**Diffuse Reflectance Spectroscopy with Infrared Thermography for Accurate Prediction of Cellulitis**

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Cellulitis is frequently misdiagnosed owing to its clinical mimickers, collectively known as pseudocellulitis. This study investigated diffuse reflectance spectroscopy (DRS) alone and in combination with infrared thermography (IRT) for the differentiation of cellulitis from pseudocellulitis. A prospective cohort study at an urban academic hospital was conducted from March 2017 to March 2018. Patients presenting to the emergency department with presumed cellulitis were screened for eligibility, and 30 adult patients were enrolled. Dermatology consultation conferred a final diagnosis of cellulitis or pseudocellulitis. DRS measurements yielded a spectral ratio between 556 nm (deoxyhemoglobin peak) and 542 nm (oxyhemoglobin peak), and IRT measurements yielded temperature differentials between the affected and unaffected skin. Of the 30 enrolled patients, 30% were diagnosed with pseudocellulitis. DRS revealed higher spectral ratios in patients with cellulitis (P = 0.005). A single parameter model using logistic regression on DRS measurements alone demonstrated a classification accuracy of 77.0%. A dual parameter model using linear discriminant analysis on DRS and IRT measurements combined demonstrated a 95.2% sensitivity, 77.8% specificity, and 90.0% accuracy for cellulitis prediction. DRS and IRT combined diagnoses cellulitis with an accuracy of 90%. DRS and IRT are inexpensive and noninvasive, and their use may reduce cellulitis misdiagnosis.

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**INTRODUCTION**

Cellulitis is a common infection of the skin and skin-associated structures that typically presents with redness, warmth, and pain in the affected area (Arakaki et al., 2014; Levell et al., 2011; Raff and Kroshinsky, 2016; Strazzula et al., 2015). Pseudocellulitis comprises several different diagnoses that can mimic the clinical appearance of cellulitis, such as lipodermatosclerosis and acute deep vein thrombosis (Raff and Kroshinsky, 2016). Difficulty in distinguishing cellulitis from its mimickers leads to misdiagnosis in over 30% of cases (Strazzula et al., 2015) and results in an estimated 130,000 unnecessary admissions and $515 million in avoidable healthcare spending in the hospital setting (Weng et al., 2017). Reducing unnecessary antibiotic coverage is also important in decreasing the emergence of drug-resistant organisms, antibiotic-associated side-effects, and costs (Jenkins et al., 2010).

Although dermatology and infectious disease consultations are considered the clinical gold standard for diagnosis of cellulitis (Arakaki et al., 2014; David et al., 2011; Jain et al., 2017; Levell et al., 2011; Strazzula et al., 2015), specialty access remains limited (Kimball and Resneck, 2008), and there exists a need to develop objective diagnostic modalities to assist clinicians. Infrared thermography (IRT) provides quantitative measurements of skin temperature and has previously been shown to aid in the differentiation of cellulitis from pseudocellulitis (Ko et al., 2018b). The average maximum temperature of the skin with cellulitis is 3.7 °C warmer than unaffected skin, and a temperature difference ≥0.47 °C conferred a 96.6% sensitivity and 82.4% positive predictive value for diagnosing cellulitis (Ko et al., 2018b).

This study investigated the utility of diffuse reflectance spectroscopy (DRS) for the prediction of cellulitis. DRS obtains quantitated color measurements of the skin and other exposed tissues and has previously demonstrated utility in the diagnosis of irritant contact dermatitis and gingivitis (Kollias et al., 1995; Zakian et al., 2008). In a DRS measurement, a broad spectrum of light penetrates the tissue and is scattered back to a detector that measures the intensity of reflected light at each wavelength, which is dependent on the color absorption properties of various substances present in the...
skin (Kollias et al., 1995). Both DRS and IRT are simple, inexpensive, and noninvasive modalities that can be deployed in portable devices readily accessible in multiple patient care settings. This prospective study specifically evaluated the utility of DRS alone and that of combined IRT and DRS for enhanced discrimination of uncomplicated cellulitis from pseudocellulitis.

RESULTS
A total of 30 patients met eligibility criteria and consented to participation (Figure 1). Examination of the study population revealed heterogeneous demographics with mean patient age of 54 years (SD = 18 years) and a 3:2 representation of male-to-female ratio (Table 1). Dermatology evaluation ascribed a diagnosis of cellulitis to 21 patients (70.0%) and that of pseudocellulitis to 9 patients (30.0%). Two patients with pseudocellulitis had bilateral lesions on the lower extremities necessitating IRT measurements of temperature differentials between the affected area and an unaffected area on the proximal lower extremity. At the predetermined follow-up time, no adverse events were noted, and no patients had their final diagnosis reclassified. Patients diagnosed with cellulitis were significantly younger than those diagnosed with pseudocellulitis (P = 0.013).

DRS measurements revealed significantly higher spectral ratios in comparing deoxyhemoglobin with oxyhemoglobin absorption (P = 0.005). The single parameter model for prediction of cellulitis with DRS alone by logistic regression demonstrated an optimal threshold value of 1.012, with spectral ratios above this value corresponding to a 50% probability of cellulitis (Table 2, Figure 2). This classification yielded a sensitivity of 86% (95% confidence interval [CI] = 64–97%), a specificity of 56% (95% CI = 14–79%), a positive predictive value of 82% (95% CI = 60–95%), a negative predictive value of 63% (95% CI = 24–91%), and an accuracy of 77% (95% CI = 58–90%). The dual parameter model for prediction of cellulitis with DRS and IRT combined by linear discriminant analysis demonstrated a sensitivity of 95% (95% CI = 76–100%), a specificity of 78% (95% CI = 40–97%), a positive predictive value of 91% (95% CI = 71–99%), a negative predictive value of 88% (95% CI = 47–100%), and an accuracy of 90% (95% CI = 73–98%) (Table 3, Figure 3). Validation of the dual parameter model on 215,460 combinations of training and validation sets estimated future accuracy of 87% (95% CI = 74–100%).

DISCUSSION
Cellulitis is a common illness whose diagnosis is often confounded by mimicking conditions, necessitating the development of objective diagnostic tools. Misdiagnosis of cellulitis is frequent, as represented by the 30% pseudocellulitis rate occurring in this study population, consistent with the findings of previous studies (Arakaki et al., 2014; Levell et al., 2011; Weng et al., 2017). This study investigated the performance of DRS alone and in combination with IRT for the objective diagnosis of cellulitis. A previous study showed that IRT set to a temperature differential of 0.47 °C in a dermatology consult cohort showed 97% sensitivity and 83% accuracy for cellulitis detection (Ko et al., 2018b). This study reported comparable performance for DRS alone with an 86% sensitivity and 77% accuracy for cellulitis detection. The use of DRS and IRT in combination performed better than the use of either technique alone and resulted in a 95% sensitivity and 90% accuracy for cellulitis detection. These technologies both benefit significantly from their simplicity, noninvasiveness, rapidity, inexpensiveness, and portability. Another major advantage of this study is its execution in a real emergency department clinical setting without the disruption of workflow. Used together, they present an opportunity to augment clinical decision making and potentially decrease the misdiagnosis rate.

DRS relies on intuitive quantitative measurements of skin changes, representing a significant advantage for the objective diagnosis of cellulitis. DRS has been used previously to quantify vascular oxygenation as a prognostic tool in breast and oral cancers (Brown et al., 2009; Mallia et al., 2010) and has shown value in the diagnosis of other dermatologic conditions, such as irritant contact dermatitis (Kollias et al., 1995). In the context of this study, DRS constituted a robust method for the quantification of color changes in the skin that

Figure 1. Screening and enrollment of the study. This flowchart shows study screening and enrollment.
is typically scrutinized in the clinical diagnosis of cellulitis. Considering that higher spectral ratios suggest increased presence of oxyhemoglobin, DRS likely detected increased dermal perfusion with highly oxygenated blood resulting from an acute inflammatory response to infection as occurs in cellulitis. In contrast, DRS likely registered lower spectral ratios for common pseudocellulitis diagnoses marked by venous congestion of poorly oxygenated blood, such as stasis dermatitis or deep vein thrombosis. Furthermore, DRS can be readily deployed at any site affected by cellulitis, as evidenced in the diverse clinical presentations included in this study.

IRT provides quantitative measurements of skin changes distinct from those provided by DRS, thus presenting an opportunity for enhanced discrimination of cellulitis as evidenced by the improved performance of these technologies in combination. IRT represents an appropriate method for the quantification of skin warmth that is typically considered in the clinical diagnosis of cellulitis (Ko et al., 2018b). Whereas DRS can be affected by optical absorption characteristics of substances other than hemoglobin that are present varyingly in the skin, such as water, lipids, and melanin, IRT is likely less impacted by this variability. This advantage is especially important for the diagnosis of cellulitis in darker skin types where the perception of underlying erythema can be obscured by melanin content, which can reduce the overall reflectance of the skin. The impact of melanin content has been recently conjectured to interfere with even commonly used photometric methods such as pulse oximetry (Sjoding et al., 2020). Interestingly, in addition, the full spectrum registered by DRS may encode helpful information about confounding optical features of the examined skin, such as melanin content, which may be amenable to extrication in future studies by more sophisticated algorithmic methods for improved diagnostic performance. Although this study took place at an institution with a predominately white patient population, 16% of patients had the skin of color. IRT may augment diagnostic accuracy in darker skin types where

| Table 1. Baseline Patient Demographics |
|--------------------------------------|
| Characteristic                      | Total (n = 30) | Cellulitis (n = 21) | Pseudocellulitis (n = 9) | P-value |
|----------|----------------|---------------------|------------------------|--------|
| Age, y, mean ± SD                    | 54 ± 18         | 48 ± 17             | 66 ± 16                | 0.013  |
| Gender, n (%)                        |                |                     |                        | 0.051  |
| Male                               | 18 (60)        | 15 (71)             | 3 (33)                 |        |
| Female                             | 12 (40)        | 6 (29)              | 6 (67)                 |        |
| Race, n (%)                         |                |                     |                        | 0.590  |
| White                              | 25 (84)        | 17 (81)             | 8 (89)                 |        |
| Asian or Pacific Islander           | 1 (3)          | 1 (5)               | 0 (0)                  |        |
| American Indian                     | 0 (0)          | 0 (0)               | 0 (0)                  |        |
| Black                               | 1 (3)          | 1 (5)               | 0 (0)                  |        |
| Hispanic                            | 3 (10)         | 2 (9)               | 1 (11)                 |        |
| Body area affected, n (%)           |                |                     |                        |        |
| Head and neck                       | 3 (10)         | 2 (10)              | 1 (11)                 |        |
| Upper extremity                     | 3 (10)         | 3 (14)              | —                      |        |
| Lower extremity                     | 24 (80)        | 16 (76)             | 8 (89)                 |        |
| Lesion laterality, n (%)            |                |                     |                        |        |
| Unilateral                          | 28 (93)        | 21 (100)            | 7 (78)                 |        |
| Bilateral                           | 2 (7)          | —                   | 2 (22)                 |        |

Baseline demographics for patients with cellulitis and pseudocellulitis.

| Table 2. Spectral Ratios for Patients with Cellulitis and Pseudocellulitis |
|-------------------------------|-----------------|-------------------|
| Ratio of 556/542 nm | Cellulitis | Pseudocellulitis |
| Mean                      | 1.0736       | 1.0159            |
| SD                        | 0.0472       | 0.0473            |
| n                         | 21           | 9                 |

The mean of the spectral ratio between 556 nm (deoxyhemoglobin peak) and 542 nm (oxyhemoglobin peak) was calculated for the affected skin in patients with cellulitis and pseudocellulitis. The mean spectral ratios were compared using a two-sided Student’s t-test with a calculated P-value of 0.0048.

Figure 2. Spectral ratio predictive model. Using logistic regression, we determined the probability of cellulitis on the basis of the spectral ratio (556/542 nm) of the affected skin. Red circles indicate patients with cellulitis, and blue circles indicate patients with pseudocellulitis. The 50% threshold corresponds to a spectral ratio of 1.012.
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Table 3. Estimation of Prediction Performance for Dual Parameter Model

| Statistic           | Mean  | Confidence Interval (2.5–97.5%) |
|---------------------|-------|-------------------------------|
| Accuracy            | 0.8681| 0.7401–1.0000                 |
| Sensitivity         | 0.9138| 0.7791–1.0000                 |
| Specificity         | 0.7766| 0.4976–1.0000                 |
| Positive predictive value | 0.9054| 0.7888–1.0000                 |
| Negative predictive value | 0.8611| 0.6430–1.0000                 |

Combinatorial resampling was used to predict the generalizability of the dual parameter model. A total of 215,460 different training and validation sets were used. The average classification performance is presented as a mean and confidence interval.

Materials and Methods

This study recruited patients presenting with presumed cellulitis for the obtaining of IRT and DRS measurements and was approved by the Partners Institutional Review Board. Adult patients aged >18 years seen in the emergency department at Massachusetts General Hospital (Boston, MA) with a presumed diagnosis of cellulitis as assessed by emergency department physicians were included after written informed consent was obtained. Patients were not considered if pregnant, incarcerated, or decisionally impaired. To minimize confounders, patients were excluded if they had clinical or radiographic evidence of abscess or osteomyelitis, if they had complicated infection sites such as those involving surgical sites <4 weeks from operation, if they had underlying hardware such as orthopedic implants and intravenous access lines, or if they had animal or human bites. Patients with abnormal vital signs, specifically temperature >100.4 °F or tachycardia >100 beats per minute, or with exposure to intravenous antibiotics for more than 24 hours were also excluded. Enrolled patients received specialty consultation by an attending dermatologist with the conferral of a final diagnosis of cellulitis or pseudocellulitis. During consultation, the attending dermatologist was blinded to any infrared thermograms or subtle erythema may be obscured by melanin content. Future multicenter studies assessing this technology in more diverse populations are needed to validate the accuracy of both methods combined. Thus, combined DRS and IRT measurements may be generalizable to patients of all skin types for highly accurate diagnosis of cellulitis, especially in comparison with clinical examination alone.

DRS and IRT are both inexpensive technologies that present an opportunity for further cost savings in the form of improved diagnostic accuracy leading to reduced unnecessary admissions and antibiotic treatments. Dermatology expertise is currently considered as one of the gold standards for management (Ko et al., 2018a; Li et al., 2018) but is not always readily available. Rather, cellulitis is commonly managed by primary care, emergency medicine, or internal medicine physicians (Arakaki et al., 2014; David et al., 2011; Jain et al., 2017; Levell et al., 2011; Strazzula et al., 2015), and an interview study among health care providers showed substantial challenges in diagnosis and variability in practice among these providers (Patel et al., 2020). Improved diagnostic accuracy also reduces unnecessary costs; a comparison of the false positive rate of the combined DRS and IRT method in this study with current misdiagnosis rates estimates savings of $284 million annually in the United States (Peterson et al., 2017). Furthermore, the improved accuracy of these combined technologies can help elucidate pseudocellulitis that may require significantly different evaluation and management as evidenced by the cases of cryoglobulinemic vasculitis and erythema chronicum migrans correctly discriminated in this study. These combined technologies can be quickly and inexpensively deployed without necessitating dermatology consultation, thus improving cellulitis management and costs possibly in a wide variety of clinical settings.

Figure 3. Dual parameter predictive model and ROC curve. (a) A linear classifier was calculated for the thermal differences and the spectral ratios using a linear discriminant analysis technique. By changing the intercept of the line, optimal sensitivity and specificity of the classifier can be selected. We show a sensitivity of 95% (95% CI = 76–100%), specificity of 78% (95% CI = 40–97%), PPV of 91% (95% CI = 71–99%), NPV of 88% (95% CI = 47–100%), and accuracy of 90% (95% CI = 73–98%). (b) ROC curve for predicting cellulitis in using spectral ratio predictive model alone and dual parameter predictive model. AUC, area under the curve; CI, confidence interval; deoxy, deoxyhemoglobin; NPV, negative predictive value; oxy, oxyhemoglobin; PPV, positive predictive value; ROC, receiver operating characteristic.
diffuse reflectance spectra obtained. Included patients also received follow-up in the form of a phone call or clinic visit to assess for disease resolution and accuracy of the final diagnosis. Relevant information on patient history and clinical course for included patients was recorded from direct medical history or chart review and was securely managed using Research Electronic Data Capture tools (Nashville, TN) (Harris et al., 2009).

DRS measurements for included patients returned a spectral ratio comparing deoxyhemoglobin-to-oxyhemoglobin absorption in the affected skin (Figure 4). The DRS apparatus consisted of a handheld optic fiber spectrometer equipped with a probe made of six broadband illumination fibers and one reflectance detection fiber. DRS measurements were obtained by placing the probe directly on the affected skin without downward pressure. To standardize the reflectance intensity for each measurement, acquired spectra were normalized to the spectrum of the illuminating light source captured using a spectralon reflectance standard. Spectral ratio was calculated as the ratio of the deoxyhemoglobin absorption peak at 556 nm to the oxyhemoglobin absorption peak at 542 nm. The DRS apparatus was made of components supplied by Ocean Optics (Largo, FL) and included the optic fiber spectrometer (USB2000), broadband light source (HL-2000), reflectance fiber probe (QR600-7-SR-125F), and spectralon reflectance standard (WS-1-SL).

IRT measurements for included patients returned a temperature differential between the affected and the unaffected skin (Figure 4). The IRT apparatus consisted of a forward-looking infrared camera capable of capturing live and still images with a temperature measurement range of $-20^\circ$C to $120^\circ$C in increments of 0.1°C. Live thermographic images were captured by roving a forward-looking infrared camera approximately 30 cm from the skin surface. Affected skin temperature was identified as the maximum skin temperature measured in the affected area, and unaffected skin temperature was identified as the skin temperature measured on the corresponding contralateral body area for unilateral cellulitis or on the ipsilateral proximal body area for bilateral cellulitis. This bilateral comparison was designed to account for global factors that can affect skin temperature such as ambient room temperature, body mass index, and anatomical characteristics of the affected site. Temperature differential was calculated as the temperature difference between the affected and the unaffected skin. The IRT
apparatus was supplied by FLIR Systems (Wilsonville, OR) and included the FLIR Generation One camera.

Statistical analysis was performed to characterize the study population and predict cellulitis on the basis of DRS alone and DRS and IRT combined. Categorical variables are reported as counts with percentages, and continuous variables are reported as means with SD or as medians with first and third quartiles, dependent on the distribution. Differences between categorical variables were compared using Pearson’s χ² test of independence, and differences between continuous variables were compared using Student’s t-test if confirmed to be normally distributed through Kolmogorov-Smirnov test of normality at a significance threshold of P < 0.05 or otherwise using the Mann-Whitney U test. Significance tests were all two-tailed at P < 0.05. A single parameter model for the prediction of cellulitis using DRS alone was created using logistic regression on spectral ratios obtained. A dual parameter model for the prediction of cellulitis using DRS and IRT combined was performed using linear discriminant analysis on the pairs of temperature differentials and spectral ratios obtained. A receiver operating characteristic curve was generated for both models to characterize the performance of optimal classification. The exact CIs for performance characteristics and their variances. Analysis was conducted in MATLAB, version 7.1, and R, version 3.2.

Given that this investigation was a study for proof of technological concept, its stringent eligibility criteria resulted in a small set of included patients. In particular, the study population was recruited from the emergency department at a single academic medical center and thus may not generalize readily to outpatient presentations of cellulitis. Future studies are needed to validate these technologies more broadly in the skin and skin-associated structure infections. In particular, future studies should account for additional patient factors that may have a physiological impact on skin temperature such as recent medication intake. A larger study population will be necessary for more robust validation of these models before clinical implementation.

Spectral ratios from DRS and temperature differentials from IRT can differentiate cellulitis from pseudocellulitis more accurately than clinical examination. These technologies are both noninvasive, inexpensive, and easy to use and may be amenable to combination in the form of a single device. The dual parameter model for the prediction of cellulitis reported in this study may help to reduce misdiagnosis rates, unnecessary hospitalization, antibiotic overuse, and healthcare costs. Further studies are needed to validate this diagnostic method in larger cohorts and varied clinical settings.

Data availability statement
Datasets related to this article can be found at https://doi.org/10.17632/bwsvw6drw5.1, hosted at Mendeley.

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Conceptualization: ABR, AOM, RRA, DK; Data Curation: ABR, AOM, SC, RR, CT, LNK, ACGM, ASD, BAP, DK; Formal Analysis: ABR, AOM, SC, RR, LNK, ACGM, ASD, DK; Investigation: ABR, AOM, SC, RR, DK

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CONFLICT OF INTEREST
ABR, AOM, RRA, and DK filed a patent for the development of diffuse reflectance spectroscopy and thermal imaging technology.

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