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New evidence on the minimal important change (MIC) for the Hand Eczema Severity Index (HECSI)

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Conflicts of interest

RO and TA are members of the HECOS (Hand Eczema Core Outcome Set) initiative. TA is an acting consultant and/or advisor for Leo Pharma, Sanofi, Pfizer and Eli-Lilly. YY states no conflict of interest. This article has no funding source.

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ABSTRACT

Background: How changes in hand eczema (HE) severity correlate with the single scores on the Hand Eczema Severity Index (HECSI) scale is sparsely investigated and particularly demanded in clinical trials.

Objectives: To find the minimal important change (MIC) for HECSI based on patients' and physician's assessments using different methods.

Methods. In this prospective follow-up study, three different anchors were used: two anchor-questions for patients and physician, respectively, and Physician Global Assessment with a photographic guide (PGA). MIC was estimated by mean change in patients with one-step increase to anchor-questions, receiver operating characteristics plot (ROC), and smallest detectable change (SDC).

Results One-hundred-and-fifty-two HE patients (63.8% females) were included at baseline (89% completed follow-up). The mean change, ROC cut-off and SDC values were 7.1, 4.5, 21.4 (patient-rating), 8.2, 4.5, 8.3 (physician-rating) and 16.6, 6.5, 27.1 points (PGA), respectively. SDC stratified by baseline severity were 2.9 and 11 points for mild and moderate-severe HE (physician-rating), respectively.

Conclusion Identifying the MIC for HECSI is important in relation to evaluation of treatment, intervention and sample-size calculations. An improvement of 8.3 points on HECSI is recommended as the MIC. MIC values may differ according to baseline severity, and this variation should be clarified in future studies.

Keywords: hand eczema, outcome research, hand eczema severity index, HECSI, clinical research, clinical trials, minimal important change, MIC

1. INTRODUCTION

Hand eczema (HE) is a frequent dermatological disease with a life-time prevalence of 15% in the general population ¹. Therapeutic options for HE have been limited with topical corticosteroids as first line treatment, and alitretinoin as the only drug registered for systemic treatment of HE.

However, new medical treatments are emerging, as well as intervention studies assessing the efficacy of patient education ²⁻⁴, underlying the importance of objective severity assessment of HE.

Although severity measurement tools are particularly essential in clinical trials, these may also be useful in daily life in dermatological clinics. Numerous clinical outcome measurement tools have been proposed to assess the severity of HE ⁵⁻¹⁰, however, according to the Hand Eczema Core Outcome Set (HECOS) initiative, the Hand Eczema Severity Index (HECSI) is the most frequently used in trials ¹¹. HECSI has been validated for inter- and intraobserver reliability and the instrument incorporates both extent and intensity of symptoms on both hands ⁹. Although this instrument has demonstrated validity and has been successfully used in many studies, only one attempt has been made to identify the minimal important change (MIC), which is the smallest measured change in HECSI perceived as important for the patient and/or physician ^{12,13}. Determining the clinically meaningful differences for HECSI is important, as small numerical changes in studies with large sample sizes may give statistically significant results, which may not have any clinical impact or meaningfulness for the patient ¹⁴⁻¹⁷. On the other hand, it is important to assess the MIC using a sensitive anchor in order not to overestimate the MIC which may hamper the assessment of relevant change in clinical studies, since the change might get falsely interpreted as irrelevant if the given MIC is higher than the real MIC of the measurement tool. A sensitive anchor is responsive to changes of even small magnitudes. If an anchor has either few or too many categories or if the categories of the anchor are abstractly worded, it will be difficult for the patient or physician to choose a category that matches the magnitude of change precisely. Consequently, patients with moderate changes may be categorized together with patients with small changes resulting in a higher MIC.

In the present study we aim to find the MIC for HECSI in a broad spectrum of HE patients, comprising both mild and severe cases, based on the patients' as well as the physician's assessments, and finally based on sensitive anchor questions.

2. MATERIALS & METHODS

Study population

The study design was prospective performed at the outpatient dermatological clinic at Bispebjerg Frederiksberg Hospital, University of Copenhagen, from where HE patients were recruited between March 16 - December 31, 2018, and between August 1- December 1, 2019. Inclusion criteria were diagnosis of HE according to guidelines ^{18,19}, age of 18 years or more, and sufficient Danish qualifications to answer a written questionnaire. Exclusion criteria were psoriasis or any other skin diseases located to the hands except for atopic dermatitis. Sample size calculation was not performed, however, a sample size of n=100 was considered sufficient for calculation of the MIC. The recruitment was determined to last until at least n=30 patients reported a minimal change according to the anchor question.

The patients were seen by the same physician at baseline and at follow-up visit >1 week from baseline. Demographic data was collected at baseline and the patients were asked to complete a follow-up questionnaire covering the magnitude of change in HE-severity since last visit at follow-up.

Study instruments

For a detailed description of HECSI, see Supplementary Materials and ⁹.

The Physician Global Assessment (PGA) was used as anchor for the HE severity and was scored by the physician using a validated photographic guide ²⁰. The PGA assesses severity using five categories: clear, almost clear, moderate, severe and very severe HE. The illustrated PGA shows photos of hands with both increasing severity and extent of eczema ²⁰.

Anchor questions (global scores)

Both the patients and the physician assessed the change of the HE severity at follow-up visit. The patients rated their HE severity by responding to the anchor question “Has your hand eczema improved or deteriorated since last visit?” with the following options: improved, deteriorated or unchanged. If improved or deteriorated, the patients determined the extent of change by following response options: not at all, little, moderately, strongly or very strongly.

The physician assessed the HECSI together with PGA and an anchor question for the global score. The anchor question for the global score (“Do you think the hand eczema has improved or deteriorated since the patient’s last visit?”) had similar response options as those presented for the patients.

Assessments in practice

In practice, HECSI and PGA were assessed by the physician at the first visit following a clinical examination of both hands and wrists. Scores for symptoms (erythema, induration/papulation, vesicles, fissuring, scaling and oedema) as well as extent of the eczema (percentage of involvement on fingertips, fingers (excl. fingertips), palms, back of hands and wrists) were registered and the total HECSI score was calculated (Supplementary Materials). Simultaneously the PGA was assessed using a photographic guide. At the second visit, HE severity was again assessed by HECSI and PGA. In addition, the physician made a decision on the level of change since last visit by answering the anchor question “Do you think the hand eczema has improved or deteriorated since the patient’s last visit?”. Without any knowledge of the physician’s decision on the level of change, the patient was also deciding the size of this change since last visit by answering the anchor question for patients “Has your hand eczema improved or deteriorated since last visit?”

Statistical analysis

The MIC - also referred to as the minimal clinically important difference (MCID) in the literature - is the smallest change in an outcome measure representing a clinically relevant outcome ¹² and can

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be determined by several methods ²¹. In this study, the MIC was determined as the minimal change within patients by using two anchor-based methods together with the smallest detectable change (SDC). The anchor-based methods comprised (a) the mean change in patients with a one-step increase to the anchor questions rated by the patient and the physician, and (b) the receiver operating characteristics (ROC) plot where a cut-off value was chosen at the point that gave the highest sum of sensitivity and specificity ²². To confirm the evidence of the received values for the MIC, the SDC was additionally applied in unchanged patients according to Jacobson et al. ¹⁷. The SDC results in a measure of statistical meaningful change which is taking the reliability (measurement error) of the instrument into account. The MIC values were based on improved patients only, since the number of deteriorated patients was smaller than the number of improved patients.

The χ^2 -test and the non-parametric Mann-Whitney U-test were used to examine differences between sexes. In addition, we applied the HECSI categorisation proposed by Oosterhaven et al. ¹³ to our data and tested the agreement between the HECSI categories and PGA by using the weighted Kappa-coefficient ²³.

Two-sided p-values <0.05 were considered statistically significant. Data were analysed with SPSSTM statistical software version 25.0.

Ethical considerations

The study was reviewed and exempted by the Local Ethics Committee, journal no.: 19052223, and approved by the Data Protection Agency. Informed consent was obtained from all patients.

3. RESULTS

A total of 152 patients participated in the study, 97 females (63.8%) and 55 males (36.2 %).

Baseline characteristics are shown in Table 1. Mean age of males (46 ± 14 years) was significantly higher than in females (42 ± 15 years). A lower mean HECSI was found in females (26.5 ± 35.5) as compared to males (34.4 ± 31.7) ($p=0.03$). The HE severity stratified by PGA and HECSI categories

are shown in Table 1. When testing the agreement between the HECSI categorisations¹³ and PGA, we found a weighted Kappa-coefficient of 0.723.

Eighteen patients (11.8%) were lost to follow-up. Reasons for not attending the follow-up visit were not having time or of unknown cause. There were no significant differences regarding sex and age between the patients lost to follow-up and those completing the follow-up visit. The mean follow-up duration was 6.8 (± 9.5) weeks.

The number of improved, deteriorated and unchanged patients based on evaluation by the patients and the physician is shown in Table 2.

The MIC

The mean changes in HECSI score in improved, deteriorated and unchanged patients are shown in Table 2. The MIC values based on patient-ratings, physician-ratings and PGA determined by mean change, ROC cut-off and SDC are given in Table 3 together with MIC values stratified by baseline severity.

Overall, the patients reported a minimal improvement of their HE with a mean of 7.1 points on the HECSI scale reflecting the MIC according to our first anchor-based method (i.e mean change with one-step increase to anchor questions). When rated by the physician, the MIC in HECSI corresponded to 8.2 points, while a change of 16.6 points reflected the MIC as assessed by the PGA.

According to the second anchor-based method using the ROC cut-off values, the MIC values were 4.5 points, 4.5 points and 6.5 points on the HECSI scale in the patient rated, physician rated and PGA-assessed anchor, respectively (Table 3). Finally, the SDC calculated in unchanged patients was 21.4 points in HECSI based on the patient-rated anchor, 8.3 points on the physician-rated anchor and 27.1 points when assessed by PGA as anchor.

4. DISCUSSION

This is the first study to provide MIC values for HECSI based on three different anchors (i.e. patient- and physician-rated global scores and PGA) together with three different methods (i.e. mean change, ROC cut-off and SDC). Based on these, our results provide data supporting a MIC value for HECSI of 8.3 points presenting a minimal important change as assessed by the physician which lies beyond measurement error and considered the most conservative interpretation of our data. However, in order not to overestimate MIC some could also argue that the patient-rated MIC, which corresponds to a change of 7.1 points in HECSI, should be applied, in order not to oversee any important change for the patient.

For an extended interpretation of the MIC for HECSI, we used two anchor-based methods together with the smallest detectable change resulting in several MIC values. In general, the MIC values found by the ROC cut-off were smaller than the mean change values, while the SDC was approximate to or higher than the mean change values. Ideally, the SDC value should be smaller than the corresponding mean change value if it should be able to indicate a change beyond measurement error²⁴. The relatively high SDC values found in this study may be explained by the small sample size and the use of PGA to stratify the unchanged patients. Using the physician-rated global score as the anchor, the SDC of 8.3 points is almost equal to the corresponding mean change value (Table 3) and therefore acceptable regarding being able to detect a change beyond measurement error. We therefore recommend using the SDC of 8.3 points as the MIC for HECSI meaning that a patient needs to improve with 8.3 points or more before the change in the HE severity is considered meaningful and important. The physician-rated global score is chosen as the most ideal anchor in this study, since the PGA seems to be less sensitive to determine the MIC as compared to the patient- and physician-rated global score, and since the HECSI is a physician rated measurement tool it seems evident that the magnitude of an important change should be determined by the physician/dermatologist.

The recommended MIC value in our study was markedly lower than the previously reported MIC value of 41 points, although we were able to replicate the banding of PGA and HECSI as previously found¹³. The study design and the methods applied in the previous study compared to our study may explain the different MIC outcomes. First, in our study the MIC values based on the PGA as an anchor were higher than the MIC values based on the two other anchors (i.e. patient-rated and physician-rated global scores). This indicates that the PGA is not a particularly sensitive outcome measure to assess change in HE patients, although a strong correlation between the PGA and the HECSI has been stated¹³. In the PGA, a greater change in the HE severity was necessary to obtain a one-step improvement particularly concerning the more severe cases as compared to the two other anchors. HE is a phenotypically very diverse skin disease including several subtypes²⁵, and it may therefore be difficult to choose a matching category based on photos provided for each category in the PGA. Taken together, the PGA may not be optimal as an anchor for estimation of MIC for HECSI as it results in overestimation of the MIC. Thus, the previously proposed MIC of 41 points¹³ based on PGA as the only anchor is considered less sensitive to detect the smallest clinically relevant changes in HECSI when compared to the other anchors in our study. Secondly, in our study the HE severity was rated by the same physician at baseline and follow-up since the response to the physician-rated anchor question (global score) had to be performed by the same physician. Although Held et al. found an absolute agreement of 0.79-0.84 in a group of raters assessing HE with HECSI indicating good inter-rater reliability for the total HECSI score⁹, the MIC is expected to be higher if different raters were used. This is a very important aspect when planning clinical trials, and future studies should further clarify this. In conclusion, the MIC for HECSI of 8.3 points found in this study can be used in clinical trials with the same raters at the different visits.

In this study, we included the patient's assessment of change at follow-up. The magnitude of change in the one-, two- and three-step improvements were comparable to the physician-rated change, however, the unadjusted 4-step improvement (i.e. very strong improvement) rated by the patients corresponded to a mean *increase* of 0.5 points on the HECSI scale, Table 2 (footnote). This

effect was driven by one patient only, who reported great improvement while his HECSI score increased by 97 points between baseline and follow-up. This is most likely due to a wrong interpretation of the anchor question resulting in a report of clinical change in the opposite way. After exclusion of this patient, the corresponding score was -18 points as shown in Table 2.

Furthermore, some patients assessed their change from *almost clear* to *clear eczema* as a “very strong improvement”, since the HE could not improve further although the size of change was small. Further, the mean change scores were smaller for the one-step deteriorations as compared to the one-step improvements particularly when reported by the patients. The patients might find it easier to report a very mild deterioration since the onset or worsening of physical symptoms (i.e. itch, pain) often accompany the deterioration and thereby easily noticed by the patients. The perception of change from the patient’s point of view is essential, however, also quite challenging as the interpretation of the anchor question may differ strongly between the individual patients resulting in different magnitudes of clinically important change ²⁶. Furthermore, Norman et al. reported that the global measure of change was highly correlated with the patient’s present state and thereby psychologically difficult for the patient to evaluate the precise magnitude of change ²⁷.

According to guidelines for patient-reported outcomes, multiple anchors should be provided for the patients in order to increase the responsiveness ²⁸, however, several questions regarding the same topic may also have the opposite effect by wearing the patients down.

When estimating the MIC values based on baseline severity in subgroups of mild HE and moderate-severe HE, the SDC values were in general larger than the mean change and ROC cut-off values except for the physician-rated SDC for mild HE cases. Since our sample size is too small to give robust estimates for mild and moderate to severe cases, the MIC values found in our study should be considered as preliminary.

Our data clearly show that the MIC is affected by the anchors and methods used and the baseline severity. Lastly, the number of raters is also likely to influence the MIC, wherefore these factors should be taken into consideration when planning future trials.

A strength of our study was the longitudinal study design which is preferred over the cross-sectional design when evaluating change ²⁶. Furthermore, we used both anchor-based methods and the SDC and included global score ratings from both the patients and physician in order to calculate the MIC for HECSI. Lastly, only 11% of the patients were lost to follow-up. Although comparable to similar studies ²⁹, one limitation was the size of our study population. A larger population would give stronger predictions of the MIC, particularly when stratifying the patients according to baseline severity. The longitudinal study setup is recommended, however, the ratings performed by the patients and physician at follow-up may be interfered with recall-bias ²⁷. Finally, more than one physician assessing the severity of HE at different visits could be optimal since it would increase the generalizability of the study. However, the physician in the present study had no skills beforehand and therefore not very different from other health care personnel that may use HECSI to assess HE severity.

5. CONCLUSION

Based on numerous anchors and methods in a longitudinal study design, our results indicate new evidence on the MIC of HECSI. In clinical trials, the SDC of 8.3 points corresponding to a MIC on the HECSI scale is recommended to be applied when physicians evaluate the HE severity, while a change of 7.1 points could eventually be considered when a patient relevant change wants to be assessed. This MIC value can also be used to calculate the sample size of future trials. Regarding stratification of the MIC based on baseline severity, more data is needed on this field. When determining the MIC, several factors such as the anchor, the method, baseline severity and number of raters should be considered.

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Table 1. Baseline characteristics of study population

	Female (n=97)	Male (n=55)	Total (n=152)
Age (years)			
Mean $\pm$ SD	42 $\pm$ 15	46 $\pm$ 14	43 $\pm$ 15
Range	18-82	24-84	18-84
HECSI			
Mean $\pm$ SD	26.5 $\pm$ 35.5	34.4 $\pm$ 31.7	29.3 $\pm$ 34.3
Median (IQR)	16 (5-32)	26 (13-48)	18.5 (7.5-39.5)
Range	0-228	0-141	0-228
Severity assessed by PGA			
Clear, n (%)	4 (4.1)	3 (5.5)	7 (4.6)
Almost clear, n (%)	34 (35.1)	8 (14.5)	42 (27.6)
Moderate, n (%)	35 (36.1)	27 (49.1)	62 (40.8)
Severe, n (%)	20 (20.6)	13 (23.6)	33 (21.7)
Very severe, n (%)	4 (4.1)	4 (7.3)	8 (5.3)
Severity according to HECSI categories ^a			
Clear, n (%)	3 (3.1)	3 (5.5)	6 (3.9)
Almost clear, n (%)	49 (50.5)	17 (30.9)	66 (43.4)
Moderate, n (%)	21 (21.6)	19 (34.5)	40 (26.3)
Severe, n (%)	22 (22.7)	13 (23.6)	35 (23)
Very severe, n (%)	2 (2.1)	3 (5.5)	5 (3.3)

SD, standard deviation; HECSI, Hand Eczema Severity Index; IQR, inter quartile range; PGA, physician global assessment

^a Categories given by Oosterhaven et al. (*Clear: 0, Almost clear: 1-16, Moderate: 17-37, Severe: 38-116, Very severe: ≥ 117*)

Table 2. Mean change in HECSI score based on three different anchors.

		Patient rated change			Physician rated change			Change in PGA		
		n	Mean change	SD change	n	Mean change	SD change	n	Mean change	SD change
Improvement	Very strong (4-step)	6	-18 ^a	48.9	3	-43.0	21.0	0	n/a	n/a
	Strong (3-step)	15	-17.7	20.7	11	-27.5	21.5	0	n/a	n/a
	Moderate (2-step)	18	-19.6	23.3	18	-12.3	32.5	4	-44.8	15.3
	Little (1-step)	25	-7.1	13.1	29	-8.2	6.8	32	-16.6	20.1
No change		32	-0.2	11.4	36	-1.5	4.3	79	-1.6	13.9
Deterioration	Little (1-step)	23	2.7	8.1	24	5.0	3.1	17	14.9	13.5
	Moderate (2-step)	9	10.2	8.0	10	22.3	14.0	2	86	14.1
	Strong (3-step)	5	24.4	40.1	1	18.0	n/a	0	n/a	n/a
	Very strong (4-step)	1	76.0	n/a	2	86.0	14.1	0	n/a	n/a

^a One patient was excluded from the analysis. The unadjusted value was 0.5 points.

PGA, physician global assessment; SD, standard deviation; n/a, not applicable

The mean change scores of Hand Eczema Severity Index (HECSI) from baseline to follow-up according to changes evaluated by three different anchors: patient rated, physician rated using the global score and the PGA using the photographic guide.

Table 3. Minimal important change (MIC) values for the different anchors based on three different MIC methods

MIC method	Baseline severity according to PGA					
	n	All	n	Mild	n	Moderate-severe
Patient rating						
Mean	25	7.1	6	1.5	19	8.9
ROC cut-off	32	4.5	17	1.5	15	9.5
SDC	32	21.4	17	3.2	15	31.6
Physician rating						
Mean	29	8.2	8	4.0	21	9.8
ROC cut-off	36	4.5	21	1.5	15	4.5
SDC	36	8.3	21	2.9	15	11.0
PGA						
Mean	32	16.6	5	4.6	27	18.8
ROC cut-off	79	6.5	30	3.5	49	8.5
SDC	79	27.1	30	4.7	49	34.2

MIC, minimally important change; PGA, physician global assessment; SDC, smallest detectable change; ROC, receiver operating characteristics.

The minimally important change (MIC) values of Hand Eczema Severity Index (HECSI) assessed by three different MIC methods for each anchor. The mean and ROC cut-off are calculated in improved patients, while the SDC is calculated in unchanged patients.

Graphical abstract highlights

The minimal important change (MIC) for HECSI was 8.3 points calculated by the smallest detectable change using the physician-rated anchor, since PGA was less sensitive and HECSI is a physician-rated tool.

When stratified by baseline severity, MIC values were 2.9 and 11 points for mild and moderate-severe hand eczema, respectively.

Identifying the MIC for HECSI is important in relation to evaluation of treatment, intervention and sample-size calculations. MIC values may differ according to baseline severity, and this variation should be clarified in future studies.

New evidence on the minimal important change (MIC) for Hand Eczema Severity Index

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