Received: 27 April 2020 | Revised: 7 July 2020 | Accepted: 15 July 2020
DOI: 10.1111/iwj.13474

ORIGINAL ARTICLE

IWJ WILEY

Hyperspectral imaging in wound care: A systematic review

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Abstract
Multispectral and hyperspectral imaging (HSI) are emerging imaging techniques with the potential to transform the way patients with wounds are cared for, but it is not clear whether current systems are capable of delivering real-time tissue characterisation and treatment guidance. We conducted a systematic review of HSI systems that have been assessed in patients, published over the past 32 years. We analysed 140 studies, including 10 different HSI systems. Current in vivo HSI systems generate a tissue oxygenation map. Tissue oxygenation measurements may help to predict those patients at risk of wound formation or delayed healing. No safety concerns were reported in any studies. A small number of studies have demonstrated the capabilities of in vivo label-free HSI, but further work is needed to fully integrate it into the current clinical workflow for different wound aetiologies. As an emerging imaging modality for medical applications, HSI offers great potential for non-invasive disease diagnosis and guidance when treating patients with both acute and chronic wounds.

KEYWORDS
diabetic foot, diabetic neuropathies, foot ulcer, haemoglobins, peripheral arterial disease

1 | INTRODUCTION

Multispectral (MSI) and hyperspectral (HSI) imaging exploit the ability to split light into multiple narrow bands beyond the three conventional red, green, and blue (RGB) visible spectral bands, enabling analysis of images not seen with the naked eye.

Several multispectral and HSI systems have focused on the technique's diagnostic capabilities. The ability to quantitatively measure oxygenation levels in tissue has been tested in various pathologies and clinical contexts, including; peripheral vascular disease,[1,2] retinal eye disease,[3,4] diabetic foot disease[5,6], and wound healing.[7,8] Numerous groups have also published work demonstrating the effectiveness of using HSI for cancer detection.[9-11] With the development of high-resolution and fast frame rate multispectral and HSI cameras, enabling the capture of a rich imaging dataset at a video rate, these imaging methods offer the potential for real-time non-invasive tissue characterisation.[6]

In this paper, we present a brief summary of the physical basis of HSI followed by a systematic review evaluating the wound-related applications of in vivo HSI. We report the different types of imaging systems used in wound prevention and treatment from a clinical perspective, review their key technical features and specifications, and evaluate their clinical utilities, reported effectiveness, and safety.

1.1 | Imaging in wound care

One of the most fundamental but powerful clinical tools when managing patients with wounds is visual observation. Unfortunately, its benefits are only useful when the observer has significant experience or training.[12-16] Images and their inclusion in the documentation, therefore, can provide clinicians with a powerful, informative, and non-invasive means to examine, quantify, and document wounds.[17] Such an approach also has the potential to allow the creation of large databases for research, educational, and diagnostic purposes, particularly those with machine learning or artificial intelligence support.[18,19]

Wound measurement is an essential part of wound assessment. Wound area (and/or volume) is a key measurement used to monitor healing.[20-23] It should be recorded on the initial presentation and at regularly defined intervals as part of the reassessment process. There are various methods available to measure wounds, and it is important to use the same method each time, with the patient in the same position.[24,25] Continuous monitoring of changes in wound size is an important way of evaluating response to treatment. One of the key components relative to a patient's wound care journey[26,27] is an ability to produce accurate, reliable, reproducible measurements. Optical technologies are a proven way to perform such measurements.

A documented assessment can also assist with communication across the multidisciplinary team, including the patient.[14] High-quality communication can, in turn, motivate and empower the patient, improving compliance.[27] Remote evaluation and assessment of the wound are also of increasing importance through the use of a telemedicine approach.[28-30] There has been considerable progress in imaging technology for wounds, including systems that include advanced features such as 3D measurement and telemedicine.[27,31]

Numerous academic and commercial groups have developed systems aimed at facilitating the goals mentioned earlier.[26,32-39]

Key Message

- we conducted a systematic review of clinical hyperspectral (HSI) and multispectral imaging systems in wound care, published over the past 32 years. We analysed 140 studies, including 10 different HSI systems
- current in vivo HSI systems generate a tissue oxygenation map. Tissue oxygenation measurements may help to predict those patients at risk of wound formation or delayed healing
- no safety concerns were reported in any studies. A small number of studies have demonstrated the capabilities of in vivo label-free HSI, but further work is needed to fully integrate it into the current clinical workflow for different wound aetiologies.
- as an emerging imaging modality for medical applications, HSI offers great potential for non-invasive disease diagnosis and guidance when treating patients with both acute and chronic wounds

1.2 | Hyperspectral imaging

Light in the visible and near-infrared (NIR) ranges of the spectrum delivered to biological tissue undergoes multiple scattering and is absorbed primarily by haemoglobins, water, fat, and melanin in the tissue. It is assumed that this reflected light from the tissue carries quantitative diagnostic information about tissue pathology.[40] In recent years advances in cameras, image analysis techniques, and computational power, make it possible for many potentially beneficial applications of HSI in medicine, including caring for patients with wounds.

In hyperspectral imaging, it refers to a large number of measured wavelength bands. Hyperspectral images are used to provide sufficient spectral information to recognise and differentiate spectrally distinctive materials.[41] Optical analysis techniques are used to detect and identify objects from a large scale of images. Hyperspectral imaging technique is one of them. A vision of the human eye is based on three primary colour bands (red, green, and blue), but spectral imaging divides the vision into many more bands.[41]

HSI aims to record the spectrum for each pixel of the image. In this sense, hyperspectral imaging is the natural extension of the colour (RGB) imaging. Spectrum at each pixel can be considered a spectroscopic input, which can be decomposed, and spectral signatures can be found.[42] There are a few different techniques for acquiring the three-dimensional (x,y,λ) dataset of a hyperspectral cube (eg, spatial scanning and spectral scanning).[43] The choice of technique depends on a specific application.

1.3 | Hyperspectral versus multispectral

Hyperspectral imaging is closely related to multispectral imaging. The distinction between hyper and multispectral is sometimes based on an arbitrary 'number of bands'. Multispectral imaging deals with several images at discrete and somewhat narrow bands, for example, located near the absorption maximums of chromophores under consideration. Multispectral images do not produce the 'spectrum' of an object, but rather sample the spectrum at several points. Hyperspectral deals with imaging narrow spectral bands over a continuous spectral range, which can be considered a spectrum.

In biomedical imaging, hyperspectral or multispectral images can be used to extract data about components of the blood, which are chromophores in the visible and NIR spectrum. In particular, HSI is able to deliver nearly real-time images of oxyhaemoglobin and deoxyhaemoglobin and provide an assessment of tissue pathophysiology based on the spectral characteristics of different tissue.[6] Therefore, HSI is increasingly being used within different clinically diagnostic areas. For example, HSI has been applied to the assessment of peripheral artery disease,[1] early detection of dental caries,[44] fast characterisation of kidney stone types,[45] detection of laryngeal disorders,[46] to name but a few of these emerging clinical areas. In this review, we focus on the applications of HSI to diagnosis and management of patients with wounds and wound-related parameters. A broad review of clinical applications of HSI has been undertaken previously.[6]

Image analysis enables the extraction of diagnostically useful information from a large medical hyperspectral dataset at the tissue, cellular, and molecular levels and is, therefore, critical for disease screening, diagnosis, and treatment.

2 | METHODS AND REVIEW PROCESS

In this review, we aim to assess the current state of hyper and multispectral imaging applications across the whole spectrum of wound care and particularly their diagnostic and prognostic utilities. This survey covers literature from the inception of HSI techniques up to June 2019. We start with the current development status of HSI technology within the field of wound prevention and management. We then consider HSI utility in different wound types.

A diagram illustrating the stages of this systematic review's methods based on the PRISMA review system[47] is presented below (Figure 1).

2.1 | Structured question

- *The populations*—Populations being assessed with hyper and/or multispectral imaging.
- *The interventions*—Hyper/Multispectral imaging technology

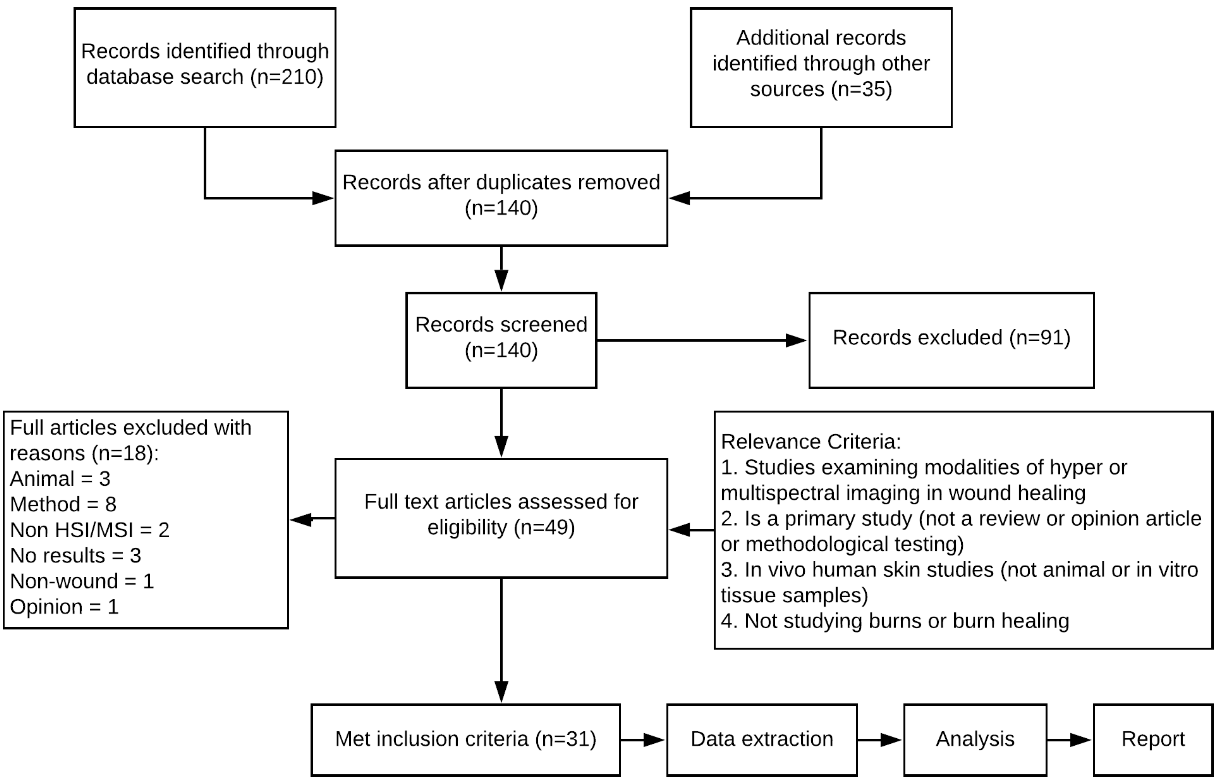

FIGURE 1 Review methods

- *The comparators*—Traditional tissue healing measurements
- *The outcomes*—Ability of HSI to measure wound healing variables.
- *The study designs*—Comparative studies of any design examining hyper and multispectral imaging techniques on in vivo skin.

2.2 | Search strategy

A search of three electronic databases was undertaken, along with additional references from the websites of medical hyper and multispectral imaging product manufacturers.

We searched PubMed, Scopus, and Cochrane databases from the inception of the database to June 2019.

The PubMed search syntax listed below served as the basis for all search strategies, using both Medical Subject Headings (MeSH) and text terms with Boolean operators.

(Hyperspectral[All Fields] OR Multispectral[All Fields]) AND ((‘wounds and injuries’[MeSH Terms] OR (‘wounds’[All Fields] AND ‘injuries’[All Fields]) OR ‘wounds and injuries’[All Fields] OR ‘wound’[All Fields]) AND s[All Fields] OR (‘ulcer’[MeSH Terms] OR ‘ulcer’[All Fields]) AND s[All Fields])

(Hyperspectral[All Fields] OR Multispectral[All Fields]) AND ((‘pressure ulcer’[MeSH Terms] OR (‘pressure’[All Fields] AND ‘ulcer’[All Fields]) OR ‘pressure ulcer’[All Fields]) OR (‘wounds and injuries’[MeSH Terms] OR (‘wounds’[All Fields] AND ‘injuries’[All Fields]) OR ‘wounds and injuries’[All Fields] OR ‘injury’[All Fields]))

(Hyperspectral[All Fields] OR Multispectral[All Fields]) AND ((‘surgical wound’[MeSH Terms] OR (‘surgical’[All Fields] AND ‘wound’[All Fields]) OR ‘surgical wound’[All Fields]) AND s[All Fields])

Additional references were sought through the websites of medical hyper and multispectral imaging product manufacturers (HyperMed, Kent Imaging, Diaspective Vision, MedX Health Corp., Artinis, Spectral MD). Product validation studies completed by these companies were read and assessed for inclusion in the review.

A PROSPERO review protocol was completed prior to submission.[48]

2.2.1 | Literature search

Data extraction was performed via manual synthesis by three reviewers based on Problem/Patient/Population, Intervention/Indicator, Comparison, Outcome criteria.[49] Data variables extracted for consideration included year of publication, article type, number of patients/participants included in the study, population studied (disease/wound type), Hyperspectral/Multispectral imaging device used, comparator (another hyperspectral/multispectral imaging device, conventional diagnosis methods, other imaging procedures (ex. laser Doppler perfusion monitoring), reference/literature, expected measurements, study outcomes, study design, length of follow-up, any stated conflict of interest, and reviewers' opinions.

2.2.2 | Literature screening

A single reviewer conducted an initial screening of titles and abstracts and obtained the full text of studies that appeared eligible for the review, according to the inclusion criteria. The reviewer then examined the full-text articles and selected studies that were eligible for inclusion.

2.3 | Inclusion criteria

Inclusion/Exclusion criteria were determined by three reviewers. Disagreements were resolved by consensus. Study populations included in the review were human subjects and patients, normal skin, wounds, chronic wounds and ulcers (pressure ulcers/injuries, diabetic foot ulcers, leg ulcers), peripheral arterial disease (PAD) and peripheral vascular disease (PVD), Cutaneous Leishmaniasis, limb amputations, and surgical wounds. A database search was also performed for bruises, but only one study[50] was found. Studies excluded from the review analysis were any measuring burns, any review or opinion articles, animal studies (eg, murine, rat, porcine), methodological testing, and in vitro testing (eg, tissue samples).

3 | RESULTS

Wound measurement and assessment are important in monitoring the healing process of chronic wounds and in evaluating the effect of treatment. The objective of this systematic review was to evaluate evidence from the literature regarding the use of hyperspectral imaging in the management of patients with wounds. Literature prior to June 2019 was included in the research. Studies were identified by searching the electronic databases PubMed, Embase, Cochrane Library, and manufacturers' websites were also included. Of the 140 studies identified some 91 were excluded during screening for various reasons (animal study-13, in vitro-8, methods-1, study design [no results]-1, burns-12, no wounds-27, not HSI/MSI-1, book-2, conference paper-1, opinion-3, review-21, poster-1) during literature screening to leave 49 for qualitative synthesis. A further 18 were then excluded upon thorough inspection (animal study-3, methods-8, no results-3, not HSI/MSI-2, no wound-1, editorial/opinion article-1) to leave 31 for inclusion in the review of different HSI techniques for measuring acute, chronic, and wound-related conditions. A total of four technologies for determining tissue oxygenation included: custom systems (14 papers), OxyVue-Hypermed (11 papers), TIVITA (5 papers), and Kent (1 paper). The number of wounds examined in the studies was highly variable (n = 2–150). None of the HSI technologies have so far had a significant impact because of their low accuracy, high cost, and complexity in handling the system set-up.

Such as patient population varies significantly between studies, we will report results for studies, where statistical significance can be derived, and only methodology and methods otherwise.

3.1 | Quality of evidence

The quality level determination reflects certainty about the evidence. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[51] We started with the assumption that Randomized Clinical Trial (RCTs) are of high quality, whereas observational studies are of low quality. Using this methodology, the overall quality can be high, moderate, low, or very low.

We have not found any RCT among our dataset. Thus, the quality of evidence is low (observational studies) and very low (case studies and case series).

While trials and studies are more impactful when gathering evidence, often individual case studies or case series can provide additional information and insight as to the effectiveness of an approach or therapeutic.[52,53]

In most cases (n = 19) the multi-patient studies were reported.[1,2,5,7,54-68] However, in some cases (n = 12), the case studies were reported.[8,50,69-78]

Daeschlein et al.[75] reported five case studies of different types of wound/lesion (infected hand-wound, systemic scleroderma, Dupuytren's contracture, chronic abscesses by Methicillin-resistant Staphylococcus aureus, and PAD). Each patient was examined with the HSI device in the context of clinical treatment to assess StO2, NIR perfusion, and tissue haemoglobin index. Rutkowski et al.[78] imaged two patients undergoing cold atmospheric plasma (CAP) therapy to evaluate StO2, NIR perfusion, and total hemoglobin index (THI) before, immediately after, and 10 minutes after receiving the treatment at points of interest (one or more in the tumour area, one as an internal control in a non-CAP treated neck/cheek area).

Wild et al.[8] assessed THI, NIR perfusion, tissue oxygenation, and tissue water index in three wound case studies at the start of treatment and after 8 weeks to determine how changes in HSI measurements relate to wound healing.

Daeschlein et al.[69] assessed two wounds (one acute and one chronic) to determine the effects of CAP therapy. The wounds were treated with CAP, and HSI images were taken before treatment, directly after, and 10 minutes after treatment.

Sicher et al.[76] reported HSI imaging of four clinical case study patients (scleroderma, Dupuytren surgery, chronic foot ulcers, and skin infections).

Berot et al.[73] reported the use of a 3D multispectral camera in two case studies: one woman with chronic loss of substance of pejorative evolution on the lateral side of left leg, one woman with spontaneous right buttock necrosis. HSI measurements were obtained under different light sources (artificial white, red, sunlight).

3.2 | Imaging systems

The use of digital photography has dramatically changed wound care tracking and documentation.[14,17,22] The advances in imaging technology have presented opportunities beyond visible light.[73] The ubiquity of less expensive digital cameras, including those in phones, maybe the key to enhanced wound imaging when used in tandem with additional technologies or components.[79]

A combination of off-the-shelf devices and custom-built devices were used (Table 1).

Spectroscopic data were used in References 64, 65, 68. Not sufficient details to make a determination were provided in Reference 73.

In several studies, combinations with other imaging technologies were used. Zhang et al.[70] reported a multimodal imaging device designed to integrate HSI, laser speckle, and thermographic imaging. Liu et al.[77] developed a 3D topography multiview/HSI integrated system. Chang et al.[72] proposed a multimodal system (3D wound size measurements, HSI, thermo, and chemical vapour sensing analysis) for pressure injury assessment.

In several studies, spectroscopic systems were used at a single[64,65] location to detect spatial heterogeneity of the blood flow. A spectroscopic system was used by Poosapadi et al.[68] to discriminate between *Staphylococcus aureus* and *Escherichia coli*.

TABLE 1 Imaging systems reviewed

Imaging modality	Wound aetiologies	Studies	Summary
HyperMed technology	11 studies used this modality covering the following aetiologies: PAD, PVD, DFU	1,2,5,7,55-61	Studies demonstrate the ability of this technology to work across a number of aetiologies. Studies are among the largest for HSI use in wounds.
Kent Imaging	One study used this modality covering the following aetiology: Chronic wounds	54	The study showed some utility but based on low patient numbers.
TIVITA System	five studies used this modality covering the following aetiologies: Surgical wounds, burn wounds, and PAD.	8,69,75,76,78	Mostly case studies on this device. They do demonstrate utility in the measurement of tissue oxygenation.
Custom designed multispectral system	five studies used this modality covering the following aetiologies: Skin flaps, erythema, and pressure injuries.	66,67,70,71,74	Studies centred around the research. Medium-sized in vivo studies show a clinical application in wound area.
Custom designed hyperspectral system	five studies used this modality covering the following aetiologies: Pressure injuries, bruises, and diabetic foot ulcers.	50,62,63,72,77	Medium-sized clinical studies show the utility of HSI techniques across a number of wound-related aetiologies.

3.3 | Wavelength range

Three main optical modalities are used to measure tissue oxygenation changes in wounds (HSI, MSI, and NIR spectroscopy). Typically, they are based on Si-based sensors, which are sensitive in visible and near-infrared ranges (400-1100 nm). The sensing depth depends on the chosen wavelength range. Skin surface tissues (dermis and epidermis) oxygenation is probed via visible light with subcutaneous tissue oxygenation being captured through the NIR light (typically between 650 and 980 nm). Systems with a broader spectral range, therefore, provide a more complete wound oxygenation map.

Different wavelength ranges in visible and near-infrared spectra were used (Table 2).

In one study, the ranges of wavelengths were compared. In Philimon et al.,[74] 530-570 nm range was compared with the 520-600 nm range. The measurements from the two ranges were significantly comparable. The 530-570 nm range provides slightly higher (5.72% on average) oxygenation numbers than the broader range.

3.4 | Algorithm

A key component of a hyperspectral approach is the algorithm used to deconvolute reflected light from multiple wavelengths and tissues. Algorithms are also used to combine images from both hyperspectral and photographic sources, generally as an overlay. This provides a more in-depth clinical picture of both the visible skin surface and the underlying subcutaneous tissue.

Different models were used to extract tissue oxygenation. For commercially available systems, algorithms were not reported in reviewed materials. However, for custom-built systems, several authors reported their algorithms. In particular, Basiri et al.[66] used the Stamatas model.[80] Huong et al.[71] used the Extended Modified Beer–Lambert model to extract oxygen saturation (SO2).

Several authors used other algorithms to predict healing outcomes, segment tissues, and reconstruct wound topology. In particular, Yang et al.[63] analysed the prognostic potential of derived SpO2 and PCA performed on the whole wavelength range. They found that the sensitivity of prediction of healing by 12 weeks using PCA (87.5%) was higher than that of SpO2 (50.0%), with both approaches showing equal specificity (88.2%).

Liu et al.[77] proposed 3D reconstruction of wound topology using 3D topography multiview system.

3.5 | Clinical variable

Wounds are complex in their nature as they are multifactorial and the patient often has multiple comorbidities that can impact the patient as a whole, including wound.[14] This complexity, however, presents an opportunity with respect to clinical measurement.[17] With many variables to measure imaging can be the easiest and most powerful.[17,25] For the purposes of this review, we will

TABLE 2 Wavelength profiles of technology used

System or source	Wavelengths studied	Study highlights
OxyVu system (Hypermed, MA)	A hyperspectral system with wavelengths between 500 and 660 nm.	Demonstrated, through multiple studies, promise in the assessment of wounds.
Kent Camera (Kent Imaging, Canada)	A multispectral system, which uses four wavelengths in the NIR range.	Demonstrated, through several studies, promise in the assessment of wounds.
TIVITA system (Diaspective, Germany)	A hyperspectral system, which uses a 500-980 nm range.	Demonstrated, through multiple studies, promise in the assessment of wounds.
Basiri et al[66]	A custom-built system with 480, 500, 520, 530, 540, 560, 580, 590, 600, 620, 630, 640, 660, 680, 700, and 886 nm wavelength	Oxygen saturation maps of healthy skin obtained with this system show values comparable to the one reported in the literature. Monitoring of tissue oxygenation during healing could be an important metric in establishing efficacy in wound treatment and care.
Zhang et al.[70]	A custom-built system with 400 to 900 nm range	The integrated multimodal imaging system has been developed and validated in an in vivo experiment following a post occlusive reactive hyperaemia (PORH) procedure.
Jeffcoate et al.[62] Yang et al.[63]	A custom-built system with 430-750 nm range (272 values)	These findings suggest that HSI may predict healing in routine practice. The results of the present study confirm a statistical relationship between the oxygenation of haemoglobin in blood vessels of the foot as determined by baseline HSI and healing by 12 weeks. HSI may be a better predictor of healing when analysed by PCA than by SpO2.
Sprigle et al.[67]	A custom design multispectral system from 400 to 950 nm at 50-nm intervals	Four algorithms enhanced contrast of erythema by order of magnitude over that of a digital photograph. The accuracy of the detection algorithms ranged from 66% to 95%. Sensitivity and specificity ranged from 0% to 100%. One fusion algorithm exhibited an accuracy of more than 90% and sensitivity and specificity of more than 90%.
Stam et al.[50]	A custom designed hyperspectral camera, which takes 131 images in 440–700 nm range.	The age of bruises can be determined accurately from the time-varying areas of haemoglobin and bilirubin measured by hyperspectral imaging.
Liu et al.[64]	a spectroscopic system in 360 to 1000 nm range, which contained 1127 channels with a bandwidth ranging from 0.6 to 0.53 nm	Future clinical studies are needed to investigate the most cost-effective application of an intelligent telemedicine monitoring system for the diabetic foot in daily clinical practice.

evaluate how HSI is used to measure the oxygenation or perfusion of skin tissues, including a wound.

In most studies, tissue oxygenation data were extracted. However, in some studies, other parameters (total oxyhaemoglobin, total deoxyhaemoglobin, total haemoglobin) were used in some combination/ ratios.[1,57-59]

Liu et al.[64] designed a spectroscopic diabetic foot ulcer (DFU) pre-sign detector/classifier with a limited number of spectral bands (3-7). The performance of the design was investigated on a dataset of 227 skin spots, classified by a clinical expert as healthy, ulcer, callus, or showing other pre-ulceration signs. The sets (3-7 wavelengths) were all able to automatically discriminate between (pre-) signs of ulceration and healthy skin spots with a specificity of 96% and a sensitivity of 97%.

Liu et al.[77] proposed 3D reconstruction of wound topology using 3D topography multiview system.

Springle et al.[67] used multispectral imaging to detect erythema in darker skin. Four algorithms enhanced contrast of erythema by order of magnitude over that of a digital photograph. The accuracy of the detection algorithms ranged from 66% to 95%. Sensitivity and specificity ranged from 0% to 100%. One fusion algorithm exhibited an accuracy of more than 90% and sensitivity and specificity of more than 90%.

3.6 | Clinical outcomes

Some clinical parameters can be more predictive of outcome than others with regard to wound status.[79] The review process looked at studies where HSI was used to be more predictive of the outcome.

In several studies, HSI was used to predict the probability of healing. In particular, Khaodhiar et al.[57] measured deoxyhaemoglobin (RHb), oxyhaemoglobin (HbO2), and SO2 of diabetic patients with ($n = 10$) and without DFU ($n = 13$) as well as non-diabetic controls ($n = 14$) four times over 6 months using HSI. Healing index (distance between the point defined by the oxy and deoxy values and the linear discriminant decision line that best separated healed ulcers from unhealed ulcers) was proposed to predict healing potential. The sensitivity, specificity, and positive and negative predictive values of the index were 93%, 86%, 93%, and 86%, respectively. Nouvong et al.[58] verified that the healing index in a small clinical trial (54 patients with 73 ulcers) and found 80%, 74%, and 90% for the sensitivity, specificity, and positive predictive value, respectively.

Yang et al.[63] analysed SpO2 and PCA methods as predictors of wound healing. SpO2 results from baseline were significantly different between ulcers that did and did not heal within 12 weeks, but not between those that did and did not by 24 weeks. In the PCA results, a clustering of data corresponding to healing within 12 weeks was observed at the PC2 threshold of (−0.62, +0.62). When the methods were compared in a receiver operating characteristic (ROC) curve, the PCA classifier was shown to be much more ideal. The sensitivity of prediction of healing by 12 weeks using PCA (87.5%) was higher than that of SpO2 (50.0%), with both approaches showing equal specificity (88.2%).

Chang et al.[72] used a multimodal system (3D wound size measurements, HSI, thermo, and chemical vapour sensing analysis) to assess the probability of healing of pressure injuries.

In some studies, HSI was used to predict the probability of ulceration. In particular, Yudovsky et al.[59] assessed the use of HSI in predicting DFU development. Diabetic patients at risk of DFU were monitored and retrospectively assessed for ulceration. Difference in HbO2 (and RHb at less degree) value between wound and peri-wound was a predictor of ulceration. The ulceration prediction index was developed. Algorithms were able to predict tissue at risk of ulceration with a sensitivity and specificity of 95% and 80%, respectively, for images taken, on average, 58 days before tissue damage is apparent to the naked eye.

In one study,[68] the spectral signatures of *S aureus* and *E coli* were used to discriminate between them. They achieved the 100% sensitivity and 75% specificity in detecting the presence of these infections with 100% negative predicted value in excluding the infection in such wounds.

Stam et al.[50] used multispectral imaging to determine the age of bruises using haemoglobin and bilirubin presence.

3.7 | Baseline measurements

Technology validation is essential from a clinical perspective, particularly with respect to any diagnostic or prognostic measurement. An element of key importance is baseline measurement to provide a reference for differential diagnosis between normal and abnormal conditions.

Greenman et al.[5] used HSI to measure haemoglobin saturation in healthy, diabetic, and diabetic neuropathic subjects. The forearm SO2 during resting was different in all three groups, with the highest value in controls (42 ± 17), followed by the non-neuropathic (32 ± 8) and neuropathic (28 ± 8) groups ($P < .0001$). In the foot at resting, SO2 was higher in the control (38 ± 22) and non-neuropathic groups (37 ± 12) than in the neuropathic group (30 ± 12; $P = ·027$).

In several studies, the HSI results were compared with gold standards. Bowen et al.[54] found that transcutaneous partial pressure of oxygen (TcPO2) and SO2 are highly correlated ($R^2 = .84$). Jafari-Saraf et al.[60] compared HSI with TcPO2. Twenty-three sections of the foot or wrist skin in four healthy volunteers were measured at 37°C, 41°C, and 45°C. TcPO2 at 37°C was 23.1 ± 24.8 mmHg, increasing to 63.0 ± 27.3 mmHg at 45°C. HbO2 levels increased from 52.4 ± 25.4 at 37°C to 101.3 ± 23.8 at 45°C. Linear regression analysis of the data at 37°C showed a positive correlation between TcPO2 and HbO2 ($R^2 = .35$, $P = .003$), TcPO2 and RHb ($R^2 = .63$, $P < .0001$), and TcPO2 and tHb ($R^2 = .60$, $P < .0001$), but not SO2 ($R^2 = .001$, $P = .92$).

3.8 | Aetiology

3.8.1 | Acute wound

Acute wounds, unlike those which are chronic, generally heal without complication.[81,82] As such, they present a good model for healing. Often acute wound studies are used as validation of any diagnostic or prognostic decision.[83] HSI can be used for both diagnostic and prognostic decisions within wound care.[75]

Zhang et al.[70] used a multimodal imaging device to monitor continuously healing progress of a 3 mm biopsy induced wound on an otherwise healthy patient.

Huong et al.[71] used HSI to determine the possible range and variation of wound bed SO2. Three patients with acute wounds and eight healthy volunteers were included in the study.

Philimon et al.[74] compared SO2 extraction using 530-570 nm range versus 520-600 nm range for one acute wound. The measurements from the two ranges were significantly comparable. The 530-570 nm range provides slightly higher (5.72% on average) oxygenation numbers than the broader range.

3.8.2 | Bruises

Bruises seem inconsequential but are really more important than they seem, particularly in patients with comorbidities that can increase their chance of a wound.[84] While there is some surface indication of injury, the damage is usually in the deeper tissues.[84] This is where hyperspectral imaging can be beneficial by providing a measure of subcutaneous damage.[85]

Stam et al.[50] used multispectral imaging to determine the age of bruises using haemoglobin and bilirubin presence, which can be useful in the area of forensic science[86] and non-accidental injuries.[87]

3.8.3 | Chronic wounds

Chronic wounds are difficult to manage.[88] As such better assessment and diagnosis lead to better management and outcomes.[89] Tracking of these wounds is vital to assess therapeutic outcomes. The visibility of the approach will help ensure the delivery of best practice. Most image tracking systems see what the camera can see.[17,90] As such, decisions are limited based on incomplete information. Hyperspectral or below the skin imaging can enhance this information providing additional, valuable clinical insight.[91]

Bowen et al.[54] used HSI in 20 patients with lower extremity wounds (venous, arterial, diabetic, and radiation injury) to compare with a TcPO2 monitor and found a strong relationship between TcPO2 and SO2 ($R^2 = .84$).

Basiri et al.[66] tested HSI on 15 patients (22 wounds) with wounds (a pressure ulcer, a diabetic ulcer, a vascular ulcer, or a post-surgical wound.) Evaluation of the wounds was conducted weekly for 4 weeks during treatment with CACIPLIQ20 and on two follow-up sessions via the standardised PUSH tool, VERG digital camera assessment, and multispectral camera assessment. The assessment of size obtained with the PUSH and VERG tools were used as indicators of wound healing and were compared with the results obtained with the multispectral camera. Data were analysed on 10 patients who completed treatment. The parametric *t*-test shows a significant decrease in the oxygen saturation value compared with PUSH and VERG tools (Paired T-test value = 4.53, *P*-value = .0001). A non-parametric analysis of SO2 using Wilcoxon criteria, repeated measures Friedman ANOVA, and repeated measures General Linear Model (GLM) confirms a significant trend in the reduction of oxygen saturation following a wound healing process, (Z-value in Wilcoxon rank test = 3.0, *P*-value = .003), (F-value in Friedman Test = 12.82, *P*-value = .012), GLM F-value = 21.7, *P*-value = .0001).

DFU

Diabetic foot ulceration is a major complication of diabetes, and diabetic patients have up to a 25% lifetime risk of developing a foot ulcer.[90] If untreated, diabetic foot ulcers may become infected and require total or partial amputation of the affected limb. Changes in the large vessels and microcirculation of the diabetic foot are important in the development of diabetic foot ulceration and subsequent failure to heal existing ulcers.[92] Hyperspectral imaging has been used to assess tissue viability and health in diabetes patients at risk of foot ulceration.[57,58,93-95]

Greenman et al.[5] used HSI to measure haemoglobin saturation in healthy, diabetic, and diabetic neuropathic subjects. The forearm SO2 during resting was different in all three groups, with the highest value in controls (42 ± 17), followed by the non-neuropathic (32 ± 8) and neuropathic (28 ± 8) groups ($P < .0001$). In the foot at resting, SO2 was higher in the control (38 ± 22) and non-neuropathic groups (37 ± 12) than in the neuropathic group (30 ± 12; $P = \cdot 027$).

Khaodhiar et al.[57] measured RHb and HbO2 of diabetic patients with (n = 10) and without DFU (n = 13) as well as non-diabetic controls (n = 14) four times over 6 months using HSI. HbO2 and RHb measurements in the peri-wound of non-healing ulcers were lower than in healing ulcers ($P < .01$) and contralateral foot ($P < .001$).

Nouvong et al.[58] followed diabetic patients (n = 44) over a 24-week period. HbO2 and RHb were measured using HSI. In the peri-wound area, higher HbO2 and SO2 values were noted around DFUs that healed (85 ± 21 and 66 ± 9%, respectively) versus non-healing (64 ± 22 and 60 ± 10%, respectively). No difference in surrounding temperature was found.

Yudovsky et al[59,] using data set[58,] assessed the use of HSI in predicting DFU development. Diabetic patients (n = 54) at risk of DFU were monitored and retrospectively assessed for ulceration. Difference in HbO2 (and RHb at less degree) value between wound and peri-wound was a predictor of ulceration. The ulceration prediction index was developed. Algorithms were able to predict tissue at risk of ulceration with a sensitivity and specificity of 95% and 80%, respectively, for images taken, on average, 58 days before tissue damage is apparent to the naked eye.

Jeffcoate et al.[62] compared HSI SO2 measurements against blood gas analysis in blood samples (in vitro) in DFUs to determine the relationship between oxygenation and healing time at 12 and 24 weeks for 43 patients. A negative association between SO2 and healing by 12 weeks ($P = .009$) was found. A significant positive correlation between oxygenation assessed by HSI and time to healing ($P = .03$). No correlations were observed at 24 weeks. A strong correlation between SO2 and blood gas measurements (r = .994) was found. Yang et al.[63] used the same dataset to compare SO2 versus principal component analysis (PCA). In the PCA results, a clustering of data corresponding to healing within 12 weeks was observed at the PC2 threshold of (−0.62, +0.62). When the methods were compared in a ROC curve, the PCA classifier was shown to be much more ideal. The sensitivity of prediction of healing by 12 weeks using PCA (87.5%) was higher than that of SpO2 (50.0%), with both approaches showing equal specificity (88.2%).

Poosapadari et al.[68] used spectroscopy to discriminate between the two most prevalent potential pathogenic microbes in DFU patients (*S aureus* and *E coli*). They achieved the 100% sensitivity and 75% specificity in detecting the presence of these infections with 100% negative predicted value in excluding the infection in such wounds.

PAD

With the rise of amputations performed every year, resulting from diabetes complications and PVD, better methods are needed to assess the severity of wounds and make data-driven treatment decisions.[96] Improved assessment tools could reduce secondary amputations, promote healing, and improve patient outcomes.[92]

Ubbink et al.[65] found high reproducibility of near infrared spectroscopy (NIRS) (ICC: 0.91) in patients with leg ischaemia. Resting SO2 (65%) in healthy controls did not differ significantly from that in patients. After exercise, a significant reduction in SO2 was observed only in patients: The ankle-brachial index (ABI) after exercise showed a good correlation with SO2 at the end of the treadmill test. No correlation between NIRS and other micro- or macro circulatory parameters has been found.

Chin et al.[1] imaged nine angiosomes of foot patients with PAD and healthy individuals. RHb values for the plantar metatarsal, arch, and heel angiosomes were significantly different between patients with and without PAD ($P < .005$). Mean RHb values for the same three angiosomes showed significant differences between patients with monophasic, biphasic, and triphasic waveforms ($P < .05$). In patients with PAD, there was also a significant correlation between RHb values and ABI for the same three angiosomes ($P < .001$). HbO2 values did not predict the presence or absence of PAD, did not correlate with PAD severity, and did not correlate with the ABI.

Chiang et al.[2] compared HSI with transcutaneous oxygen pressure measurements (TCOM) and ABI in patients with PVD. They found inter-operator reliability: 86% to 94% across the four hyperspectral imaging device outputs; intra-operator reliability: 92% to 94%. The HbO2, SO2, TcPCO2, and ABI of the diseased limb correlated significantly with the severity of PVD. SO2 significantly correlated with TcPO2 (R = .19), TcPCO2 ($R = -.26$), ABI ($R = .42$), and skin temperature ($R = .56$). RHb is also correlated with TcPCO2 ($R = .27$).

Amputation stumps

Amputation can have longer-term issues with respect to the skin at risk and also potentially 'remainder' of a limb at risk. While it can take some time for visible skin lesions or trauma, some subcutaneous indicators may identify risk profiles.[97]

Rink et al.[55] performed HSI for individuals with transtibial (TT) and transfemoral (TF) amputations and found that compared with able-limb (AL) controls, amputees have significantly lower transcutaneous oxygen tension, higher transepidermal water loss, and higher surface electrical capacitance in the residual limb. SO2, as measured by the HSI, was unchanged across AL, TT, and TF subjects.

Pressure injuries

A pressure injury is localised damage to the skin and underlying tissue caused by pressure, shear, or friction.[84] Diagnosis, care, and treatment of pressure injuries can result in significant costs for healthcare systems. A reliable diagnosis supported by precise skin/wound evaluation is crucial in order to treat the patient appropriately.[84] However, current clinical evaluation procedures, focused mainly on visual inspection, do not seem to be accurate enough to accomplish this important task.[98]

Chang et al.[72] validated their multimodal system on 23 patients with pressure injuries. They found that peri-wound temperature difference correlates most strongly with the healing trend with a threshold of $-2°C$. If the peri-wound temperature is more than $2°C$ lower than the normal skin, the wound tends to be non-healing. They also derived an empirical rule that if the wound bed $SO2 > 60$, the injury is non-healing.

3.8.4 | Intervention

In some studies, various interventions have been used.

Greenman et al.[5] measured endothelium-dependent vasodilatation in the cutaneous microcirculation by iontophoresis of acetylcholine. HSI measurements were performed before and after iontophoresis. They found that oxyhaemoglobin at baseline and after iontophoresis was reduced in patients with (baseline 19 ± 7, post-iontophoresis 38 ± 9) and without neuropathy (20 ± 5, 41 ± 8) compared with controls (29 ± 7, 50 ± 12; both $P < .0001$). Baseline and post-iontophoresis values of deoxyhaemoglobin did not differ significantly between control individuals (baseline 41 ± 16, post-iontophoresis 52 ± 15), and those with (49 ± 10, 50 ± 9) or without neuropathy (44 ± 10, 50 ± 10). After iontophoresis, SO2 in the neuropathic group (43 ± 7) was lower than in controls (49 ± 10; $P = \cdot 004$).

Arm occlusions

Arm occlusion is generally a technique used to evaluate the impact of reduced perfusion.[99] It is generally used for research studies. The use of this test can validate or provide a baseline for tissue perfusion.[100]

Basiri et al.[66] used a blood pressure cuff inflated to 140 mmHg to mimic ischaemic conditions in the arm (n = 1). The cuff was inflated for the duration of 220 seconds, and then the pressure was released.

Zhang et al.[70] used an occlusion experiment (180 mmHg for 2 minutes) to compare SO2 to TcPO2 and laser Doppler perfusion monitoring measurements.

Liu et al.[77] used an occlusion test (180 mmHg period of 2 minutes, and a reactive hyperaemia period of 4 minutes) to validate Multiview/HSI integrated set up. Measurements were compared with simultaneous laser Doppler perfusion monitor and TcPO2 electrode measurements of blood perfusion and PO2.

Wild et al.[8] performed an occlusion test during HSI measurements on 10 healthy volunteers. Measurements were taken in four phases: normal, venous occlusion, arterial occlusion, and reperfusion.

Leg occlusion

Leg occlusion, like arm occlusion, is a technique used to evaluate the impact of reduced perfusion. It is generally used for research studies. The use of this test can validate or provide a baseline for tissue perfusion.[101]

Unbbink et al.[65] used provocations (a treadmill test, arterial occlusion, and a change in posture) to assess peripheral blood pressure and microcirculatory in patients with leg ischaemia and healthy individuals. They found that resting SO2 (65%) in healthy controls did not differ significantly from that in patients. After exercise, a significant reduction in SO2 was observed only in patients: The ABI after exercise showed a good correlation with SO2 at the end of the treadmill test. No correlation between NIRS and other micro- or macro circulatory parameters.

Springle et al.[67] emulated erythema by a pneumatic cuff and indenter on the shanks of 56 subjects (including 28 with darker skin) to test pressure injury detection algorithms. The medial tibial flare was selected as the loading site because it is relatively flat and can be loaded without discomfort. The accuracy of the detection algorithms ranged from 66% to 95%. Sensitivity and specificity ranged from 0% to 100%. One fusion algorithm exhibited an accuracy of more than 90% and sensitivity and specificity of more than 90%.

3.9 | HSI as a research tool

Like most diagnostic tools, hyperspectral imaging can be used in research.

Basiri et al.[66] measured SO2 using HSI in a clinical trial to assess whether PCMGS (Poly Carboxy Methyl Glucose Sulfate) promotes wound healing (15 patients 22 wounds) with wounds (a pressure ulcer, a diabetic ulcer, a vascular ulcer, or a post-surgical wound.)

Evaluation of the wounds was conducted weekly for 4 weeks during treatment with CACIPLIQ20 and on two follow-up sessions via the standardised PUSH tool, VERG digital camera assessment, and multispectral camera assessment. The assessment of size obtained with the PUSH and VERG tools were used as indicators of wound healing and were compared with the results obtained with the multispectral camera. Data were analysed on 10 patients who completed treatment. The parametric *t*-test shows a significant decrease in the oxygen saturation value compared with PUSH and VERG tools (Paired T-test value = 4.53, *P*-value = .0001). A non-parametric analysis of SO2 using Wilcoxon criteria, repeated measures Friedman ANOVA, and repeated measures GLM confirms a significant trend in the reduction of oxygen saturation following a wound healing process, (Z-value in Wilcoxon rank test = 3.0, *P*-value = .003), (F-value in Friedman Test = 12.82, *P*-value = .012), GLM F-value = 21.7, *P*-value = .0001).

Chiang et al.[7] performed HSI assessment in a clinical trial to assess the effect of topical negative pressure (TNP) therapy. Vascular patients with acute wounds after surgical debridement or minor amputation were randomly assigned to a treatment group (TNP or regular topical). Each wound was assessed at baseline and day 14 of treatment (volumetric assessment, biochemical analysis of hydroxyproline levels, and HSI tissue oxygenation measurement).

Chiang et al.[56] performed HSI assessment in a clinical trial to assess the effect of Perioperative adjuncts during infrainguinal bypass (IIB) surgery. Patients undergoing IIB surgery were allocated into three treatment arms (perioperative high-dose oxygen, extended warming, and a synthetic prostacyclin) or a control group. Healing and perfusion were assessed via accumulation of hydroxyproline, levels of growth factors and cytokines, tissue oxygenation of wound and foot (measured by HSI), and ankle-brachial index. Clinical outcomes observed to day 30, long-term follow-up of 12 months.

Rink et al.[61] used HSI to quantitatively assess residual-limb circulation in response to elevated vacuum suspension (EVS) in 10 amputees. In particular, HSI was used to quantify reactive hyperaemia.

Daeschlein et al.[69] assessed two wounds (one acute and one chronic) to determine the effects of CAP therapy. The wounds were treated with CAP, and HSI images were taken before treatment, directly after, and 10 minutes after treatment.

Rutkowski et al.[78] imaged two patients undergoing CAP therapy to evaluate StO2, NIR perfusion, and THI before, immediately after, and 10 minutes after receiving the treatment at points of interest (one or more in the tumour area, one as an internal control in a non-CAP treated neck/cheek area.

4 | DISCUSSION

4.1 | Hyperspectral imaging technology

While spectral analysis has been in the medical arena for some time, it is relatively recent to the world of wound care. That being said, there are a small number of commercial devices being targeted to wounds. Most of the research to date in this area has been with custom devices from the research environment.

One commercial technology, OxyVue (Hypermed), has the most significant quantity of clinical research and evidence. But even that is limited in its scope and size.

The varying wavelengths utilised in multiple research and clinical studies confuse the arena as to the most appropriate for use in wound care. Or if any particular wavelength or range of wavelengths is more suitable for any specific aetiology.

Reported studies vary significantly in methodology. Most of the reported studies are proof-of-the-concept. It is probably can be explained by a very early stage of the HSI technology in wound care. Most studies have not benchmarked healthy individuals and not performed any comparison with a gold standard (We identified just three studies, which compare HSI with TCOP). Even when the comparison was performed, a very broad set of clinical tools was used (laser Doppler, ABI, blood gas analysis, StO2).

4.2 | Clinical application of hyperspectral imaging

Albeit the evidence is limited, it does include a number of wound aetiologies showing the breadth of scope of HSI. Wounds come in all shapes and sizes, with a myriad of underlying casualties or impactors (eg, diabetes). Wound patients are complex, and often clinical signs and symptoms can be subcutaneous and note readily visible to the human eye.

HSI offers a technological solution to help better understand patients with wounds and the outcomes of treatment. While this is significant in itself, HSI offers significant potential in the preventative area by allowing the identification of 'skin at risk' (eg, impending deep tissue injury).

4.3 | Limitations

The present systematic review and the availability of evidence have several limitations. First, given the substantial clinical and methodological heterogeneity between studies, a variety of ways HSI data were presented, and the small numbers of available studies, it was not possible to perform a meta-analysis and quantitatively analyse the data. Consequently, we were unable to draw any firm conclusions concerning the effectiveness of the described HSI techniques. Second, the studies were of mixed methodological quality and reported a variety of customised HSI systems, limiting our discussion to a qualitative discussion of a small number of higher-quality studies. Third, the amount of details about HSI systems varied significantly in available studies, with particularly very scarce details available for proprietary systems. Thus, it complicates the comparison between results even further. Finally, the results reported in our review are not cross-validated and limited by the accuracy of the previously reported data.

4.4 | Future studies

Future hyperspectral imaging studies are required to more fully quantify the tissue-oxygenation-based assessment that can provide subclinical physiological status to combine with visual clinical assessment. Higher powered studies would provide more evidence of approach and applicability with regard to wound type or wound-related conditions.

Particular attention needs to be paid to the benchmarking of the physiological normal conditions and comparison with gold standards.

Research and development efforts are focused on performing an image overlay of tissue oxygenation maps onto white light images. This will assist in determining areas of changed oxygenation and comparing them with visual wound areas, providing a more compelling visual representation of the wound and its underlying and surrounding subcutaneous structures.

5 | CONCLUSION

Wounds are common and complex.[102] An accurate assessment is urgently required as part of routine clinical assessment. Such accurate, reliable, reproducible measurements are important in clinical practice to objectively assess and benchmark outcomes.[103] The accurate determination of wound size is widely accepted as an indication of wound progression. It is evident that wound imaging with clinically validated measurement can be beneficial to the healing process.[104,105]. Other wound-related parameters are subcutaneous and, as such, cannot be seen easily.[106]

Hyperspectral imaging analysis has significant potential in healthcare.[107] It has the potential to transform wound prevention and treatment. Numerous studies have evaluated its use in pre-clinical in vivo animal models,[102-114,] and others have demonstrated the usefulness of ex vivo tissue analysis.[115] The use of in vivo HSI systems has not been widely tested in the prevention and treatment of wounds, but the small number of studies demonstrate its current capabilities[115-119] and highlight avenues for future research. Since most studies are small and inadequately powered, there is a need for further data to prove the ultimate clinical utility. Most studies, to date, have been essentially in the research area, but the real need is a point of care test.

However, in order to translate this promising imaging technique into regular clinical use[120] within wound prevention and management, it must be seamlessly integrated into the clinical workflow. Since most patients with wounds are 'in and out' of multiple care settings across the continuum of care, technologies have to be both practical and adaptable. Hardware development, therefore, needs to leverage recent advances in the miniaturisation of hyperspectral systems, and robust real-time image analysis models must be developed.

It has been shown that ischaemic and hypoxic conditions are detrimental to many different types of wounds.[121,122] Monitoring of tissue oxygenation is, therefore, an important metric in the management of patients with wounds. Hyperspectral imaging is a promising technique for assessment of optical tissue properties and non-invasive monitoring of wound healing.[116]

Telemedicine, facilitated by electronic imaging and measurement systems,[28-30] which could include HSI, has great potential to reduce cost and improve standards in wound care; this derives from reducing patient and clinician transport and providing higher-level and more immediate access to expert clinical knowledge. While this technology has potential, it needs to influence practice to make a difference. This may require the primary adoption to be in specialist clinical centres to increase awareness and provide educational support for other clinicians.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Saiko G, Lombardi P, Au Y, Queen D, Armstrong D, Harding K. Hyperspectral imaging in wound care: A systematic review. *Int Wound J*. 2020;1–17. https://doi.org/10.1111/iwj.13474