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Relationship and probabilistic stratification of EASI and oSCORAD severity scores for atopic dermatitis

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To the Editor,

The Harmonizing Outcome Measures for Eczema (HOME) recommended the Eczema Area and Severity Index (EASI) as the core outcome instrument for measuring the clinical signs of atopic dermatitis (AD)¹. However, EASI may not have been used in previous clinical trials, and other scores, e.g. SCORAD (SCORing Atopic Dermatitis), the objective component of SCORAD (oSCORAD) and the Investigator Global Assessment (IGA), remain widely used. It is useful to establish a method to convert these scores into EASI to compare the results from different studies effectively. Indeed, EASI and oSCORAD have been found to be strongly correlated ($r_{\text{Spearman}} = 0.92$)⁷, suggesting a possibility to find a relationship between the two scores.

We analysed the raw data from an already published study that assessed multiple AD severity scores (SCORAD, oSCORAD, EASI and IGA) for each of 43 adults AD patients at weeks 0, 2, 4, 8, 12 and 24 of a systemic therapy⁵ (238 observations in total). Our data analysis confirmed that SCORAD, oSCORAD, EASI and IGA are strongly (Spearman) correlated and their relationship could be described as a monotonic function (Figure 1A).

We first derived a relationship between EASI and oSCORAD, while discarding SCORAD, as SCORAD is similar to oSCORAD but contains subjective terms not measured in EASI. EASI and oSCORAD have a Spearman correlation coefficient of $r=0.93$ but a linear fit does not capture their relationship appropriately (Figure

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1A). To capture the nonlinear relationship, we applied an isotonic regression and smoothed the fit with LOWESS (Figure 1B). The identified regression was validated using a repeated k-fold cross-validation (k=4, 25 repeats). We split our dataset for the training set and the testing set to have different patients, to avoid an overestimation of the performance due to correlations of the AD severity scores within a same patient. The root-mean-square error for the cross-validation was 4.77 and the accuracy, measured by the ratio of the EASI values predicted from oSCORAD being within a MCID (=6.6 for EASI⁶), was 83% (Figure 1C).

Our data analysis (Figure 1A) also demonstrated overlaps of EASI values between different categories of IGA, suggesting a probabilistic outcome. IGA is often used to classify AD patients into different severity categories in an anchor-based approach^{2, 3}. The cut-off values of EASI separating the categories are determined to optimize a classification metric. However, condensing EASI, which ranges from 0 to 72, to IGA of about 4 to 6 poorly defined categories⁴ in a deterministic manner results in information loss. We therefore built a probabilistic fit of EASI to p-IGA, a probabilistic IGA represented by a continuous score (Figure 1D), by summing up the predicted probabilities of five logistic regression models, each of which classifies IGA between 0 and 1, 1 and 2, etc. For example, p-IGA = 2.2 means a 20% probability of IGA=3 and 80% probability of IGA=2.

This fit allowed us to propose a probabilistic stratification of AD severity into six severity categories (Figure 1E). A simple way to define a cut-off EASI value between IGA=2 and IGA=3 is to use EASI=11 corresponding to p-IGA=2.5 (with 50% probability of IGA=2 or IGA=3), which represents a point of change in the most likely outcome (Figure 1E, top). More generally, the cut-off EASI values for stratification could be tuned to reflect the perceived importance of misclassification. The corresponding cut-off can be determined using Bayes decision rule with $c = \frac{\text{cost}(FP)}{\text{cost}(FP) + \text{cost}(FN)}$, where cost(FP) and cost(FN) represent the cost for false positives and that for false negatives and the positive class is a severer category. For example, if we want to avoid misclassifying patients into a less severe category (high cost(FN)), at the expense of misclassifying them into a severer category (low cost(FP)), then we set a small c (e.g. $c = 0.1$, Figure 1E bottom) to define cut-off EASI corresponding to p-IGA = 0.1, 1.1, 2.1 etc. If we value precision (avoidance of type I error) than the sensitivity (avoidance of type II error), we set c closer to 1.

In conclusion, we proposed methods for deriving a relationship between EASI and oSCORAD, as well as a probabilistic stratification of EASI based on IGA. The proposed methods will help interpret results of clinical trials coherently in terms of EASI, while we hope that the core outcome set for AD will be used in all future AD trials to harmonise outcomes. The derived relationship between EASI and oSCORAD is valid only for a given accuracy (83%) evaluated by cross-validation, assuming that the data used here is taken from representative AD patients. The proposed computational methods are available as an app (www.bg.ic.ac.uk/research/r.tanaka/adconversionapp.html) to convert and visualise oSCORAD and severity strata by IGA in light of EASI, and can be further applied to data from different AD populations to confirm the preliminary results described here.

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Figure 1: **Conversion between oSCORAD, EASI and IGA** derived from the published data⁵ on multiple AD severity scores (SCORAD, oSCORAD, EASI and IGA) for each of 43 adults AD patients at weeks 0, 2, 4, 8, 12 and 24 of a systemic therapy (238 observations in total). The data covers the entire range of severity (EASI between 0–61.4, SCORAD between 1–82 and IGA between 0–5). All the analyses were performed using R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

A: Relationships between SCORAD, oSCORAD, EASI and IGA.

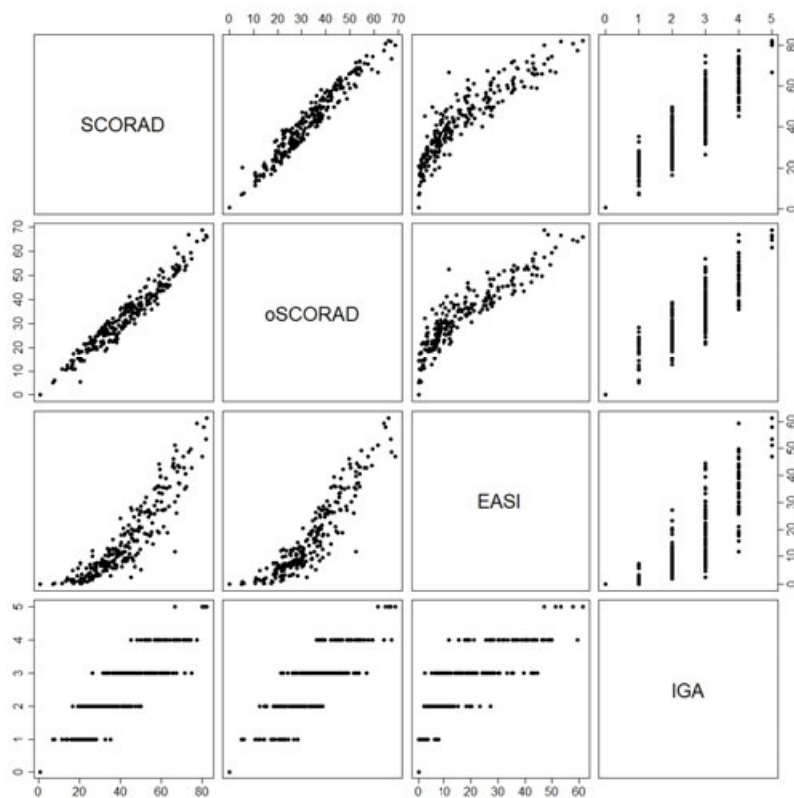
B: Smoothed isotonic fit between oSCORAD and EASI.

C: Cross-validated predictions of EASI by oSCORAD (y-axis) against the corresponding, measured values of EASI. The solid and dashed lines represent a perfect prediction and the area within one MCID of the perfect prediction (accuracy area), respectively.

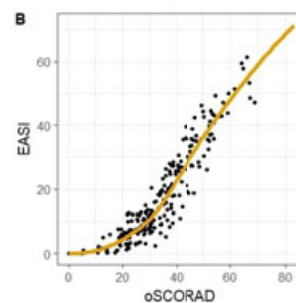
D: Probabilistic fit between EASI and IGA.

E: Stratification of oSCORAD and EASI. The upper values correspond to the default stratification where the cut-off is 0.5 between each category. The lower values correspond to a personalised stratification where we value sensitivity more than precision with a cut-off of 0.1 between each category.

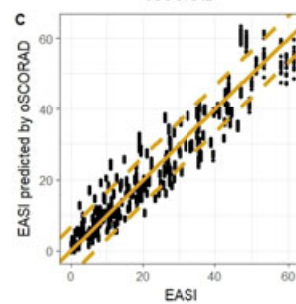
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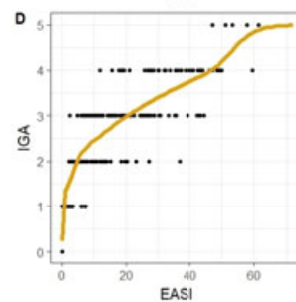
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E

