

Evaluation of a simple image-based tool to quantify facial erythema in rosacea during treatment

Jade G. M. Logger  | Elke M. G. J. de Jong | Rieke J. B. Driessen | Piet E. J. van Erp

Department of Dermatology, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence

Jade G. M. Logger, Department of Dermatology, Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

Email: Jade.Logger@radboudumc.nl

Abstract

Background: Facial erythema is a common symptom in rosacea. To overcome subjectivity in scoring erythema severity, objective redness quantification is desirable. This study evaluated an image-based erythema quantification tool to monitor facial erythema in rosacea patients during treatment and compared these values to clinical scores.

Materials and Methods: Twenty-one rosacea patients were treated with topical ivermectin for 16 weeks. Clinical erythema scores and clinical photographs were taken at week 0, 6, 16 and 28. Using ImageJ, RGB images were split into red, green and blue channels to measure the green/red ratio of lesional skin compared with a green sticker. With CIELAB colour space, a^* (indicating colour from green to red) of a lesional and non-lesional facial site was measured, calculating Δa^* . Interobserver concordance and correlation between quantitative and clinical erythema values were determined.

Results: Treatment resulted in reduction of clinical erythema scores. No significant changes in red/green ratios were measured. Lesional a^* and Δa^* significantly decreased from baseline to week 16 and 28 ($P < .05$). A weak correlation existed between clinical scores and lesional a^* ($R_s = 0.37$), and between clinical scores and Δa^* ($R_s = 0.30$), with a clear trend towards higher a^* and Δa^* for higher clinical scores. Interobserver correlation was high ($R^2 = 0.82$).

Conclusion: ImageJ is a simple, rapid, objective and reproducible tool to monitor erythema in rosacea patients during treatment. The photographs allow retrospective analysis, evaluation of large and small lesions, and discrimination of subtle redness differences. We recommend using lesional a^* to monitor erythema of inflammatory dermatoses in clinical practice.

KEYWORDS

clinical photography, computer-aided image analysis, erythema, ImageJ, rosacea

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1 | INTRODUCTION

Rosacea is a common inflammatory skin disease, often accompanied by facial erythema.¹ Erythema is visible due to increased haemoglobin in the papillary dermis, caused by inflammation, vasodilation and vasculature changes.² To achieve optimal results, rosacea treatment is preferably adjusted to clinical symptoms and disease severity. Unfortunately, evaluation of facial erythema by visual assessment lacks objectivity and precision, and is prone to inter- and intra-observer variability.³⁻⁶

To overcome subjectivity, an objective, noninvasive technique for the measurement of skin colour is desirable. Various noninvasive techniques have already been used to quantify redness in rosacea, for example, spectrophotometry and computer-aided image analysis (CAIA).⁷ Nevertheless, they have some limitations. With spectrometry, erythema is measured in only one point, questioning representativeness of the entire face. Moreover, spectrophotometers require skin contact, changing skin colour due to skin pressure application.⁸⁻¹⁰ For CAIA, analysis protocols often included multi-step, complex, time-consuming approaches with expensive and extensive software, or protocols are poorly described, not validated nor standardized,^{2,11-19} and therefore difficult to reproduce or use in clinical practice. Additionally, VISIA, a commercially available system with quantitative facial imaging analysis software, does not enable point/segmented erythema analysis, imposing difficulties in areas with diffuse erythema.² Lastly, two different colour space methods have been applied in previous studies, namely RGB and CIELAB. RGB represents object "appearance", but does not correct for brightness; CIELAB indicates colour perception, and has the advantage of correcting for variations in brightness.^{10,20} Due to these various limitations for erythema quantification in rosacea, a reliable, rapid, non-contact and simple erythema quantification tool is needed.

The aim of this study was to test an easy-to-use, image-based software tool to quantify and monitor facial erythema in rosacea patients during treatment with topical ivermectin. Additionally, quantified erythema values were correlated to clinical scores and interrater concordance was determined.

2 | MATERIAL AND METHODS

2.1 | Study participants

Twenty-one patients (9 males, 12 females; skin type I-III; median age 49 years; range 24-81 years) participated in this study. They were recruited between January 2018 and April 2019 at the Department of Dermatology, Radboudumc, Nijmegen, The Netherlands. Subjects were included if they had moderate-to-severe rosacea, defined as an Investigator's Global Assessment (IGA) score of 3 or 4. Patients currently using ivermectin cream or having other facial dermatological conditions able to interfere with rosacea diagnosis or assessment were excluded. They were instructed to avoid known offending environmental factors and foods triggering rosacea, and not to sunbathe or to use a tanning bed throughout the study.

2.2 | Treatment, procedures, and photography setup

Treatment consisted of topical ivermectin 1% once daily during 16 consecutive weeks. Ivermectin is a potent and easy-to-use anti-inflammatory/acaricidal agent for rosacea with little side effects, making this a suitable intervention to monitor erythema.²¹ Clinical erythema was graded using an erythema scale from 0 to 4 (Table 1) at week 0, 6, 16 and 28 (follow-up). During these visits, high-resolution facial photographs were acquired in JPG format with a commercially available single-lens reflex digital camera (Nikon), equipped with a complementary metal-oxide semiconductor (CMOS) sensor and an AF S Micro Nikkor 105 mm 2.8 objective. All photographs were taken under the same light conditions in a photo studio, with a green circular sticker (0.5 inch diameter) attached at the cheek. The camera was manually held perpendicular to the skin and the sticker, at a distance sufficient to image both the erythematous areas as well as the sticker. Two Broncolor monolights were used to maintain absolute light consistency with respect to exposure and colour. The following settings were used to take photographs: manual focus and mode (M), with aperture and shutter speed adjusted to match optimal exposure; ISO 200; image

TABLE 1 Clinical erythema severity assessment

| Score | Grade | Description of erythema |
|-------|--------------|---|
| 0 | Clear | No redness present. Erythema is consistent with non-involved areas. |
| 1 | Almost clear | Slight and localized erythema in involved areas of the face, usually limited to the malar prominence of the cheeks. Gives the impression of a healthy glow to the cheeks. |
| 2 | Mild | Slight to mild erythema NOT limited just to the cheeks, but extends to the lateral cheeks, chin or forehead. |
| 3 | Moderate | Definite background redness, easily recognized, and extending to lateral cheeks, chin or forehead. |
| 4 | Severe | Severe erythema over the entire face. |

quality “JEPfine S,” corresponding to images with a low (1:4) compression ratio; and colour space sRGB.

2.3 | Erythema quantification

Photographs were analysed with ImageJ® freeware (<http://imagej.nih.gov/ij>). First, the RGB colour split function was used to divide the original RGB photographs into their constituent red, green and blue channels. The mean green intensity of the green sticker was measured. Next, a region of interest (ROI) with the most intense visible facial erythema (=lesional skin) was selected; this was the cheek ($n = 19$), the forehead ($n = 1$) or the chin ($n = 1$). The mean red intensity of this ROI was measured. Then, the mean intensity of the sticker and the ROI was used to calculate the red/green (R/G) ratio as a standardized measure for skin redness. Secondly, the RGB image was converted to CIE $L^*a^*b^*$ colour space. L^* indicates light intensity from 0 (black) to 100 (white), while a^* indicates colour from green (-60) to red ($+60$), and b^* indicates colour from blue (-60) to yellow ($+60$).^{9,22} The mean a^* value of the stored ROI was measured, and compared to a representative non-lesional site (neck), serving as a control site for background erythema; Δa^* was calculated (a^* of lesional skin minus a^* of non-lesional skin). Incidental regions of specular reflection were avoided when selecting areas for analysis. A step-by-step guideline for the entire procedure is found in Table 2. Analyses of week 0 and 28 were performed by two independent researchers (JGML and PEJE) to determine interobserver variation; week 6 and 16 analyses were performed by one researcher (JGML).

2.4 | Statistical analysis

Differences in R/G ratio, a^* and Δa^* between the various time points were evaluated with Wilcoxon signed-rank tests. No correlation for multiple comparisons was applied, because of the exploratory character of this study. Differences in a^* between lesional and non-lesional skin per visit and for both researchers were explored using Mann-Whitney U tests. To test for a possible relationship between clinical and quantified erythema results, Spearman rank correlation (R_s) was used. Lastly, linear regression analysis was applied to determine interobserver variation. Statistical analysis was performed using Instant Clue Software.²³ For all tests, $P < .05$ was considered statistically significant. Missing values were excluded from the analyses.

3 | RESULTS

3.1 | Clinical scores

Figure 1 presents the clinical scores. At baseline, 71% of patients had an erythema score of 3 or 4, decreasing to 33% at week 6, 10% at week 16, and 0% at week 28. Only 10% of patients reached an erythema score of 0 at week 28, compared to 0% at baseline.

3.2 | R/G ratio and a^*

Surprisingly, we found no significant changes in R/G ratios during the study (Figure 2). A significant decrease in median lesional a^* was measured from baseline (24.97, range 19.94-32.95) to week 16 (20.98, range 18.12-34.92; $P = .005$) and week 28 (20.68, range 15.17-29.46; $P < .001$). No significant differences in non-lesional a^* values were seen during the study, see Figure 3A. The a^* was significantly higher in lesional skin compared with non-lesional skin at all time points ($P < .001$). Δa^* also significantly decreased from baseline (12.23, range 5.52-19.56) to week 16 (9.18, range 1.61-15.40; $P = .001$) and week 28 (7.97, range 3.17-16.13; $P = .002$), see Figure 3B.

3.3 | Correlation of quantified vs clinical erythema values

A weak correlation was found between clinical erythema scores and lesional a^* ($R_s = 0.37$, $P < .001$; Figure 4A), and between clinical erythema scores and Δa^* ($R_s = 0.30$, $P = .007$; Figure 4B). Despite this, a clear trend towards higher a^* and Δa^* for higher clinical scores was visible.

3.4 | Interobserver concordance

Interobserver correlation was high. No significant differences in a^* were found between the two researchers (Figure 5A), and linear relationship was strong ($R^2 = 0.82$, $P < .001$; Figure 5B).

4 | DISCUSSION

In this study, we evaluated ImageJ, a simple image-based software tool, for the quantification and objective monitoring of facial erythema in rosacea during treatment, and we compared these values to clinical scores. Lesional a^* and Δa^* decreased significantly during treatment, corresponding to a reduction in clinical erythema. The interobserver concordance of a^* was high. R/G ratios did not change during the study and seem unsuitable to monitor redness. Our method is rapid, simple, objective and reproducible; the photographs allow retrospective analysis, evaluation of large and small lesions, and discrimination of subtle redness differences. We recommend using lesional a^* to monitor erythema in daily clinical practice.

Visual erythema assessment, which is currently frequently applied in daily practice for redness monitoring in rosacea, has some important drawbacks. First, visual examination of skin colour is poor at quantifying subtle differences of erythema.¹¹ Namely, colour is a subjective and nonlinear sensory perception, because ocular sensitivity to visible light depends on wavelength and shows intraindividual variation.²⁴ Furthermore, skin colour is a mixture of “redness”

TABLE 2 Step-by-step protocol for erythema quantification using ImageJ, used in this study [Colour table can be viewed at wileyonlinelibrary.com]

Original JPG image

1. Drag original JPG photograph into ImageJ (*Photo 1*).
- Split image into the three RGB channels (red, green, blue):
Image→ **Colour**→ **Split Channels**.
 Close blue image, you do not need this one.



RGB green image

2. In *green image* (*Photo 2*):
- Zoom in on green sticker at the cheek.
 Draw a circle inside the green sticker with **“Freehand selections.”**
Analyse→ **Measure**: record mean green value for green sticker.
 Close green image.



TABLE 2 (Continued)

RGB red image

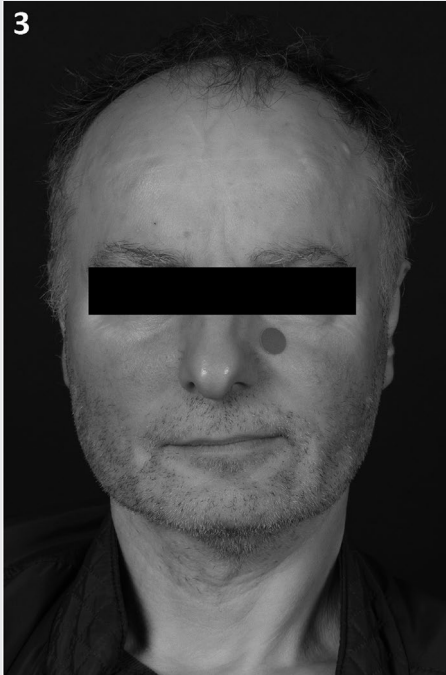
3. In the *red* image (Photo 3):

Choose region of interest of lesional skin. Outline ROI with "Freehand selections." Make sure to avoid any skin colour inconsistency due to pen lines, hair, tattoos, jewelry etc inside ROI.

Analyse → **Measure**: record mean red value.

Save ROI: **Analyse** → **Tools** → **ROI manager**. Click **Add [t]** → **More** → **Save**.

Close red image.

**CIELAB a* image**

4. In *original* image (Photo 1):

Split image into CIELAB colour space: **Image** → **Colour** → RGB to CIELAB.

Scroll to second image (*a**, Photo 4).

Drag saved ROI into ImageJ; ROI is placed into the *a** image.

Analyse → **Measure**: record mean *a** of lesional skin.

Choose a region with non-lesional skin (eg the neck), outline this region with "Freehand selections."

Analyse → **Measure**: record mean *a** of non-lesional skin.



5. Transfer all recorded values to a digital database for data analysis.

from cutaneous blood flow, and "tanning" derived from epidermal melanin, imposing challenges in isolating these components by visual inspection only.⁸ So, visual erythema scoring is a subjective and quite unreliable method in therapeutic monitoring, and its robustness, also by experienced dermatologists, can therefore be questioned.⁵

Various methods to objectify erythema have already been tested in dermatological research.⁷ These studies showed that quantified erythema values correlate well with clinical scores, both in rosacea,^{11-15,17,18} and in other inflammatory skin diseases.^{25,26} Despite

their promising value, none of these proposed methods have so far been implemented in daily clinical practice. We hypothesize that this is because they are too complex, expensive or time-consuming to use. In this study, we evaluated a very simple method for erythema monitoring in rosacea using ImageJ, which is easy-to-use, freely available and widely accepted for image analysis.²⁷ Interobserver correlation is high, making our results reproducible; no extensive training is needed, so calculations can be easily performed by clinicians who are unexperienced with image software. Moreover, ImageJ allows

FIGURE 1 Clinical erythema scores of the rosacea patients at week 0, 6, 16 (during treatment) and 28 (follow-up) [Colour figure can be viewed at wileyonlinelibrary.com]

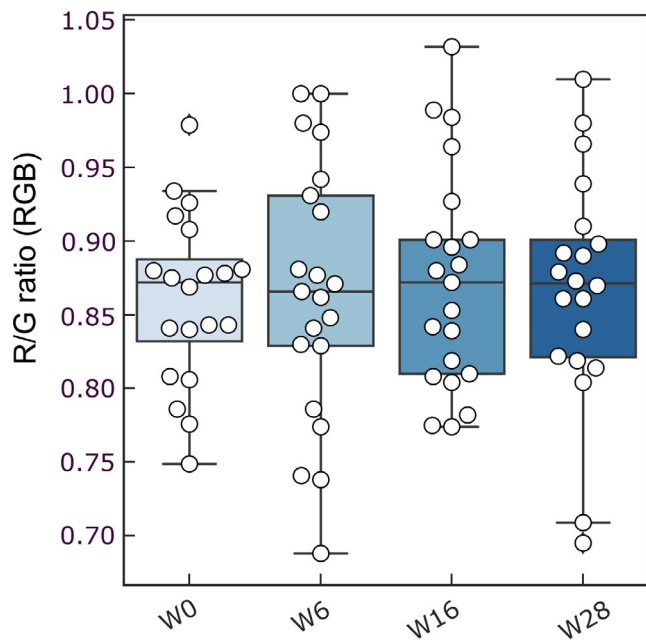
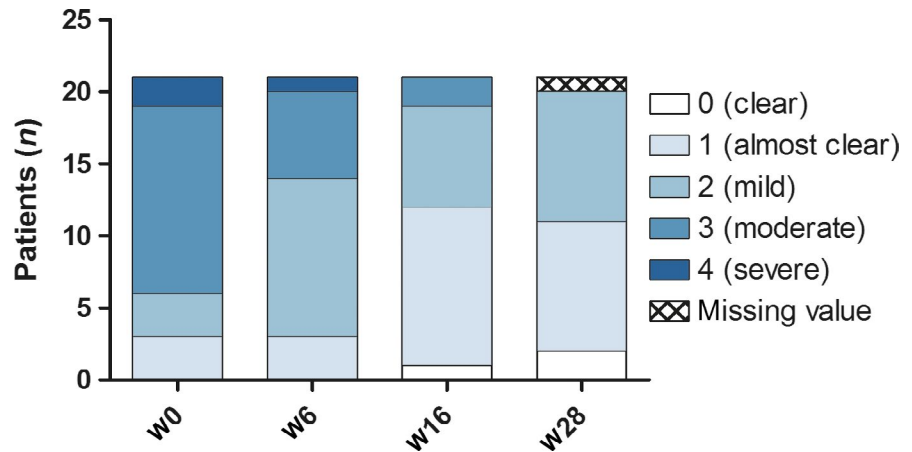


FIGURE 2 Red/green ratios of lesional skin in rosacea patients per visit. The green values were assessed using a green sticker attached to the cheek. The black lines indicate the median value; the white dots indicate individual values [Colour figure can be viewed at wileyonlinelibrary.com]

temporal monitoring of exactly the same skin location due to ROI saving options. The ROI can be easily adjusted for analysis of both small as well as large skin areas to obtain distributions maps, only requiring sufficient image resolution.⁸ This is a great advantage over spectrophotometric measurements which are point measurements, also prohibiting use in small skin locations (eg the nose).²² In this study, we chose a circular ROI with clearly visible facial erythema, serving as a representative piece of lesional skin. Moreover, this is a non-contact method, so it does not change skin colour due to capillary construction and consecutive blanching of the skin.^{8,9,22} In addition to avoiding pressure to the skin, there is no need to apply an instrument to the lesional skin, having hygienic disadvantages.⁹

In this study, both RGB and CIELAB colour space were used to calculate redness. RGB indicates how a colour of an object “appears”

corresponding to the three types of colour sensors (cones) in the human eye.⁹ Using RGB, no differences in R/G ratio were measured, corresponding to earlier work focussing on rosacea severity.¹² An explanation for this could be that RGB values are not only influenced by colour but also by brightness, which probably varied slightly between photographs. With CIELAB colour space, one does not encounter this problem, as brightness is separated from the a^* -axis of the colour space. CIELAB provides the perception of colour to a human observer, and closely approximates and linearly correlates with the response of the eye.^{6,9,20,22} Despite the relatively low R_s , a clear relationship between lesional a^* values and clinical scores was seen. The weak correlation may be caused by the subjectivity of the determined clinical scores. As there is no noninvasive golden standard tool to provide the “real” erythema value, there was no other suitable noninvasive technique to compare all our results to.¹⁵

It is important to take into account that a^* represents erythema of both physiologic and pathologic cause,¹² as it correlates with haemoglobin, skin blood flow and vascularization.^{8,15,22,28-30} However, the correlation of a^* with haemoglobin is almost linear, and independent of the amount of melanin.¹⁰ Furthermore, erythema values can be influenced by various individual- and environmental-related variables such as age, medication, caffeine intake, orthostatic effects, physical activity, regional and seasonal variation, ambient temperature and humidity rate, and lighting inconsistencies.^{9,10,20,29} In this study, photographs were taken under standardized conditions, four time points were included per patient, and a non-lesional site was measured as an internal control. We deliberately chose not to correct for other possible influencing variables, because this limits clinical application immensely; still, the quantified a^* and Δa^* values showed a clear correlating trend with clinical scores, and both parameters decreased significantly during treatment with ivermectin. This is probably caused by a reduction in inflammation, as topical ivermectin has moderate-to-high certainty evidence for reducing papules and pustules in rosacea.²¹ However, even after 16 weeks of treatment, lesional erythema values remained higher than non-lesional values, suggesting that persisting erythema is a partly non-inflammatory feature (eg due to telangiectasias).

Our method appears to be rapid, and can in our opinion compete with clinical assessment, which is highly recommended for

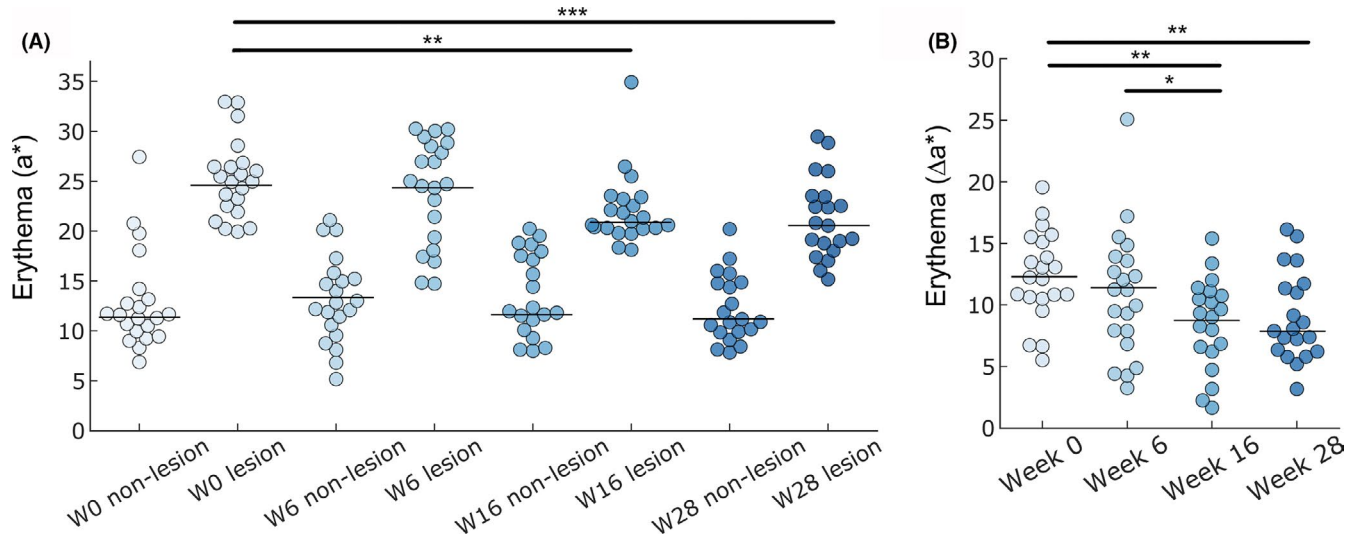


FIGURE 3 A, a^* values of lesional and non-lesional facial skin in rosacea patients per visit. B, Δa^* values (lesional skin minus non-lesional skin) per visit. The black lines indicate the median value. $.01 \geq P < .05$, $0.001 \geq P < .01$, $***P < .001$ [Colour figure can be viewed at wileyonlinelibrary.com]

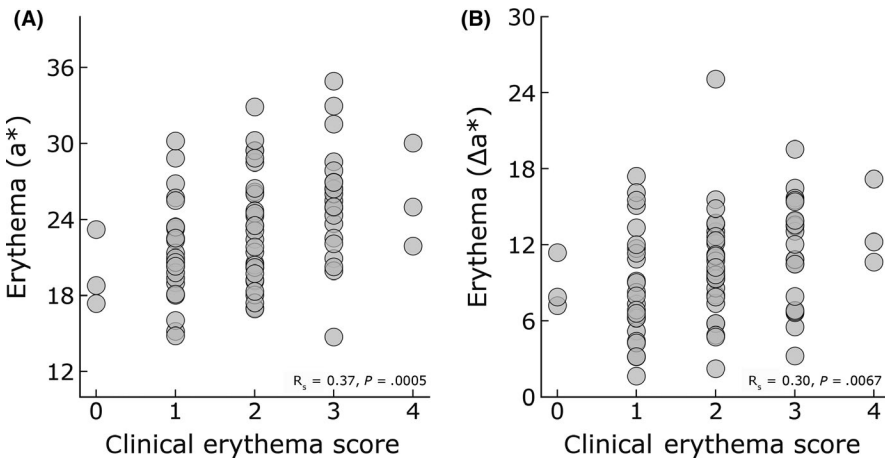


FIGURE 4 Spearman correlation analysis of clinical erythema scores vs quantified erythema values. Data of all visits were merged. A, Clinical scores vs lesional a^* values. B, Clinical scores vs Δa^* values (=lesional skin minus non-lesional skin)

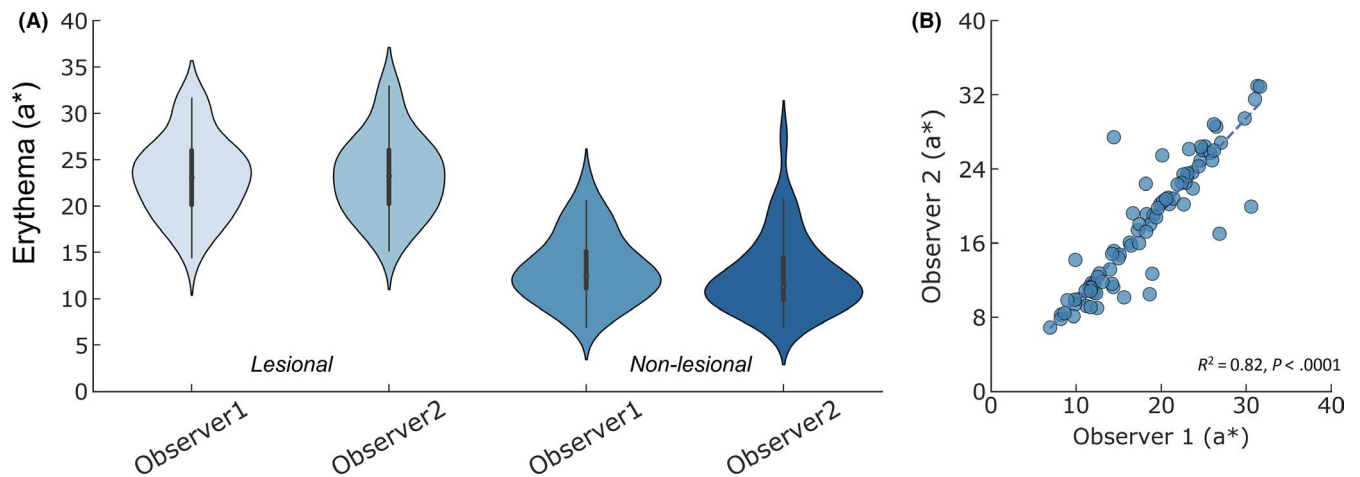


FIGURE 5 Interobserver variation of a^* at week 0 and 28. A, Lesional and non-lesional a^* values of both observers are displayed separately in a violin plot (median, interquartile range, upper and lower adjacent values; density plot width corresponds to frequency). B, a^* of lesional and non-lesional skin of both observers are merged for the linear regression analysis [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Step-by-step guideline for erythema quantification using ImageJ, recommended for daily clinical practice

Drag original JPG photograph in ImageJ.

Split image into CIELAB colour space: **Image**→ **Colour**→ **RGB to CIELAB**.

Scroll to second image (a^*).

For first visit:

Choose a region of interest (ROI) including lesional skin. Outline ROI with “Freehand selections.” Make sure to avoid any skin colour inconsistency due to pen lines, hair, tattoos, jewelry etc inside ROI.

Analyse→ **Measure**: record mean a^* of lesional skin.

Save ROI: **Analyse**→ **Tools**→ **ROI manager**. Click **Add [t]**→ **More**→ **Save**.

For follow-up visits:

Drag saved ROI into ImageJ; ROI is placed into the a^* image.

Analyse→ **Measure**: record mean a^* of lesional skin.

Transfer all recorded values to a digital database for data analysis.

application in clinical practice. Moreover, retrospective analysis of images is possible, preventing the use of extra time in the consultation room. It could possibly be expanded to quantify erythema in a wide range of inflammatory dermatoses, such as rosacea, atopic dermatitis and psoriasis. We suggest to use only a^* values, and not Δa^* , because correlations of both parameters with clinical scores are comparable, but a^* determination is faster than Δa^* . We recommend applying standardized, consistent, photography conditions in a studio setting.

5 | CONCLUSION

The tested image-based software tool is a simple, free, rapid and reproducible method to objectify and monitor erythema in rosacea patients during treatment. The only two requirements necessary for erythema analysis are: (a) ImageJ software, able to convert RGB images to CIELAB colour space and to quantify colour intensity (a^*) of a selected ROI; (b) clinical photographs, taken under standardized conditions in a studio. The photographs allow retrospective analysis, evaluation of large and small lesions, and discrimination of subtle redness differences. We recommend using lesional a^* in follow-up of erythema in inflammatory diseases in daily clinical practice (Table 3). We believe that this method is easily applicable for clinicians, and in the future, ideally would replace determination of subjective clinical scoring.

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ORCID

Jade G. M. Logger  <https://orcid.org/0000-0003-0627-0696>

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