risen to 69 patients (73%) after 12 months (median score 2.5, interquartile range 1–4). No reversibility was observed in any systemic damage item; however, many of the proposed items remained undetected in all patients by the end of the period of observation.

**Expert validation**

The data as described above and set out in Tables 1 and 2 was presented to 11 ophthalmologists with a specialist interest in corneal and external disease, 14 oral medicine specialists and 8 general rheumatologists. Their comments are summarized subsequently:

**Ophthalmologists.** Both corneal scarring and previous tear duct surgery were deemed useful surrogate markers of damage...
consequent to long-term ocular dryness. When documenting the occurrence of tear duct surgery in future indices it was suggested that a distinction should be made between punctal plugging and punctal cautery: plugging is less invasive and is thus likely to be employed before cautery, and may therefore be considered to represent a less severe degree of ocular damage. Whilst the Schirmer-I result showed some intra-patient variability, most ophthalmologists (72%) considered a score of 0 mm/5 min without the use of anaesthetic in both eyes, an appropriate indicator of ‘damage’. Many of the ophthalmologists commented that a separate, absolute score for each eye is of more use clinically. This data is likely to be recorded in any event. A value above 0 mm/5 min in either eye indicates some residual function and may be a more useful indicator of potential reversibility. Conversely, most ophthalmologists (72%) commented that retinal change and cataract were unsuitable for inclusion in the index, as neither of these items were felt causally related to the presence of PSS. It was, however, concluded that both are important comorbidities, which should be recorded (but not scored) to allow accurate interpretation of other disease-related ocular findings. Chronic blepharitis was felt not to be directly related to damage in PSS as well as felt to be potentially reversible (55% suggested removal from damage index).

Oral medicine specialists. Caries and teeth loss were considered important, although many respondents commented that data regarding the number of decayed, missing or filled teeth (DMF score) would be of more clinical value (although this would require specialist evaluation). Our data suggests that four study participants experienced ‘resolution’ of their caries over the period of observation. This is highly unlikely to have occurred; a carious tooth may be removed or filled, but in these instances should still register a score in the damage index. This inconsistency may be addressed by the incorporation of DMF scores as suggested by many of the oral medicine specialists. This information, however, may be difficult to convert to a cumulative score of oral damage and would be difficult for rheumatologists to record in a routine setting. Greater attention will, therefore, be needed to be paid to ensure accurate data recording of caries in practice. Ninety-three percent of oral medicine specialists suggested removal of gum disease, oral ulceration and dysphonia from the damage index, with most citing a lack of evidence to link either gum disease or dysphonia to PSS, and many commenting on the multifactorial aetiology of oral ulceration. Similarly, both the occurrence of parotid gland surgery and oral infection were considered too multifactorial for use in a disease-specific damage index.

Salivary gland swelling was deemed to be a useful indicator of damage if persistent (by definition, a damage item must be present for at least 6 months before it is registered in our index) and was recommended for inclusion by 86% of respondents, and whilst the unstimulated salivary flow rate was noted to display a degree of variability, 64% of respondents thought it a useful item to record in a damage index. Due to the highly subjective nature of this measure, it was decided that unstimulated salivary flow should be recorded simply as a score of 0 if undetectable or 1 if ≥0 ml/15 min.

Rheumatologists. The major changes to the systemic index were suggested in the cardiovascular, gastrointestinal and endocrine domains, with respondents commenting on the lack of evidence linking these items to the pathophysiology of PSS. Due to their autoimmune aetiology, coeliac disease, hypothyroidism and primary biliary cirrhosis were considered useful comorbidities to record as part of the clinical record or a research study proforma, but not to include or score in the damage index. Similarly, OA was considered an important yet unrelated comorbidity, which should be recorded if present. Osteoporosis and avascular necrosis were recommended for inclusion as a result of their association with steroid therapy, and not due to a direct link with PSS, and again may therefore be useful to record but not include in an overall score.

Further to these comments items were removed from the preliminary damage index as highlighted in Tables 1 and 2. The remaining items form the revised damage index as evaluated subsequently.

Statistical validation
All statistical analyses were performed using the revised damage index scores resulting from the process of expert validation. Spearman correlation analysis revealed a statistically significant association between disease duration at study entry and ocular damage score \( \rho = 0.351; P = 0.001 \), oral damage score \( \rho = 0.308; P = 0.004 \), systemic damage score \( \rho = 0.296; P = 0.002 \) and total damage score \( \rho = 0.436; P < 0.001 \) at study entry. No correlation was observed between age at diagnosis and damage score at study entry.

There was no correlation between damage scores and the presence of autoantibodies at study entry.

Spearman correlation analysis of the association between damage totals and domain scores for PROFAD-SSI, SF-36, BDI and SCAI measures are illustrated in Table 3. Statistically significant but weak associations were observed throughout the data; however, the majority were not consistently present at 0 and 12 months, and these were therefore deemed clinically insignificant. Consistent modest correlations were seen between the ocular domain of the damage index and the ‘eye dry’ domain of the PROFAD-SSI (\( \rho = 0.228 \) and \( 0.365 \), respectively), and between the total damage index score and the physical functioning domain of SF-36 (\( \rho = -0.25 \) and \( -0.261 \), respectively).

A consistent association was observed between the SCAI total score and the damage index total score (\( \rho = 0.271 \) and \( 0.301 \), respectively) and with the systemic damage domain total score (\( \rho = 0.213 \) and \( 0.215 \), respectively) but not with either the ocular or oral damage domains. There were no consistent associations between the ‘Modified SCAI’ score and any of the damage domains (data not shown).

The systemic damage score correlated with the ‘skin dry’ domain of the PROFAD questionnaire at both visits. The clinical significance of this is unclear.

Statistically significant (\( P < 0.01 \)) but weak correlations were seen between the oral and ocular domain scores both at \( T = 0 \) and \( T = 12 \) months (\( \rho = 0.315 \) and \( 0.251 \), respectively) and the oral and systemic domain scores (\( \rho = 0.265 \) and \( 0.228 \), respectively) but not between the systemic and ocular domain scores (\( \rho = 0.098 \) and \( 0.92 \), respectively). The oral domain scores correlated most closely with the total damage score (systemic + oral + ocular) (\( \rho = 0.874 \) and \( 0.840 \)) followed by the ocular domain scores (\( \rho = 0.649 \) and \( 0.629 \)) and systemic domain scores (\( \rho = 0.466 \) and \( 0.478 \)). These findings are simply likely to reflect the frequency of positive scores within each domain of the revised damage index: at \( T = 0 \) months, 74.3% of patients had an oral damage score of \( \geq 0 \) (range 1–4), 44.6% had an ocular damage score of \( \geq 0 \) (range 1–3), but only 14.9% had a systemic damage score of \( \geq 0 \) (range 1–3). At \( T = 12 \) months, the figures are 78.4, 55.4 and 17.6% respectively. No obvious ‘cut-off’ was seen for any of the domain scores, which demonstrated normal or ‘skewed-normal’ distribution patterns (data not shown).

Wilcoxon matched-pair analysis comparing damage scores at 0 and 12 months revealed a statistically significant difference between the ocular domain (\( z = -2.814; P = 0.001 \)), oral domain (\( z = -2.055; P = 0.05 \)) and total damage score (\( z = -3.262; P < 0.01 \)). The difference in systemic domain scores came close to, but did not achieve statistical significance at the level of \( P < 0.05 \) (\( z = -1.890; P = 0.059 \)).
Discussion

We have successfully piloted a disease-specific damage index for use in the longitudinal assessment of patients with PSS. Since it was first proposed in 2000 [7], the index has been subject to a lengthy process of refinement involving both appraisal by specialists in the fields of ophthalmology, oral medicine and rheumatology, and a comprehensive statistical validation.

This index provides a three-domain assessment of patients with PSS, suitable for use in both a specialist and non-specialist clinical setting. As such, it is perhaps most useful if considered as three separate rating scales (ocular, oral and systemic damage). This proposal is supported by the weak correlations between the three domain scores. Nevertheless, there may be situations where an empirical ‘total damage’ score may be useful, albeit interpreted with caution.

Our sample of 104 patients is similar to other cohorts in terms of baseline demographics and disease features [1], and once again exemplifies the relatively benign course of disease progression in PSS with a low incidence of extra-glandular manifestations in a 12-month period [5, 6]. Despite this, our Wilcoxon analysis has proven our index to be sensitive to change over a 12-month period of observation, and as a result we believe it is thus able to detect incident damage.

The Spearman correlation analysis supports the hypothesis that the index is measuring clinically detectable change related to accumulated damage: a correlation is observed between damage scores and time since diagnosis at study entry.

In general, there were few associations between the damage scores and other measures of disease status, and this reflects the findings of several earlier studies [19, 20]. Scattered associations were observed throughout the data; however, only those consistently present on both assessments were considered to be clinically significant.

Those correlations that were observed, can largely be explained on clinical grounds; a modest association between ocular damage and the ‘eye dry’ domain of the PROFAD-SSI questionnaire is expected, as impaired tear production is the initial event in each of our three recorded items of ocular damage. Similarly, an association between the damage score and the ‘physical functioning’ domain of SF-36 is not unreasonable, as accumulated damage equates to impairment of normal function in the organs or tissues concerned, and this will likely have an impact on global function for the patient.

A modest statistical association is observed between the SCAI disease activity score and the systemic (ρ = 0.213 and 0.215, respectively) and total (ρ = 0.213 and 0.301, respectively) damage scores but not consistently with the ocular or oral damage scores. The ‘Modified SCAI’ that excluded most patient-reported symptom components such as fatigue, etc. had no consistent associations with any of the damage scores. These findings are compatible with previous data in both PSS and SLE; whilst levels of disease activity can predict subsequent accumulation of long-term damage in the future, the relationship is complex and is not typically present in analyses of data at a single time-point (15, 19, 20). We can conclude, therefore, that the Sjögren’s Syndrome Damage Index damage index is measuring systemic disease status in a different way to disease activity as measured by the SCAI.

Vitali et al. [15] recently published a damage index for use in the longitudinal assessment of patients with PSS. To our knowledge, this is the only other damage index currently proposed for use in PSS. Their methodology differed significantly to ours, with data collected over a shorter, 3-month period, and validation occurring through comparison of damage scores with a gold standard of ‘physician global assessment’ (PhGA). We used a collective approach to ‘expert validation’ whereas the PhGA is based on individual expert judgement and our approach offers an alternative means to validate a damage index using an independent cohort of patients.

Despite these differences in approach, our final damage index bears a strong resemblance to that generated by Vitali et al., with most items common to both indices. We have, however, retained an additional number of uncommon but well-recognized cardiovascular, gastrointestinal and musculoskeletal items in our index as well as proposing that a number of non-scored comorbidity items are recorded alongside the damage index.

One objective of our study is that although in an ideal setting we would recommend requesting the input of ophthalmologists, oral medicine specialists and rheumatologists, with each collecting the data relevant to their area of specialist training, it should be possible for non-specialists to complete the damage index. Most of our data was collected by rheumatologists, often without access to specialist examination equipment (such as slit-lamps), and as a result some ocular and oral damage items were self-reported by
the study participants and verified through cross-examination of medical records. To ensure accurate use of this index in clinical trials/clinical practice such instances should be clearly identified. We have demonstrated, however, that the index can be used pragmatically in a non-specialist setting with reasonable accuracy.

Strict definitions for many of the individual damage items were not clarified prior to this study. Clinicians were asked to score items based on their own experience and usual clinical diagnostic criteria. As a result we cannot exclude a certain degree of inter-rater variability vis-à-vis the scoring, and this is perhaps an area for consolidation in future work.

As with Vitali et al. [15] our damage index was developed in a single national cohort, and thus may not completely cover the wide spectrum of PSS. The similarity of the resulting measures, however, is encouraging. Ultimately, this and all other potential limitations can only be addressed through further experimental trials of these indices in the clinical environment, on a multi-national basis, by different groups of investigators on different cohorts of patients.

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