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ORIGINAL ARTICLE

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Thermo-SPT: A new skin prick test evaluation framework based on low-cost, portable smartphone thermography

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Abstract

Background: Although the skin prick test (SPT) is a reliable procedure to confirm IgE-dependent allergic sensitization in patients, the interpretation of the test is still performed manually, resulting in an error-prone procedure for the diagnosis of allergic diseases.

Objective: To design and implement an innovative SPT evaluation framework using a low-cost, portable smartphone thermography, named Thermo-SPT, to significantly improve the accuracy and reliability of SPT outcomes.

Methods: Thermographical images were captured every 60 s for a duration of 0 to 15 min using the FLIR One app, and then analysed with the FLIR Tool®. The definition of '*Skin Sensitization Region*' area was introduced to analyse the time-lapse thermal changes in skin reactions over several time periods during the SPT. The Allergic Sensitization Index (ASI) and Min–Max Scaler Index (MMS) formulae were also developed to optimize the identification of the peak allergic response time point through the thermal assessment (TA) of allergic rhinitis patients.

Results: In these experimental trials, a statistically significant increase in temperature was detected from the fifth minute of TA for all tested aeroallergens (all p values $< .001$). An increase was observed in the number of false-positive cases, where patients with clinical symptoms not consistent with SPT were evaluated as positive on TA assessment, specifically for patients diagnosed with *Phleum pratense* and *Dermatophagoides pteronyssinus*. Our proposed technique, the MMS, has demonstrated improved accuracy in identifying *P. pratense* and *D. pteronyssinus* compared with other SPT evaluation metrics, specifically starting from the fifth minute. For patients diagnosed with *Cat epithelium*, although not statistically significant initially, an increasing trend was determined in the results at the 15 min (ΔT ($T_{15} - T_0$), $p = .07$; ASI_{T15}, $p < .001$).

Conclusions: This proposed SPT evaluation framework utilizing a low-cost, smartphone-based thermographical imaging technique can enhance the interpretability of allergic

Polat Goktas and Ozge Can Bostan contributed equally to this work (Polat Goktas and Ozge Can Bostan are co-first authors).

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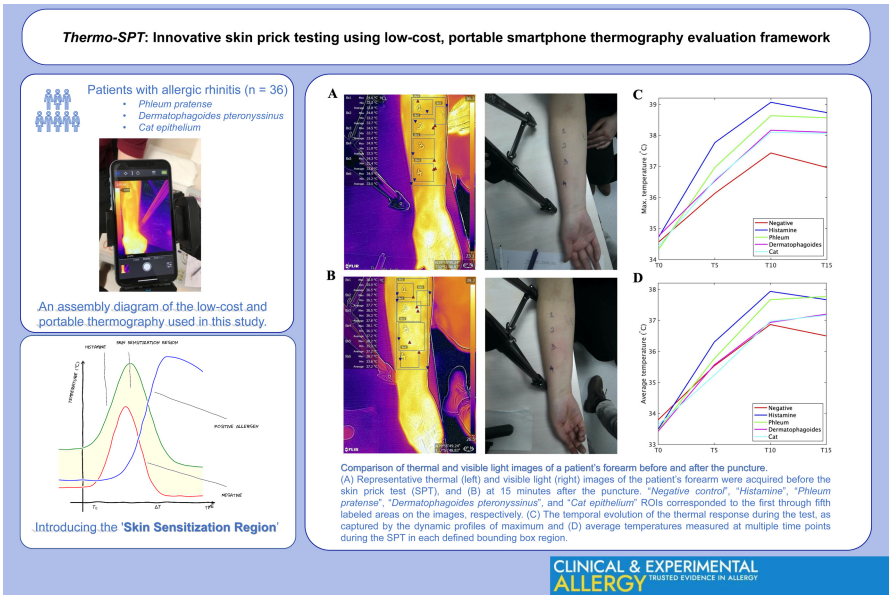
responses during the SPT, potentially reducing the need for extensive manual interpretation experience as standard SPTs.

KEYWORDS
allergic rhinitis, infrared thermography, skin prick test, smartphone, thermal camera, thermal imaging



GRAPHICAL ABSTRACT

To improve the accuracy and reliability of skin prick test (SPT) outcomes, an innovative SPT evaluation framework using low-cost, portable smartphone thermography is presented. The proposed framework has the potential to effectively assess allergen-induced skin reactions at multiple time points during the SPT, as an alternative to the extensive manual interpretation experience as standard SPTs.

1 | INTRODUCTION

Allergic rhinitis (AR) is a prevalent global health concern that significantly impacts individuals' productivity, social interactions and overall quality of the life.[1] The current diagnosis of AR includes the patient's medical history, physical examination and sensitization tests such as serum allergen-specific immunoglobulin E (sIgE) and skin prick test (SPT) if needed.[2] SPT is the currently preferred diagnostic method not only for identifying triggers of allergic diseases but also for elucidating the underlying mechanisms, due to its simplicity, reliability and cost-effectiveness.[3] It is typically performed in clinics by using a lancet to apply small droplets of allergen extracts to the skin surface, usually on the volar surface of the forearm. A positive allergic reaction is characterized by the presence of an induration or a raised, itchy bump (wheal) and erythema or redness (flare) at the site of the allergen application area. To identify the specific allergens responsible for allergic sensitization, the size of induration in the SPT is evaluated 15–20 min after administration. A positive result is determined when the mean wheal diameter (MWD) is greater than 3 mm and at least 2 mm greater than the negative control.[4] However, despite the advancements in this field, the evaluation procedure of measuring the contour of the induration still relies on manual measurements. The traditional method of visually defining the induration form using an ellipse or circle is prone to errors, thus leading to unreliable outcomes.[5,6] In addition, the results need to be evaluated by trained specialists and outcomes can have a more subjective interpretation. In clinical practice, a significant number of patients have reported negative results from SPTs despite the presence of confirmed sensitivity to aeroallergens in their medical history. In

Key messages

- Interpretation of skin prick test (SPT) is a manual task and more automated methods are needed.
- Thermo-SPT ensures precision and accuracy for SPT interpretation, as validated by this proof-of-concept study.
- Thermo-SPT shortens the time required for evaluating SPT results.

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addition to discrepancies in the measurement, technical errors, such as insufficient penetration of the lancet into the skin, can occur and should be minimized to ensure reliable identification of allergic sensitization. Furthermore, cost-effective and simple-to-use diagnostic test method that shorten test process duration and increase the reliability of the result should benefit both practitioners and patients. To the best of our knowledge, there is currently no standardized evaluation framework regarding the screening of the measurement site and interpretation of allergy test results to address the above-mentioned challenges in the SPT. Therefore, there is a need for a specific, standardized and automated SPT evaluation framework for the diagnosis of allergic sensitization.

In this study, an infrared thermography (IRT) system was integrated into the standard SPT procedure for the evaluation of allergen-induced skin reactions at multiple time points, thus improving the capabilities of the SPT. IRT is a non-invasive and contactless method that uses infrared radiation to monitor skin surface temperature in the human body.[7–9] Previous studies, such as the research by Phipatanakul et al. laid the foundation for the use of thermal imaging in skin prick test,[10] and it has been suggested that thermographical imaging systems could be useful to diagnose allergic diseases, but the implementation of this technology into clinical practice remains a concern.[9,11–14]

The aim of this study was to introduce a cutting-edge SPT evaluation framework utilizing a low-cost, portable smartphone thermography application to improve the accuracy and reliability of SPT outcomes for allergen-induced skin reactions. Experiment trials were conducted to evaluate its use to be able to increase the repeatability and applicability of the IRT imaging modality in clinical settings. Using the temperature change distribution as a function of time, an optimal reading time point formulation that discriminates the specific aeroallergen sensitivity was also investigated, particularly for the identification of the positive allergic sensitization in AR patients.

2 | METHODS

2.1 | Study population and design

This feasibility study included patients aged ≥18 years who presented at the Hacettepe University Adult Allergy and Clinical Immunology Department between December 2019 and June 2020, with AR symptoms ongoing for at least 1 year. According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline, the diagnosis of AR was determined based on the presence of at least one of the symptoms of runny nose, sneezing, nasal itching and nasal congestion, as well as a physical examination by a specialist physician.[15] Patients with symptoms throughout the year were classified as having perennial rhinitis, whereas those with symptoms between March and June, the pollination period of the study region, were classified as having seasonal rhinitis. Patients were excluded if they had the presence of active dermatitis or dermographism on their arms, pregnancy or had used any of the following within 7 days before the test: antihistamines, antidepressants or other drugs that can affect SPT results. Each participant in this feasibility study underwent a standard SPT with aeroallergens and thermographical assessment (TA) with a panel including negative control, histamine (positive control), *Phleum pratense*, *Dermatophagoides pteronyssinus* and *Cat epithelium*.

2.2 | SPT and thermographical imaging measurements

SPT was performed on each participant using a standard aeroallergen extract panel (Lofarma®, Milan, Italy) including histamine (10 mg/mL) and 50% glycerine solution as positive and negative controls respectively. Aeroallergens for *Phleum pratense*, *Dermatophagoides pteronyssinus* and *Cat epithelium* were tested using individually packaged, single-use, disposable lancets (ALK-Lancet® for Prick Test) for each aeroallergen used in the SPT. The experimental protocol was modified to be a negative control, a positive control, and the three above-mentioned aeroallergens, spaced at a fixed distance of approximately 6–7 cm. The standard procedure of the SPT was then performed by puncturing the volar surface of the forearm to a depth of 1 mm with a lancet. As a matter of routine, a trained specialist assessed the induration as an indicator of the skin reactivity with a transparent millimetre ruler, at 15–20 min after the puncture. In this study, an aeroallergen reaction was considered positive if an induration surrounding the prick had a maximum diameter greater than 3 mm for histamine and at least 2 mm greater than the negative control, and if there was no reaction to the negative control, as confirmed by the clinical specialists involved in the study.

The FLIR One® Pro (FLIR-Systems, Wilsonville, USA) is a low-cost, portable thermographical imaging method that requires a smartphone and a FLIR One application.[16] It features a multispectral dynamic imaging (MSX) mode that merges visible light and thermal images to increase the level of detail in the image. It has thermal resolution of 160 × 120 pixels, visual resolution of 640 × 480 pixels, angle of view of 50° ± 1°/43° ± 1°, and thermal sensitivity/noise equivalent temperature difference (NETD) of 0.07°C/70 mK.[17] During the course of the SPT, the room temperature was maintained at 23°C. The patient's forearms were positioned on a table with the smartphone-based thermal camera placed above them at a distance of 40 cm. The forearms were arranged in a perpendicular orientation to the camera (see Figure 1).

Notably, the most important aspect of any thermal image is to match the temperature colour palette with the atmospheric and object temperatures within the field-of-view. In this study, the iron colour palette was chosen as the visual temperature indicator to screen the reaction behaviour of different aeroallergens applied to the volunteers. During the SPT, the FLIR One app was used to capture thermographical images every 60 s from 0 to 15 min, which were then analysed with the FLIR Tool® Thermal Analysis and Reporting software tool.

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FIGURE 1 An assembly diagram of the low-cost and portable thermography used in this study, which consists of a smartphone attached to a FLIR One Pro device and a support structure placed above the forearm.

2.3 | Data analysis

For thermal image analysis, the region-of-interest (ROI) was determined for each negative control, histamine and three aeroallergens bounding box regions on the volar surface of the forearm of each patient. In this clinical experiment; *negative control*, *histamine*, *Phleum pratense*, *Dermatophagoides pteronyssinus* and *Cat epithelium* ROIs corresponded to the first through fifth-labelled areas on the images respectively. All the ROIs were bilaterally analysed for each participant. The maximum and average temperature patterns for each ROI were then computed using the FLIR Tool® Thermal Analysis and Reporting software tool to account for the patient-to-patient variability as well as vessel interactions on the volar surface of the forearm. The temperature change distribution as a function of time was investigated for all datasets and when the area under the curve (AUC) for a particular aeroallergen was determined to exceed a specific threshold temperature range, this was defined as positive allergen-induced skin reaction at that time point (see Figure 2). Based on this evidence, we established a conceptual diagram of dynamic behaviours of aeroallergens at multiple time points during the SPT, named as the *Skin Sensitization Region*, to determine positive allergic sensitization in patients (see Figure 3). Here, two SPT evaluation metrics were proposed for assessing allergic sensitization in patients based on the fundamental mechanism of aeroallergen behaviour, to be used in thermal assessment (TA). In the rough data analysis, the temperature patterns were scaled between −1 and 1, referred to as the Allergic Sensitization Index (ASI), as follows:

$$\mathrm{ASI} = \frac{\left|T_a - T_{\mathrm{Neg}}\right| - \left|T_a - T_{\mathrm{Hist}}\right|}{\left|T_{\mathrm{Hist}} - T_{\mathrm{Neg}}\right|} \quad (1)$$

where T_a is the temperature value of the aeroallergen, T_{Neg} is the temperature value of the negative control and T_{Hist} is the temperature value of the histamine at time point T, respectively. An aeroallergen was evaluated as positive if the value of the ASI exceeded zero.

In addition, the temperature values were converted by scaling each feature to a particular range for fine-tuning aeroallergen behaviour distribution across time points, named as the Min–Max Scaler Index (MMS). The formula of the MMS was defined as follows:

$$\mathrm{MMS} = \frac{\left|T_a - T_{a_0}\right| - \left|T_{\mathrm{Neg}} - T_{\mathrm{Neg}_0}\right|}{\left|T_{\mathrm{Hist}} - T_{\mathrm{Hist}_0}\right| - \left|T_{\mathrm{Neg}} - T_{\mathrm{Neg}_0}\right|} \quad (2)$$

where T_{a_0} is the temperature value of the aeroallergen, T_{Neg_0} is the temperature value of the negative control and T_{Hist_0} is the temperature value of the histamine at $t = 0$ min, respectively. An allergen reaction was evaluated positive if the value of the MMS was greater than 0.5. It was considered that this proposed SPT evaluation technique, the MMS, would allow the analysis of a wide range of aeroallergen behaviour at multiple time points during the SPT, leading to the determination of an optimal reading time point for the diagnosis of allergic sensitization in patients.

To determine the effectiveness of the proposed SPT evaluation techniques, they were compared against the relative temperature and temperature difference, ΔT ($T_5 - T_0$, $T_{10} - T_0$ and $T_{15} - T_0$) measures used in this study.[13] For the case of relative temperature, an aeroallergen was considered positive if its temperature at time point T was higher that of the histamine at $t = 15$ min. Furthermore, an aeroallergen was evaluated as positive if the value of the temperature difference (ΔT) at time point T was greater than that of the histamine at the same time point.

2.4 | Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to evaluate the normality of distribution of the continuous variables. Unless otherwise stated, descriptive statistics were presented as mean ± standard deviation and median (interquartile range; 25th–75th percentiles) values for normally and non-normally distributed data, respectively. The Wilcoxon sign-rank test was applied in the

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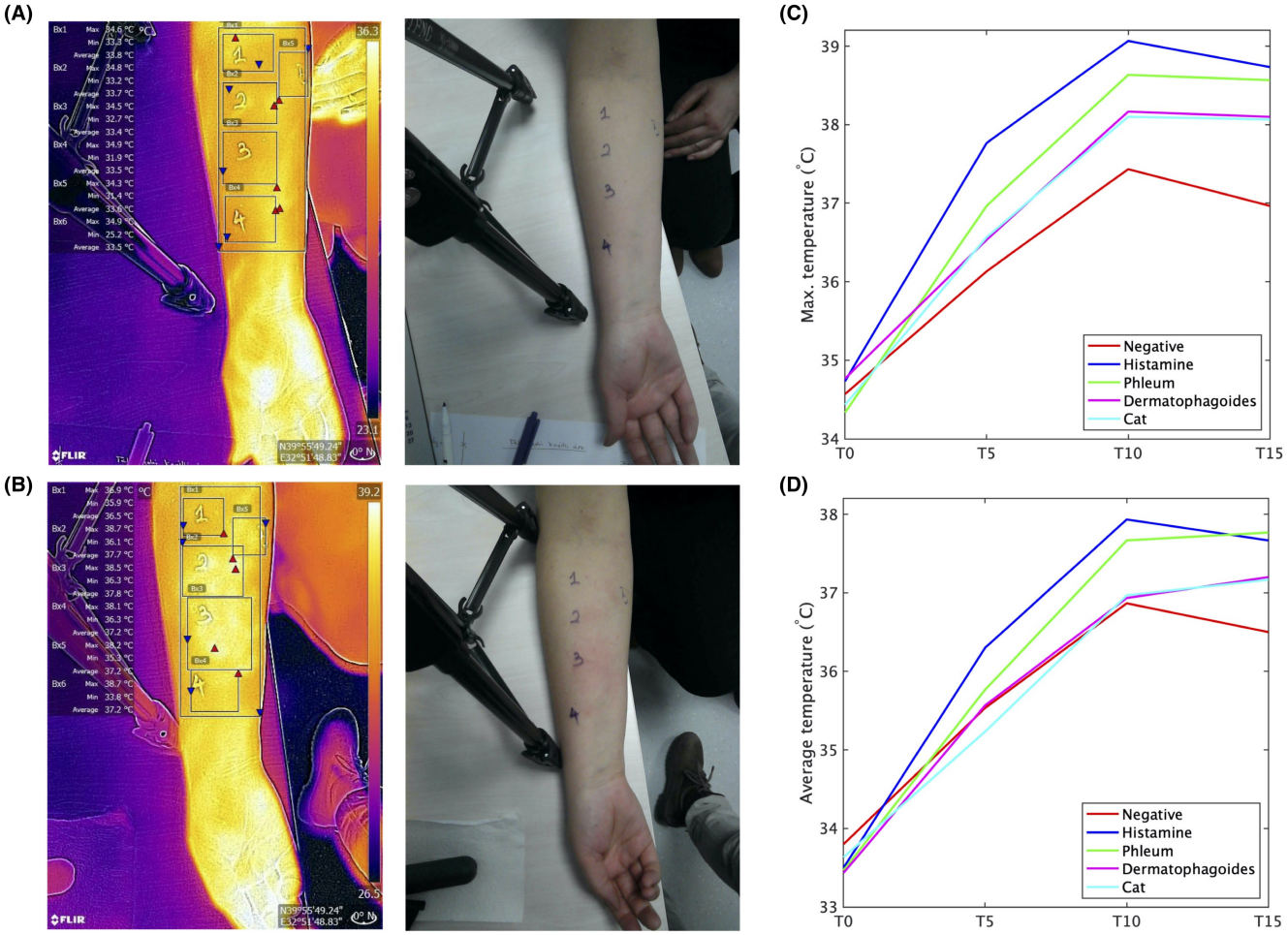

FIGURE 2 Comparison of thermal and visible light images of a patient's forearm before and after the puncture. (A) Representative thermal (left) and visible light (right) images of the patient's forearm were acquired before the skin prick test (SPT), and (B) at 15 min after the puncture. '*Negative control*', '*Histamine*', '*Phleum pratense*', '*Dermatophagoides pteronyssinus*' and '*Cat epithelium*' ROIs corresponded to the first through fifth-labelled areas on the images respectively. (C) The temporal evolution of the thermal response during the test, as captured by the dynamic profiles of *maximum* and (D) *average* temperatures measured at multiple time points during the SPT in each defined bounding box region.

comparisons of the values of average or maximum temperatures at the 0, 5, 10 and 15 min for each aeroallergen. The Mann–Whitney *U* test was used to compare values of the temperature difference (ΔT) and allergic sensitization index (ASI) techniques assessed by TA between confirmed SPT-negative and SPT-positive patients. The correlations between the results of SPT evaluation techniques and standard SPT were examined using Cohen's Kappa (κ) coefficient. Additionally, the performance metrics, including positive predictive value (PPV), negative predictive value (NPV), specificity, sensitivity and accuracy were analysed for the comparison of the proposed SPT evaluation technique and the standard SPT for aeroallergen detection in patients. The level of statistical significance was set as $p < .05$.

2.5 | Ethical approval and informed consent

The study was approved by the Clinical Research Ethics Committee (Approval No: GO 19/1099) of the Hacettepe University, Ankara, Turkey. All the participants were informed about the purpose of the study and provided written informed consent. All procedures in this study involving human subjects were conducted in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments.

3 | RESULTS

This feasibility study included 36 patients who were admitted to the Hacettepe University, Adult Allergy and Clinical Immunology clinic with the symptoms of AR. Twenty-four (66.7%) of the included subjects were female and their median age was 33.5 (22.5–42.0). The median duration of AR was 4.0 (2.0–8.5) years. Seasonal symptoms were determined in 14 (38.9%) patients, perennial symptoms in 18 (50.0%) and perennial symptoms with seasonal exacerbations in 4 (11.1%). All the patients tested positive with histamine in the SPT, and none had a reaction in the negative control. SPTs showed that

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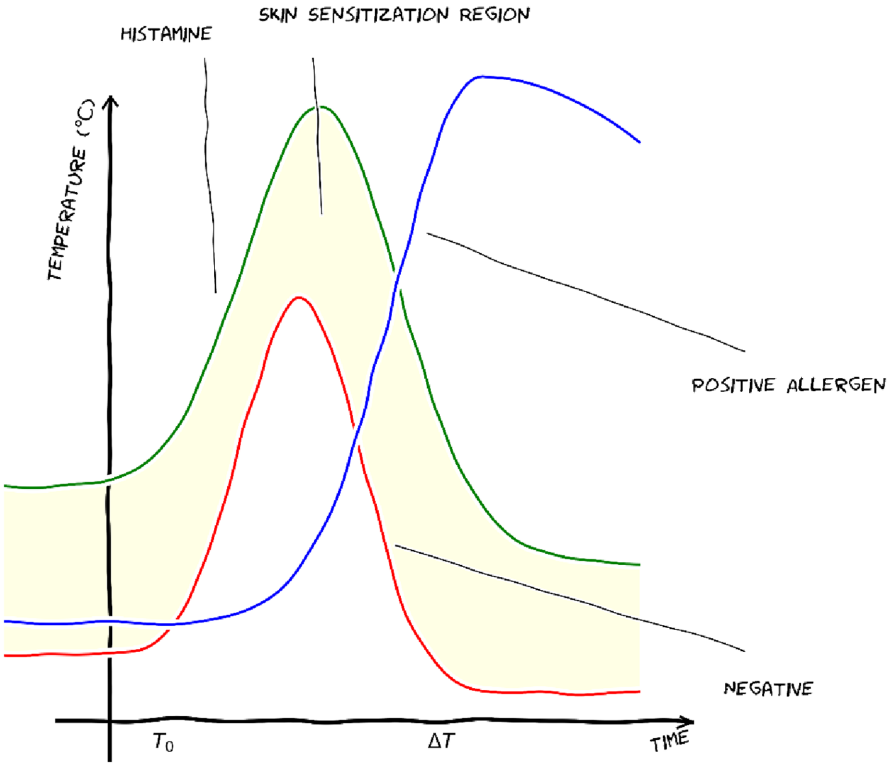

FIGURE 3 A visual representation of the temporal evolution of allergen-induced thermal responses over time.

TABLE 1 Patient characteristics of the study population ($n = 36$).

Variables	*n* (%)
Age, Median (IQR), years	33.5 (25.5–42)
Rhinitis duration, years	4.0 (2.0–8.5)
Female gender, *n* (%)	24 (66.7)
AR classification	
• Seasonal	14 (38.9)
• Perennial	18 (50.0)
• Perennial with seasonal exacerbations	4 (11.1)
SPT-positive results	
• Phleum pratense	19 (52.8)
• *D. pteronyssinus*	13 (36.1)
• Cat epithelium	11 (30.6)

19 (52.8%) patients had a positive reaction to *Phleum pratense*, 13 (36.1%) to *Dermatophagoides pteronyssinus* and 11 (30.6%) to *Cat epithelium* (Table 1).

During the SPT, the average temperature (T_{avg}) measured in the ROI for histamine was 33.5°C (32.1–34.7) at 0 min (prior to puncture on the volar surface of the forearm) and 35.1°C (34.0–36.1) at 15 min ($p < .001$). The maximum temperature value (T_{max}) in the ROI for histamine was determined to be 34.3°C (32.6–35.3) at 0 min and 36.2°C (34.8–37.2) at 15 min ($p < .001$). The temperature values for both *maximum* and *average* metrics in the ROI for histamine, *P. pratense*, *D. pteronyssinus* and *Cat epithelium*, all of which were measured as positive in the SPTs, increased considerably at the 5, 10 and 15 min compared to the initial time (all p values <.001) (Table 2). The analysis of the changes in average temperatures within the ROI for each aeroallergen showed that the incremental temperature changes in confirmed SPT positivities were significantly higher for *P. pratense* and *D. pteronyssinus*, compared to confirmed SPT negativity (*P. pratense*: ΔT ($T_5 - T_0$), $p = .049$. ΔT ($T_{10} - T_0$), $p = .002$. ΔT ($T_{15} - T_0$), $p = .011$; *D. pteronyssinus*: ΔT ($T_5 - T_0$), $p = .09$. ΔT ($T_{10} - T_0$), $p = .011$. ΔT ($T_{15} - T_0$), $p = .004$) (Table 3). The proposed SPT evaluation technique, the MMS, improved the accuracy of identifying *P. pratense* and *D. pteronyssinus* in comparison to other SPT evaluation metrics, specifically starting from the fifth minute (*P. pratense*: $\kappa = .450$, $\kappa = .668$ and $\kappa = .778$ at the 5, 10 and 15 min respectively; *D. pteronyssinus*: $\kappa = .253$, $\kappa = .500$ and $\kappa = .713$) (Table 4). No statistically significant difference was observed in the patients diagnosed with *Cat epithelium* sensitivity, but there has been a trend towards an increase at $t = 15$ min (*Cat epithelium*: ΔT ($T_5 - T_0$), $p = .86$. ΔT ($T_{10} - T_0$), $p = .18$. ΔT ($T_{15} - T_0$), $p = .07$; ASI_{T5}, $p = .183$. ASI_{T10}, $p = .002$. ASI_{T15}, $p < .001$) (Tables 3 and 4).

Of the total patients, 17 (47.2%) had symptoms with *Phleum*, 17 (47.2%) with *House-Dust Mites (HDM)* and 8 (22.2%) with *Cats*. The proposed SPT evaluation technique, the MMS, showed a stronger association with clinical symptoms of *HDM* and a linear correlation with *Phleum*. A slightly lower correlation was seen with symptoms of *Cat* (Table 5). In the comparison of the proposed SPT evaluation technique, the MMS, with the standard SPT in patients presenting with clinical symptoms, the sensitivity of the proposed SPT evaluation technique for *P. pratense* was 64.71%, with a specificity of 73.68%, resulting in accuracy of 69.94%. The positive predictive value (PPV) was 68.75%, and the negative predictive value (NPV) was 70.00%. For *D. pteronyssinus*, sensitivity was 47.83%, specificity was 69.23%, NPV was 42.86% and PPV was 73.33%. The sensitivity for *Cat epithelium* was 75.00%, specificity was 78.57%, PPV

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TABLE 2 Average and maximum temperatures of the skin with positive aeroallergens during the skin prick test.

	T_0		T_5		T_{10}		T_{15}		
Variables[a]	T_{avg}	T_{max}	T_{avg}	T_{max}	T_{avg}	T_{max}	T_{avg}	T_{max}	p^*
Histamine	33.5 (32.1–34.7)	34.3 (32.6–35.3)	35.0 (33.9–35.6)	36.0 (35.1–36.8)	35.0 (33.8–35.9)	36.3 (35.0–37.0)	35.1 (34.0–36.1)	36.2 (34.8–37.2)	<.001
Phleum	33.3 (31.9–34.5)	33.9 (32.8–35.1)	34.7 (33.9–35.1)	35.6 (34.9–36.1)	35.3 (34.1–36.1)	36.4 (35.5–37.2)	35.4 (33.6–36.7)	36.2 (34.9–37.6)	<.001
HDM	34.1 (31.8–35.0)	34.7 (32.6–35.7)	34.8 (34.5–35.4)	36.0 (35.1–36.5)	35.4 (34.4–36.1)	36.1 (35.6–37.3)	35.5 (35.1–35.8)	36.5 (35.9–37.2)	<.001
Cat	34.7 (32.7–35.1)	35.0 (33.2–35.7)	34.7 (33.9–36.2)	35.9 (34.5–36.5)	35.2 (34.4–36.0)	36.7 (35.1–37.1)	35.5 (34.4–36.1)	36.5 (35.4–37.1)	<.001

[a]Median (Interquartile range); p^*, the statistical differences between the values of maximum and average temperature patterns at the 0, 5, 10 and 15 min for each aeroallergen. We measured the temperature at four different time points: T_0, prior to puncture on the volar surface of the forearm; T_5, five minutes after puncture; T_{10}, ten minutes after puncture; T_{15}, fifteen minutes after puncture. HDM, house-dust mite, *Dermatophagoides pteronyssinus*.

TABLE 3 Comparison of allergic sensitization index (ASI) and temperature differences (ΔT) of skin with allergens between confirmed SPT-negative and SPT-positive patients.

	Phleum pratense			***D. pteronyssinus***			**Cat epithelium**		
Variables[a]	**SPT+ ($n=19$)**	**SPT− ($n=17$)**	***p***	**SPT+ ($n=13$)**	**SPT− ($n=23$)**	***p***	**SPT+ ($n=11$)**	**SPT− ($n=25$)**	***p***
ΔT (T_5–T_0)	1.6 (0.65 to 2.4)	0.8 (−0.6 to 1.43)	**.049**	1.3 (0.7 to 2.1)	0.7 (0.4 to 1.5)	.093	0.8 (−0.1 to 2)	0.8 (0.4 to 1.5)	.86
ΔT (T_{10}–T_0)	2.1 (1.05 to 3.6)	0.7 (−0.1 to 1.3)	**.002**	2.1 (1.1 to 2.7)	0.8 (0.1 to 1.31)	**.011**	0.9 (0.5 to 3.1)	0.96 (0.2 to 1.4)	.18
ΔT (T_{15}–T_0)	0.6 (1.05 to 3.8)	0.6 (0.13 to 1.4)	**.011**	1.9 (1.5 to 3.7)	0.73 (0.15 to 1.6)	**.004**	1.8 (0.7 to 3.4)	0.6 (0 to 1.8)	.07
ASI_{T5}	−1 (0.02 to 1)	0.85 (−1 to −0.26)	**<.001**	1 (0.6 to 1)	−0.98 (−1 to 0.3)	**<.001**	0.14 (−1 to 1)	−1 (−1 to 0.1)	.183
ASI_{T10}	0.97 (0.02 to 1)	−1 (−1 to −0.33)	**<.001**	0.85 (0.3 to 1)	−1 (−1 to 0.3)	**<.001**	0.6 (−1 to 1)	−1 (−1 to 0.5)	**.002**
ASI_{T15}	1 (0.5 to 1)	−1 (−1 to −0.55)	**<.001**	1 (0.53 to 1)	−1 (−1 to 0.23)	**<.001**	0.8 (−0.05 to 1)	−1 (−1 to 0.7)	**<.001**

[a] Median (Interquartile range); SPT, skin prick test; +, positive results; −, negative results. We measured the temperature at four different time points: T_0, prior to puncture on the volar surface of the forearm; T_5, five minutes after puncture; T_{10}, ten minutes after puncture; T_{15}, fifteen minutes after puncture. ΔT, differences in maximum temperatures; ASI, allergic sensitization index. The values that have a statistical significance with $p < .05$ indicated in bold

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TABLE 4 Cohen's Kappa analysis for assessing the reliability of the thermal test evaluation methods for each aeroallergen compared with the standard skin prick test.

	Relative *T*			ΔT			ASI			MMS		
Variables	T_5	T_{10}	T_{15}	T_5	T_{10}	T_{15}	T_5	T_{10}	T_{15}	T_5	T_{10}	T_{15}
Phleum (κ)	.073	.393	.666	.355	.616	.670	.273	.381	.549	.450	.668	.778
HDM (κ)	.003	.184	.661	.189	.465	.540	.339	.381	.484	.253	.500	.713
Cat (κ)	.084	.396	.607	.271	.362	.586	.361	.477	.525	.253	.170	.448

Note: Relative *T*, the temperature value at specific time point (t); ΔT, differences in average temperatures; ASI, allergic sensitization index; MMS, min–max scaler index; HDM, house dust mite, *Dermatophagoides pteronyssinus*.

TABLE 5 Skin prick test results for patients with clinical symptoms.

		AR tests	
Variables	*N*	SPT +	TA +
Symptoms with Phleum	17	11 (64.7%)	11 (64.7%)
Symptoms with HDM	17	9 (52.9%)	11 (64.7%)
Symptoms with Cat	8	7 (87.5%)	6 (75.0%)

Abbreviations: HDM, house dust mite, *Dermatophagoides pteronyssinus*; SPT, skin prick test; TA, thermal assessment.

50.00% and NPV 91.67% (Table 6). The use of the MMS to identify *P. pratense* and *D. pteronyssinus* sensitivity in patients with clinical symptoms yielded higher performance results compared to the standard SPT test. However, when the MMS was used to identify *Cat epithelium* sensitivity, slightly lower performance metrics were observed, primarily due to an increase in false-negative results.

4 | DISCUSSION

In this study, a novel SPT evaluation framework using low-cost and portable smartphone thermography is presented to provide an alternative to the standard SPT for the diagnosis of allergic sensitization over several time periods during the SPT. A low-cost, portable thermal imaging dataset was evaluated in relation to the clinical symptoms of the patients and the proposed thermal assessment metric, the MMS, was found to improve accuracy in identifying specific aeroallergen reactivities compared to the standard SPT in this proof-of-concept study, making it the first low-cost, portable imaging solution to be reported in the literature. Rokita et al. showed that using a thermal imaging system as a non-invasive tool can effectively measure changes in skin surface temperature during allergic reactions.[18] Nonetheless, taking all the current study findings into account, it was demonstrated that this SPT evaluation framework, when integrated with a low-cost, portable smartphone thermography, correlated with the existing results in the literature, and generated a reference dataset of the optimal reading points for specific aeroallergens at multiple time points, providing a more comprehensive evaluation as it allows the tracking of allergic reactions over time. This is in contrast to the standard SPT which only assesses at a single point in time, potentially missing critical allergic reactions that occur after the initial 5 min. This can be beneficial for both practitioners and patients in the clinics, as it provides a more detailed understanding of the allergic sensitization in the patients.

Although SPTs are commonly performed in clinics, interpreting the results can be a challenging and imprecise process as it lacks a temperature change distribution profile of the allergen-induced skin reactions. It is also important to note that studies have shown that the traditional allergy skin testing can produce false-negative results due to the use of high histamine control concentrations.[19] Moreover, relying on subjective interpretation of skin test

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TABLE 6 Comparison of the proposed skin prick test (SPT) evaluation technique and the standard SPT for aeroallergen detection in patients: performance analysis of temperature variations.

	Positive Predictive Value (%)		Negative Predictive Value (%)		Sensitivity (%)		Specificity (%)		Accuracy (%)	
Variables	SPT	MMS	SPT	MMS	SPT	MMS	SPT	MMS	SPT	MMS
Phleum	57.89	68.75	64.71	70.00	64.71	64.71	57.89	73.68	61.11	69.94
HDM	69.23	73.33	39.13	42.86	39.13	47.83	69.23	69.23	50.00	55.56
Cat	63.64	50.00	96.00	91.67	87.50	75.00	85.71	78.57	86.11	77.78

Abbreviations: HDM, house dust mite, *Dermatophagoides pteronyssinus*; MMS; min–max scaler index; SPT, skin prick test.

responses can lead to errors in the diagnosis of AR in patients. In recent years, there have been a few attempts to automate the assessment of induration with the use of IRT, such as the use of SWIR cameras as a novel solution to allergy skin testing.[14] However, as with any new technology, it is important to be aware of potential pitfalls. Tversky et al. highlighted that thermal imaging for skin prick testing showed greater variability and difficulty in detecting and localizing the wheal response, as well as being complicated by the presence of vasculature, mottling and other dermal variations.[14] Given the potential limitations of thermal imaging for skin prick testing, the results of the current study suggest that using low-cost, portable thermal cameras could be an effective and cost-efficient alternative method of confirming allergic sensitization in patients. This approach has the potential to improve the accuracy of SPT outcomes and address some of the issues related to traditional SPT evaluation methods.

Here, a time-lapse image analysis procedure was employed to assess allergen-induced skin reactions. However, the analysis focused on determining the temperature change distribution at multiple time periods during the SPT, rather than determining the area or size of the induration. This approach allowed the presence of the allergic sensitization reactions to be identified without the need for any size determination. The results were then evaluated by determining the presence or absence of aeroallergen sensitivity using the SPT evaluation formula, which analysed the temperature patterns within the ROI for each aeroallergen. It was thought that evaluating the outcome of the test during the experimental stage would be crucial to minimize the number of false-negative diagnoses associated with clinical symptoms for patients. Thus, a cut-off value of the proposed SPT evaluation technique, the MMS, greater than 0.5 was determined to result in the minimum false-negative ratio for confirmed SPT-positive cases, as proven in these proof-of-concept experimental trials. By computing the outcome of the SPT during the experimental stage, it was aimed to improve the accuracy in identifying specific aeroallergen reactivities and provide more reliable results in AR patients.

The study results revealed that among 14 patients, there were cases where a positive diagnosis was assessed by TA, but the patient's clinical symptoms were not associated with the aeroallergen being SPT tested. These false-positive findings were also correlated with the clinical symptoms. This suggests that the standard SPT may not be sufficient in providing an accurate diagnosis in some cases, highlighting the need for alternative methods of assessment. An increase was observed in the number of false-positive cases, specifically for patients diagnosed with *P. pratense and D. pteronyssinus*. These findings indicate that TA could be used as a more sensitive and objective indicator for the assessment of allergen-induced skin reactions over multiple time points, providing a more comprehensive understanding of the allergen reactions compared to the standard SPT, which only assesses a single point in time.

Despite the promising results, there are also several limitations that need to be considered. A major limitation of allergen channel models is that they are specific to the study population. Another drawback is that vessel interactions in the ROI are likely to influence temperature measurements, hence patient-to-patient variability may have affected the results. A limitation of low-cost, portable thermal imaging is that bleeding over from adjacent positives and/or vessels can lead to over-estimation of the sensitivity compared to standard SPT. This occurs when a positive result on the low-cost, portable thermal imaging is not an actual positive reaction to the aeroallergen, but rather an artefact caused by the proximity of blood vessels or a reaction in an adjacent test area. To address this constraint, several measurements and controls were included in the study to minimize the effects of bleeding over from adjacent positives and/or vessels with respect to the proposed formulae. One measure was to avoid vascular traces on the volar surface of the forearm. By ensuring that the aeroallergens were applied and analysed in areas where there were no blood vessels, the study minimized the risk of false positives caused by bleeding over from adjacent vessels. Another measure was to evaluate all patients' readings over time with their own initial temperatures. This was performed to reduce the impact of temperature variations on the study results. Even though the room temperature was maintained at 23°C, minor temperature variations can still occur and can affect the results in the study environment. By assessing all patients' readings at multiple time points, while taking into account their initial temperatures, every effort was made to minimize the influence of temperature variations on the statistical outcomes of the study. Despite these measures, there is a need for further validation and the use of different allergen challenge models to establish the diagnostic performance of low-cost, portable thermal imaging in a more comprehensive manner.

In conclusion, the proposed SPT evaluation framework using low-cost, portable smartphone thermography appears promising

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for the evaluation of allergen-induced skin responses at multiple time points during the SPT. This facilitates a more in-depth examination of the evolution of the allergic sensitization over time, which can provide valuable insights into the duration of the reaction. In addition, the use of low-cost, portable thermography allows for easy and convenient data collection, preparation and analysis procedures. This methodology can be considered to eliminate discrepancies among trained specialists, specifically for the purpose of personalized patient-oriented medicine, and to provide a clinical contribution to achieve the results in a shorter time. Overall, this SPT evaluation framework could potentially provide valuable insights into the diagnosis and better management of allergic reactions in the clinics.

AUTHOR CONTRIBUTIONS

P.G., E.D. and A.F.K. conceived the presented idea. P.G., O.C.B., D.G., M.E.C. and S.B.K., contributed to sample preparation. P.G. and O.C.B. contributed to the statistical analysis of the results and wrote the manuscript. P.G. took the lead in the implementation of the research. E.D., G.K. and A.F.K. contributed to the design of the research. All the authors have read and approved the final manuscript.

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The authors declare that they have no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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