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Perfusion measured by laser speckle contrast imaging as a predictor for expansion of psoriasis lesions

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Abstract

Background: Skin microvasculature changes are crucial in psoriasis development and correlate with perfusion. The noninvasive Handheld Perfusion Imager (HAPI) examines microvascular skin perfusion in large body areas using laser speckle contrast imaging (LSCI).

Objectives: To (i) assess whether increased perilesional perfusion and perfusion inhomogeneity are predictors for expansion of psoriasis lesions and (ii) assess feasibility of the HAPI system in a mounted modality.

Methods: In this interventional pilot study in adults with unstable plaque psoriasis, HAPI measurements and color photographs were performed for lesions present on one body region at week 0, 2, 4, 6 and 8. The presence of increased perilesional perfusion and perfusion inhomogeneity was determined. Clinical outcome was categorized as increased, stable or decreased lesion surface between visits. Patient feedback was collected on a 10-point scale.

Results: In total, 110 lesions with a median follow-up of 6 (IQR 6.0) weeks were assessed in 6 patients with unstable plaque psoriasis. Perfusion data was matched to 281 clinical outcomes after two weeks. A mixed multinomial logistic regression model revealed a predictive value of perilesional increased perfusion (OR 9.90; $p < 0.001$) and perfusion inhomogeneity (OR 2.39; $p = 0.027$) on lesion expansion after two weeks compared to lesion stability. HAPI measurements were considered fast, patient-friendly and important by patients.

Conclusion: Visualization of increased perilesional perfusion and perfusion inhomogeneity by noninvasive whole field LSCI holds potential for prediction of psoriatic lesion expansion. Furthermore, the HAPI is a feasible and patient-friendly tool.

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1 | INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease with a multifactorial pathophysiology, in which vascular alterations and angiogenesis are considered key features.[1–4] In the inflammatory process several angiogenic mediators like hypoxia-inducible factors, angiopoietins, and pro-angiogenic cytokines as well as vascular endothelial growth factor are upregulated.[1,5] On a histological level dermal papillary capillaries display increased dilatation, tortuosity, and permeability and show prominent elongation.[1,6] Angiogenesis and dilatation of dermal papillary capillaries are considered one of the first objectifiable skin changes, which even precede epidermal hyperplasia and are closely correlated with enhanced cutaneous blood flow.[1,7–10] Therefore, angiogenesis is even thought to be an inducer of psoriasis plaque development.[1,6,11,12] Noninvasive perfusion imaging in the pre-psoriatic skin could visualize these (early) vascular changes. Previous research by our group using a laser Doppler perfusion imaging (LDPI) system revealed increased perilesional perfusion in plaque psoriasis. Furthermore, a remarkable heterogeneous perfusion within psoriasis lesions was noted.[13–15] Perfusion heterogeneity was found to be associated with RNA and protein expression levels, with higher expression levels correlating to higher perfusion intensity.[14] We hypothesize that increased perilesional perfusion and perfusion inhomogeneity within a plaque predicts lesion expansion. Prediction of lesion expansion by noninvasive perfusion imaging could ultimately lead to early and patient friendly detection of disease progression, facilitating early intervention.

Methods available for noninvasive imaging of blood vessels in vivo include (video) capillaroscopy,[1,16,17] confocal laser-scanning microscopy,[18] optical coherence tomography[17,19] and optical micro-angiography.[20] The covered surface area of these imaging techniques varies between several micrometers and millimeters, limiting the potential use of these techniques in monitoring psoriasis plaques. With a covered imaging area of 7×7 cm^2, the LDPI system previously used by our group showed potential for the use of perfusion imaging in psoriasis.[13–15] However, to study the applicability of perfusion imaging for prediction of psoriasis plaque expansion, larger imaging areas combined with a short processing time are needed. Recently, the Handheld Perfusion Imager (HAPI) was developed, a laser speckle contrast imaging (LSCI) device with an approximate imaging field of 13×17 cm^2 with a real-time imaging function, enabling quick assessment of large skin surfaces.

This interventional pilot study aimed to assess whether (i) increased perilesional perfusion and perfusion inhomogeneity can predict psoriatic lesion expansion, and (ii) assess feasibility of the HAPI system in a mounted modality in a clinical research setting.

2 | MATERIALS AND METHODS

2.1 | Study design and population

In this interventional pilot study, six adult patients with unstable plaque psoriasis were included with a mean age of 56.0 ($\pm$14.7) years and a median psoriasis area and severity index (PASI) score of 5.8 (interquartile range [IQR] 4.4–7.2). Unstable psoriasis was defined as recent extension of psoriasis lesions according to the patient and/or treating physician. Patients with other concurrent inflammatory skin diseases were excluded. Patients were recruited at the outpatient clinic of the Department of Dermatology at the Radboud university medical center, Nijmegen, the Netherlands, between October 2019 and March 2020. Written informed consent was given by all patients. The study protocol was approved by the ethics committee of the Radboud university medical center, Nijmegen, the Netherlands (NL69174.091.19).

During follow-up, patients refrained from topical treatment on the body region of interest except emollients to increase the probability to capture lesion expansion. In five patients, the body regions of interest were arms, whereas in one patient a leg was assessed. Three patients were treated with systemic agents (two with methotrexate and one with adalimumab), which was continued in a stable dose. One subject dropped out after four study visits due to unbearable itch at the untreated body region, needing corticosteroid treatment. Due to the COVID-19 pandemic, another subject attended only two study visits. The visits of these two patients were included in the analysis. Additional patient characteristics can be found in Table S1.

2.2 | Study procedures

At baseline, the body region (one extremity) identified by the patient as most unstable was chosen for follow-up as the body region of interest. Visits were performed by the same physician (M.J. Schaap) at week 0, 2, 4, 6, and 8 including HAPI measurements and color photographs taken with the HAPI system of all clinically visible lesions on the body region of interest. The body surface area (BSA) of the body region of interest was determined along with the PASI score (range 0–72). Additionally, lesion outlines on transparent sheets, demographics and information on current treatment were collected. Feedback regarding the patient friendliness of the HAPI was determined on a 10-point scale at the end of follow-up. Patients did not use emollients on the investigated body region at the day of the visits. At least 30 min before each visit patients avoided local pressure and refrained from scratching the skin, smoking, drinking caffeine, and physical exercise.

2.3 | HAPI measurement

The HAPI was designed by the Biomedical Photonic Imaging group of the Faculty of Science and Technology, University of Twente, Enschede, the Netherlands. A technical description of the HAPI is provided in the Supplemental Information. The system was aligned and calibrated before each visit. Clinically visible lesion borders on the body region of interest were marked with a black marker for reference. Although handheld mode was available, HAPI measurements were performed in a mounted modality to avoid potential movement artefacts (Figure S1). Measurements lasted 7 s with 30 frames per second and 40 cm distance from the skin corresponding with an imaging field-of-view of 13×17 cm^2. All measurements were done with identical system settings (such as exposure time and diaphragm size) and were performed in the same dark and air conditioned room.

Perfusion maps were generated by first aligning all 210 frames. Second, the average perfusion intensity was determined for each frame by selecting a 2.1×2.1 cm^2 region in the center of the psoriatic lesion. To limit the influence of heartbeat and movement artefacts caused by involuntary motions of the patient, perfusion maps were generated by temporarily averaging 40 frames with the lowest average perfusion intensity. To correct for other natural perfusion fluctuations over time, perfusion maps were normalized to the average perfusion of non-lesional skin (background perfusion). The background perfusion was calculated by averaging the perfusion of three distant non-lesional areas. All perfusion values were divided by this non-lesional background perfusion.[13]

2.4 | Data analysis

Clinical lesion course was assessed based on color images and lesion outlines on transparent sheets. Lesion size was compared between two visits, and the lesion course was classified as increased, stable, or decreased. The lesion course was reviewed completely independent from the perfusion maps.

Perfusion maps were assessed for the presence of increased perilesional perfusion and perfusion inhomogeneity. Furthermore, mean lesion perfusion and perfusion levels of increased perilesional perfusion and the highest perfused area in inhomogeneously perfused lesions were determined. Different visualization scales were used for appropriate assessment of increased perilesional perfusion (maximum perfusion scale set at three times the background perfusion) and perfusion heterogeneity (normalized to the highest perfused area). Increased perilesional perfusion was defined as perfusion ≥ 1.5 times the background perfusion and exceeding the marked lesion borders (Figure S2). Perfusion inhomogeneity was defined as visual inhomogeneity with a perfusion level in the highest perfused area of ≥ 1.5 times the mean perfusion (Figure S3).

Clinical lesion course and perfusion maps were assessed in a random order to avoid confirmation bias. Full data analysis was performed by Mirjam J. Schaap and a random 30 percent of the data were blindly assessed by Ata Chizari and Marieke M. B. Seyger. Inconsistencies (<5% of the 30% random blinded sample) were resolved by consensus. Analyses were performed with Matlab R2018a.

2.5 | Statistical analysis

Baseline categorical characteristics were presented as frequencies and percentages, and continuous variables were presented as means and standard deviation ($\pm$SD) or medians and IQR. Perfusion variables were matched to the clinical lesion outcome (increase, stable or decrease) after two weeks. A mixed multinomial logistic regression (MMLR) model, correcting for multiple measures within one patient, was conducted to estimate the probability on lesion increase, decrease and stability after two weeks (outcome) as a function of the presence of increased perilesional perfusion and perfusion inhomogeneity. Relations were indicated by odds ratios (OR). As the clinical interpretation of OR is challenging, additional probabilities were computed by the model to improve interpretation of the results. Two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were performed using statistical package SPSS, version 25 (IBM, Armonk, NY, USA.).

3 | RESULTS

3.1 | Clinical lesion outcomes

In total, 110 lesions were followed during a median follow-up time of 6 weeks (IQR 6.0). Lesion diameter varied from 0.3 to 13.7 cm. Apart from the shortened follow-up time in two patients, the follow-up time of lesions varied due to the natural disease course. At baseline, a total of 73 lesions were present in the body regions of interest of all patients, while 102 lesions were present at the end of follow-up. Lesion course classification (increased, stable, or decreased) over 2 weeks could be performed 281 times. Patient 5 contributed 39.9% of these data points, while the other patients contributed 6.8%–18.9%. In 124 (44.1%) occasions lesions stayed stable, 90 (32.0%) times lesions increased, and in 67 (23.8%) occasions lesions decreased. The affected BSA on the extremity of interest slightly increased in most patients. However, patient 2 showed a decrease at the end of follow-up, and the BSA of patient 5 substantially increased (Figure 1).

3.2 | Prediction of lesion expansion by perfusion imaging

Increased perilesional perfusion was found 101 (35.9%) times, with a median perfusion of 1.8 (IQR 1.6–2.0) times the background perfusion. Increased perilesional perfusion was frequently followed by lesion expansion after 2 weeks ($n = 66$; 65.3% [Table 1]). Less frequently, it resulted in clinical stability ($n = 27$; 26.7%) or decrease ($n = 8$; 7.9%). In absence of increased perilesional perfusion, 24 (13.3%) lesions increased. Perfusion inhomogeneity was observed in 98 (34.9%) occasions, mostly resulting in lesion increase

TABLE 1 Lesion clinical outcomes with and without preceding increased perilesional perfusion or perfusion inhomogeneity

Outcome	Increased perilesional perfusion, N (%)	No increased perilesional perfusion, N (%)	Perfusion inhomogeneity, N (%)	Homogeneous perfusion, N (%)
Increase	66 (65.3)	24 (13.3)	57 (58.2)	33 (11.7)
Stable	27 (26.7)	97 (53.9)	32 (32.7)	92 (50.3)
Decrease	8 (7.9)	59 (32.8)	9 (9.2)	58 (31.7)
Total	180	101	98	18

Lesion clinical outcomes after two weeks with and without preceding increased perilesional perfusion or perfusion inhomogeneity. Increased perilesional perfusion is defined as ≥1.5 increased in relation to the background perfusion. Perfusion inhomogeneity is defined as visual inhomogeneity and a perfusion level in the highest perfused area of ≥1.5 times the mean lesion perfusion.
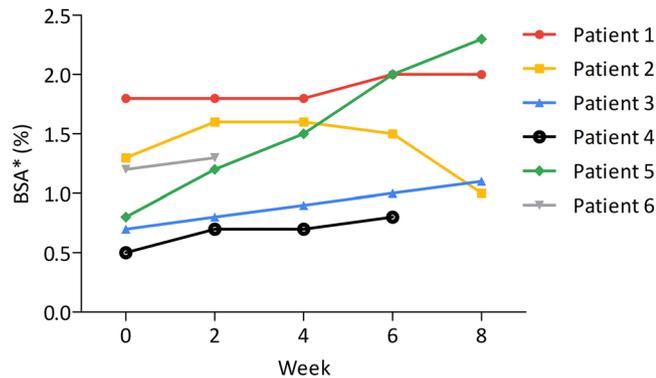
FIGURE 1 Affected body surface area on the body region of interest in each patient during follow-up. Each line represents an individual patient. *Affected body surface area (BSA) on the extremity of interest, one palm of the hand reflects 1% BSA (of the whole body surface area).

($n = 57$; 58.2%), followed by stability ($n = 32$; 32.7%), and decrease ($n = 9$; 9.2%). If lesion perfusion was homogeneous, this mostly resulted in a stable ($n = 92$; 50.3%) lesion after 2 weeks. An example of increased perilesional perfusion and perfusion inhomogeneity preceding lesion increase with corresponding color images over several weeks is shown in Figure 2.

An MMLR, correcting for multiple measures within one patient, assessing the predictive value of increased perilesional perfusion and perfusion inhomogeneity on lesion course showed that increased perilesional perfusion (OR 9.90; $p < 0.001$, OR 10.85; $p < 0.001$) and perfusion inhomogeneity (OR 2.39; $p = 0.027$, OR 3.76; $p = 0.002$) were significantly associated with a greater odds of lesion increase compared to stability and decrease after 2 weeks, respectively (Table 2). Additionally probabilities computed by the model revealed a 15.5 times increased chance of lesion increase (72.8%) compared to decrease (4.7%) after 2 weeks in the presence of both increased perilesional perfusion and perfusion inhomogeneity (Figure 3).

3.3 | Patient feedback

Feedback was collected on a 10-point scale during the last visit of five patients. A score of 8.20 ± 1.30 was given for the general impression

of the HAPI (0; negative, 10; positive). Patients rated the importance of prediction of lesion expansion by the HAPI very high: 8.80 ± 1.30 (0; not valuable, 10; very valuable). Patients did not experience much measurement burden: 9.20 ± 1.10 (0; high burden, 10; no burden). Last, the duration of a single measurement was considered relatively short: 7.80 ± 2.59 (0; very long, 10; very short).

4 | DISCUSSION

In this explorative study, we used the HAPI, an LSCI based system, to reveal an increased probability of psoriatic lesion expansion after two weeks if increased perilesional perfusion and perfusion inhomogeneity were present, corresponding with a 72.8% chance of lesion expansion in the presence of both. To the best of our knowledge, the potential predictive value of perfusion characteristics on psoriatic lesion expansion has not been described to date. Our study provides new insights into the influence of the microvasculature on lesion expansion. We showed that both increased perilesional perfusion outside the clinically visible lesion borders, as well as clinical expansion of the lesions 2 weeks later, was usually only several millimeters. This corresponds with the finding that most instable psoriasis lesions only increase several millimeters a week.[9] Even though the clinical increase of psoriasis lesions over a short time span is subtle, it can be regarded as a sign of disease instability. Therefore, in clinical practice, perfusion imaging could be used to assess disease instability.[21,22] In the present study, perilesional perfusion and perfusion inhomogeneity were assessed in lesions in one body region. However, if full body perfusion imaging would be feasible in future clinical practice, this assessment could provide additional information on overall disease instability, support treatment decisions, facilitate early intervention, and prevent undertreatment.

To explore if the predictive value of perfusion imaging on lesion course is also valid for a longer time period, we performed a post hoc-analysis assessing lesion course prediction over 6 weeks. This MMLR model based on 68 lesions in five patients revealed increased perilesional perfusion to be significantly associated with lesion expansion after six weeks compared to lesion stability (OR 14.77; $p = 0.001$) and decrease (OR 6.96; $p = 0.012$). However, perfusion inhomogeneity was not found to be significantly associated with lesion expansion after 6 weeks (Table S2).
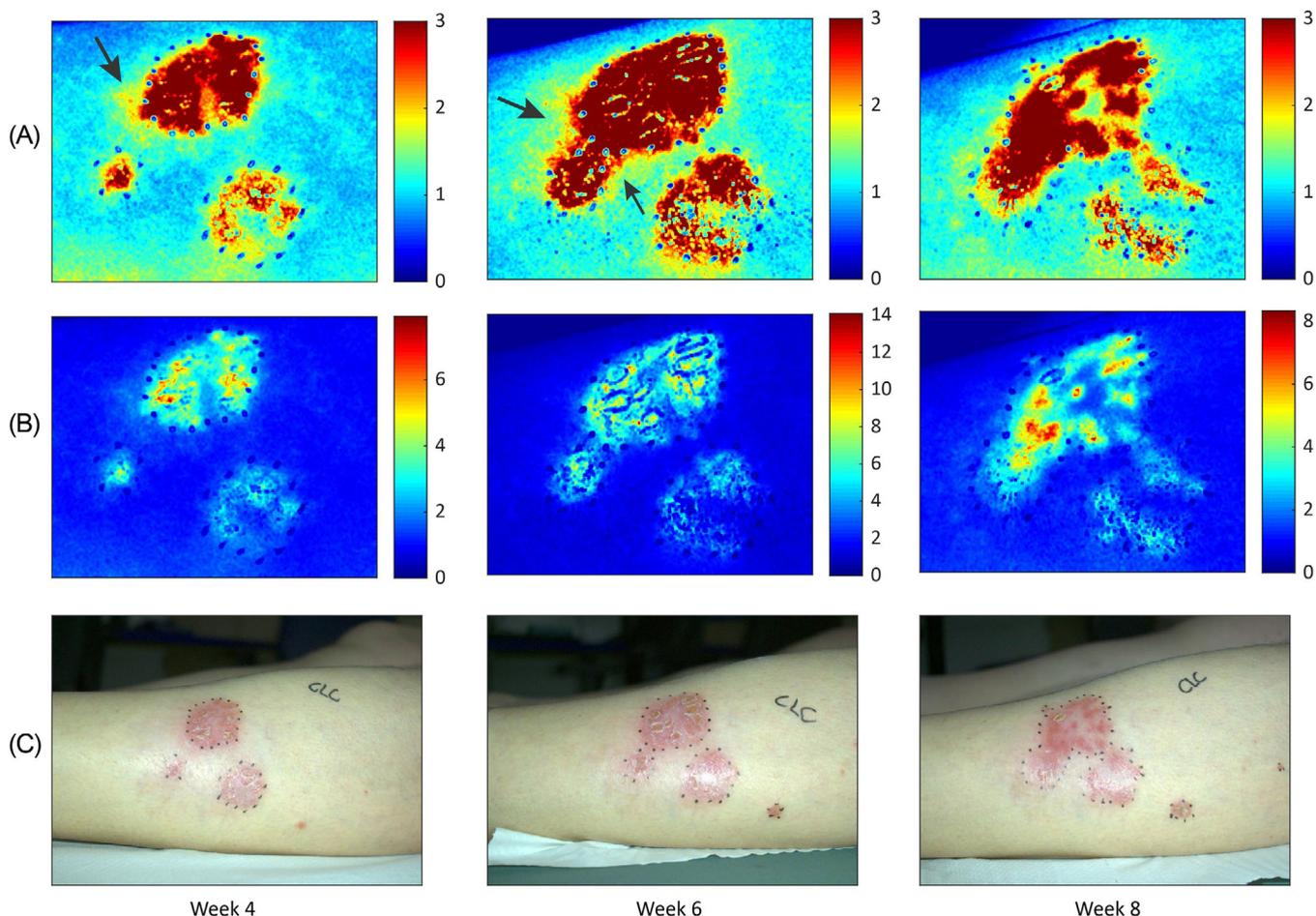
FIGURE 2 Increased perilesional perfusion and perfusion inhomogeneity preceding clinical lesion expansion. Perfusion intensity expressed as background value (number of times increased compared to non-lesional skin). Perfusion is shown in different scales for appropriate assessment of (A) perilesional perfusion (downscaled to visualize increased perfusion with respect to non-lesional skin) and (B) perfusion heterogeneity (normalized to the highest perfusion level to visualize relatively lower and higher perfused areas within a lesion). Increased perilesional perfusion is defined as ≥1.5 increased perfusion in relation to the background perfusion. Perfusion inhomogeneity was defined as visual inhomogeneity with a perfusion level in the highest perfused area of ≥1.5 times the mean lesion perfusion. Clinical expansion is shown on color images (C). The size of the color images (C) corresponds with the full imaging field of the HAPI system.

Previous research revealed an increased blood flow in psoriatic lesions compared to non-lesional skin.[13,23–28] It was also shown that microvasculature changes and increased perfusion in a lesion precede the clinical expansion of a psoriasis lesion.[1,7–10] Our study, which was performed with a larger imaging field and in substantially more psoriasis lesions, underlines these findings. Because our group is the first to image full psoriasis lesions, perfusion inhomogeneity, and the perilesional area of these psoriasis lesions, we were now able to show the potential of perfusion inhomogeneity and increased perilesional perfusion as a predictor for expansion of psoriasis lesions.

Some limitations should be addressed. The number of lesions, and therefore the contribution to the dataset, per patient varied. However, we corrected for this in our MMLR model. Although it is unlikely that results have been influenced by imaging artefacts, this cannot be fully ruled out. Artefacts caused by substantial desquamation were observed occasionally, caused by reflection of the laser light and inad-

equate penetration depth. In theory, desquamation artefacts could result in an underestimation of lesion perfusion. However, this does not influence the assessment of increased perilesional perfusion and perfusion inhomogeneity. Even though LSCI is susceptible for motion, we did not identify evident motion artefacts.

Patients considered the HAPI system a friendly tool for noninvasive assessment of skin perfusion and highly valued the prediction of lesion expansion. For clinical application, it has to be noted that lesion borders were manually marked in this study, which is not feasible in daily clinical practice. Incorporating automated clinical lesion border detection (e.g., by using color image based natural landmarks) would benefit the clinical feasibility of perfusion imaging. Moreover, the HAPI holds potential for handheld use which would drastically increase clinical feasibility.[29]

This study explored the predictive value of skin perfusion on psoriatic lesion expansion in one body region in six patients reporting to have unstable psoriasis. However, despite the cessation of topical treatment on the studied body region, actual disease progression

TABLE 2 Predictive value of increased perilesional perfusion and perfusion inhomogeneity on lesion course after two weeks

Predictor	Outcome	Versus	OR	95% Confidence Interval	p value
Increased perilesional perfusion[†]	**Increase**	Stable	9.90	4.61–21.28	<0.001
		Decrease	10.85	4.80–24.52	<0.001
	Stable	Increase	0.10	0.05–0.22	<0.001
		Decrease	1.10	0.48–2.51	0.827
	Decrease	Increase	0.09	0.04–0.21	<0.001
		Stable	0.91	0.40–2.10	0.827
Perfusion inhomogeneity[‡]	**Increase**	Stable	2.39	1.11–5.14	0.027
		Decrease	3.76	1.65–8.56	0.002
	Stable	Increase	0.42	0.19–0.90	0.027
		Decrease	1.58	0.69–3.60	0.278
	Decrease	Increase	0.27	0.12–0.61	0.002
		Stable	0.63	0.28–1.45	0.278

Odds ratios (OR) calculated with a mixed multinomial logistic regression model estimating the probability on lesion surface increase, stability and decrease after 2 weeks (outcome) as a function of the presence of increased perilesional perfusion (yes or no) and perfusion inhomogeneity (yes or no). For example, the odds of lesion increase versus stability after 2 weeks is 9.90 times greater in the presence of increased perilesional perfusion compared to the absence of increased perilesional perfusion.

[†]Presence of increased perilesional perfusion, defined as ≥1.5 increased in relation to the background perfusion.

[‡]Presence of perfusion inhomogeneity, defined as visual inhomogeneity and a perfusion level in the highest perfused area of ≥1.5 times the mean lesion perfusion.
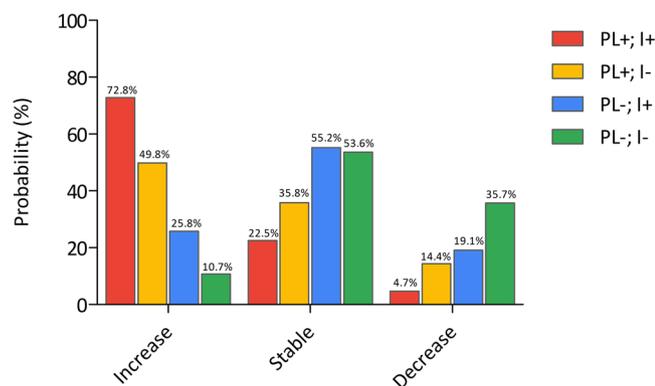
FIGURE 3 Probabilities of lesion increase, stability or decrease in the presence (+) or absence (−) of increased perilesional perfusion (PL) and/or perfusion inhomogeneity (I) as computed by the model. Probabilities calculated by a mixed multinomial logistic regression model, correcting for multiple measures within one patient, assessing the predictive value of the presence of increased perilesional perfusion or perfusion inhomogeneity on lesion increase, decrease or stability after 2 weeks

in this region varied during follow-up, underlining the challenge of determining psoriasis (in)stability in clinical practice. Since psoriasis lesions of one body region were assessed, and all other body areas were topically treated during follow-up, we used the regional BSA to report the disease course of the studied body region. As all other body areas were treated during follow-up, the association of perfusion measurements with overall severity scores (e.g., PASI) could not be assessed. To assess the association between (peri)lesional perfusion and the overall disease course, future studies should focus on full body perfusion imaging. In addition, to further determine the value of perfusion imaging in psoriasis in clinical practice, larger studies have to be performed in a population reporting both stable and unstable psoriasis.

In conclusion, perfusion imaging holds potential for the prediction of psoriatic lesion expansion by detecting increased perilesional perfusion and perfusion inhomogeneity. Since lesion expansion indicates psoriasis instability, noninvasive detection of disease instability by whole field perfusion imaging might aid treatment decisions and enable early treatment.

CONFLICT OF INTEREST

Mirjam J. Schaap has carried out clinical trials for Amgen, Celgene, Janssen, and Lilly and has acted as a paid speaker for AbbVie; fees were paid directly to the institution. Ata Chizari, Tom Knop, Hans M.M. Groenewoud, Piet E.J. van Erp has no conflict of interest to declare. Elke M.G.J. de Jong has received research grants for the independent research fund of the department of dermatology of the Radboud university medical center Nijmegen, the Netherlands from AbbVie, Novartis, Janssen Pharmaceutica, Leo Pharma and UCB and has acted as consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie,

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.