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REVIEW ARTICLE

Non-invasive skin autofluorescence as a screening method for diabetic retinopathy

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Abstract

Diabetic retinopathy (DR) is a public health problem and a common cause of blindness. It is diagnosed by fundus examination; however, this is a costly and time-consuming method. Non-invasive skin autofluorescence (SAF) may be an accessible, fast and simple alternative for screening and early diagnosis of DR. The aim of this study was to evaluate the accuracy of SAF as a screening method for DR. A systematic search of MEDLINE, Scopus, and Web of Science databases was performed. Random effects models for sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR), diagnostic odds ratio (dOR) value and 95% CIs were used to calculate test accuracy. In addition, hierarchical summary receiver operating characteristic curves (HSROC) were used to summarise the overall test performance. Four studies were included in the meta-analysis. Pooled sensitivity and specificity were 0.79 (95% CI 0.72–0.88; I^2 = 0.0%) and 0.54 (95% CI 0.32–0.92; I^2 = 97.0%), respectively. The dOR value for the diagnosis of DR using SAF was 5.11 (95% CI 1.81–14.48: I^2 = 85.9%). The PRL was 2.17 (95% CI 0.62–7.64) and the NRL was 0.27 (95% CI 0.07–1.03). Heterogeneity was not relevant in sensitivity and considerable in specificity. The 95% confidence region of the HSROC included all studies. SAF as a screening test for DR shows sufficient accuracy for its use in clinical settings. SAF may be an appropriate method for DR screening, and further research is needed to recommend it as a diagnostic method.

KEYWORDS

accuracy, advanced glycation end products, diabetic retinopathy, meta-analysis, non-invasive skin autofluorescence, screening

1 | INTRODUCTION

Diabetic retinopathy (DR) occurs due to sustained hyperglycemia, oxidative stress, and inflammation leading to microangiopathy at the level of retinal arterioles, capillaries, and venules.[1–4] It is the most frequent complication of diabetes and a common cause of blindness.[5–8] Until 2020, it was estimated that this microvascular complication affected 103.12 million people worldwide,[9] but by 2045 these figures are estimated to increase to 160.50 million and the burden of DR is expected to continue increasing, especially in

countries in the Middle East, North Africa, and the Western Pacific.[9]

According to the Early Treatment Diabetic Retinopathy Study (EDTRS),[10,11] the multidisciplinary Global Diabetic Retinopathy Project Group (GDRPG)[12] proposed the classification of DR. Nowadays, this classification is considered the reference and stablishes the standard seven-field 30° colour fundus image (7SF), commonly called fundus examination, as the gold standard for the diagnosis of DR. This test is recommended annually for patients with diabetes,[13,14] although it has certain limitations. It only captures 34% of the retina, is a subjective method, and requires a lot of time, pupil dilation, trained ophthalmologists, and a determined clinical setting with large resources not influenced by socioeconomic, geographic, and cultural factors.[15–19] In addition, it has been suggested to be a very complex and not effective method for clinical practice.[1]

The use of other tests of retinal imaging has been suggested, including <7SF or UWF, but all have limitations that[15,20] may result in the late diagnosis of DR, leading to an urgent need for innovative strategies to foster early detection of DR to prevent complications from this pathology.[15] Furthermore, the diagnostic performance of an autonomous artificial intelligence (AI) system with manual scoring for the diagnosis of DR has also been explored with 100% sensitivity and 82% specificity.[21] However, all these methods are time-consuming or invasive, and therefore, not particularly useful for early and in-situ diagnosis in outpatient clinics.

In the search of non-invasive methods for the diagnosis of DR, a systematic review and meta-analysis was performed to compare the accuracy of fasting plasma glucose (FPG), 2h-plasma glucose (2h-PG), and glycated haemoglobin A1c (HbA1c). That study found that, although the accuracy of the 2h-PG test and the HbA1c were similar, HbA1c appears to be a more appropriate method as it has less variability and drawbacks.[22] In recent years, advanced glycation end products (AGE) measured with skin autofluorescence (SAF) have been used for diagnostic purposes,[23,24] especially among patients with diabetes,[25] as they offer a noninvasive and inexpensive diagnostic tool with a high degree of reproducibility.[23] Previous studies have revealed that the retinal microvasculature responds to hyperglycemia with biochemical changes such as AGE formation[4] and several investigations point to a correlation between DR and cutaneous AGEs,[26–28] however, others report a lack of association.[29–32]

Due to the need for a novel, simple, rapid, and accessible method for the early diagnosis of DR, the characteristics of SAF and its possible association with DR, this systematic review and meta-analysis was conducted to evaluate the accuracy of SAF on the early diagnosis of DR.

2 | MATERIALS AND METHODS

2.1 | Data source and literature search

This meta-analysis was reported according to the preferred reporting items for the protocol Statement Extension of Meta-analysis and Systematic Review (PRISMA)[33] and addressed the recommendations of the Cochrane Handbook for Systematic Reviews of the Accuracy of Diagnostic Tests.[34] This systematic review and meta-analysis were previously registered in PROSPERO (registration number: 341349) and Institutional Ethics Research Committee approval was not required because this study did not include individual patient data.

The systematic search for studies was performed through the databases Scopus, MEDLINE (via Pubmed), and Web of Science from their inception to 20 April 2022.

The search strategy included the following key words: Retinopathy, 'Diabetic retinopathy', DR, NPDR, PDR, 'Chronic diabetes complications', 'Microvascular complications', 'Type 2 Diabetes', DM2, DM, 'Diabetes Mellitus', 'Skin autofluorescence', SAF, AGE, AGEs, 'Advanced glycation end products', and 'Advanced glycation end-products'. This strategy is shown in Table S1.

In addition, we searched for additional relevant studies in the reference list of the included articles, and previous systematic reviews and meta-analyses. The literature search was performed independently by two reviewers (IMG and ICR), and inconsistencies were resolved by consensus.

2.2 | Eligibility or selection criteria

In this meta-analysis, we included studies on patients with diabetes predisposed to develop DR in which AGEs were measured using the SAF test.

Inclusion criteria were, studies: (i) including patients with diabetes; (ii) cross-sectional or case-control studies; (iii) studies including the SAF test to measure AGEs; (iv) reporting sensitivity and/or specificity data of the SAF test as a diagnosis of DR; and (v) using fundus diagnostic test as reference for the diagnosis of DR.

Exclusion criteria were, studies: (i) in which all patients had confirmed retinopathy; (ii) in which patients' microvascular complications (retinopathy, nephropathy, or neuropathy) were not differentiated; (iii) in which AGEs were not measured using SAF; (iv) experimental studies; or (v) reporting insufficient data to calculate sensitivity or specificity.

2.3 | Study selection and data extraction

Study selection and data extraction were performed following the proposed inclusion and exclusion criteria.

The following data were collected independently from each included study: (i) reference (author and year of publication), (ii) country of study, (iii) participants´ characteristics (sample size and age), (iv) measurement characteristics (SAF and gold standard), and (v) parameters summarising the SAF test accuracy (cut-off points, sensitivity, specificity, and area under the curve [AUC]), and (vi) diagnostic odds ratio (dOR). When missing information was detected in any of the studies included in the meta-analysis, the authors were contacted by e-mail.

Data extraction was performed independently by IMG and ICR, and inconsistencies were resolved by consensus.

2.4 | Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was used to assess four domains of each study: patient selection, index test, reference standard, and patient flow and timing of testing. Each domain was assessed in terms of risk of bias, and the first 3 domains were also assessed in terms of concerns regarding the applicability of the results.[35]

Quality assessment was performed independently by IMG and ICR, and inconsistencies were resolved by consensus.

2.5 | Statistical analysis and data synthesis

Sensitivity, specificity, PLR, NLR, and dOR results from the different studies were pooled using random-effects models with the Der Simonian and Laird method,[36] and their results were shown by forest plots. The dOR was calculated using Moses' constant of a linear model, indicating that this approach is based on linear regression of the logarithm of the dOR of a study (dependent variable) and an expression of the positivity threshold for that study (independent variable). The dOR is a measure of the precision of the test that combines sensitivity and specificity into a single value. Values of dOR could range from 0 to infinity, with higher values indicating better discriminatory test performance. A dOR of 1.0 indicates that the test does not discriminate between those patients with DR and those without DR.[37] The PLR and NLR were calculated; the higher the PLR and the lower the NLR, the better the utility of the test.[38,39]

The heterogeneity of results between studies was assessed using the I^2 statistic. I^2 values 0%–30%, 30%–50%, 50%–75%, and 75%–100% correspond to no important, moderate, substantial, and considerable heterogeneity, respectively.[40] Hierarchical summary receiver operating characteristic curves (HSROC) were used to summarise the overall test performance. HSROC has been proposed to estimate the diagnostic test performance of SAF using data from this meta-analysis.

The separate influence of each study on the pooled dOR was estimated by recalculating the pooled dOR estimate after exclusion

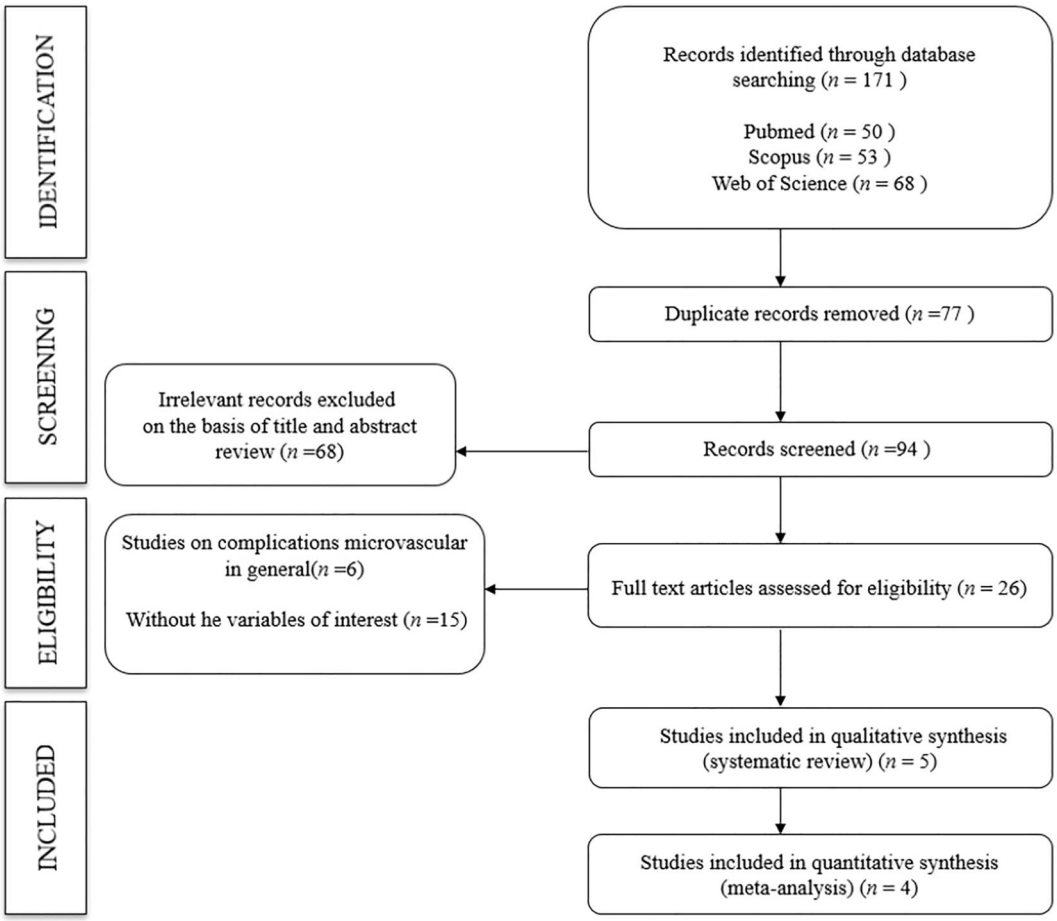

FIGURE 1 Flowchart of the literature search.

TABLE 1 Characteristics of the studies.

Reference	Country	Type of study	Groups	Age (SD)	*n*	*n* diabetics	Prevalence of DR	Diagnostic test	Gold standard	Diagnosis of diabetic retinopathy				
										Cutoff points (AU)	Sens. (%)	Spec. (%)	AUC	dOR
Hirano, T et al. (2014)	Japan	Cross-sectional observational	DM2: - NDR: 36 - NPDR (mild: 16, moderate: 17, severe: 38): 71 - PDR: 31 Control: 111	DM: 63.7 ± 12.2 Control: 62.2 ± 15.4	249	52	30.76%	Non-invasive skin autofluorescence	Fundus examination	2.25	77.0	69.0	0.78	6.82
Yasuda, M et al. (2014)	Japan	Cross-sectional observational	DM2 - NDR: 15 - NPDR: 31 - PDR: 21 Control: 67	DM: 61 ± 7.81 Control: 62 ± 7.87	134	67	77.61%	Non-invasive skin autofluorescence	Fundus examination	0.53	Not reported	Not reported	0.79	Not available
Kim, JJ et al. (2018)	South Korea	Cross-sectional observational	DM2 - Diabetic complications (retinopathy: 60*, neuropathy: 39*, nephropathy: 69*): 110 - Without complications: 56	With complications: 60.9 ± 11.5 Without complications: 59.3 ± 10.7	166	166	36.1%	Non-invasive skin autofluorescence (measured at the first dorsal interosseous muscle of the hand)	Fundus examination	4.83	71.67	55.36	0.669	3.18
Januszewski, AS et al. (2020)	Australia	Cross-sectional observational	DM1 (children and adults): 269 - Diabetic complications (micro: Retinopathy: 29, nephropathy, both or macro): 67 - Without complications: 202 Control (children and adults): 114	DM1: With complications: 31 ± 18 Without complications: 26 ± 14* Control: 31 ± 16	383	269	10.78%	Non-invasive skin autofluorescence	Fundus examination	1.82	93.0	75.0	0.89	40.50
Ying, L et al. (2021)	China	Cross-sectional observational	NDR: 1099 NPDR (mild to moderate): 332 VTDR: 40	Total: 60 ± 12	1471	1471	25.3%	Non-invasive skin autofluorescence	Fundus radiography	Not reported	79.6	31.3	0.560	1.77

Note: Data are shown as mean ± standard deviation (SD). Values for *n* indicates sample size.

Abbreviations: AU, arbitrary units; AUC, area under the ROC curve; dOR, diagnostic odd ratio; DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; NDR, no diabetic retinopathy; NPDR, mild, moderate, or severe non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; Sens., sensitivity; Spec., specificity; VTDR, PDR was combined with severe NPDR and were defined as vision-threatening DR.

of individual studies. Finally, publication bias was visually assessed using a funnel plot as well as the method proposed by Deeks.[41]

Statistical analyses were performed using StataSE software version 15 (StataCorp).

3 | RESULTS

3.1 | Sample characteristics

A total of 171 articles were retrieved from the literature search, from which five articles were included in this systematic review and meta-analysis (Figure 1).[42–46]

The five studies included 2403 participants, of whom 2025 were patients with diabetes. The studies were conducted in Japan, South Korea, Australia, and China. The mean age of the participants ranged from 26.0 to 63.7 years. The prevalence of DR in the sample ranged from 31.3% to 75.0% among diabetic participants. All studies measured AGEs in the forearm with SAF, except one that measured AGEs in the palm of the hand.[44] The device used to measure SAF differed among studies. All studies provided information on patient sex, smoking status, baseline value of AGEs, and DR severity, especially distinguishing between non-proliferative and proliferative DR. In addition, most of the studies assessed HbA1c (Table 1).

3.2 | Quality of studies

The assessments of bias and applicability of the included studies using the QUADAS-2 scale are shown in Table S2 and Figure S1. All studies scored as low risk when reporting the reference standard and the flow and time of the participants, in the risk of bias. However, of the selected patients, only two studies showed low risk and the rest showed unclear risk. Furthermore, all studies had shortcomings when reporting the index test, since it is unclear whether the results of the index test were interpreted with knowledge of the results of the reference standard. In addition, all studies scored as low risk in concerns regarding applicability, except one study, which showed unclear risk of the patient selection.

3.3 | Meta-analysis

Figure 2 shows the funnel plot for the dOR of the SAF test. The pooled dOR for the diagnosis of DR was 5.11 (95% CI, 1.81–14.48); ($p < 0.001$). The heterogeneity of the dOR results for SAF was considerable ($I^2 = 85.9\%$).

The pooled sensitivity and specificity of SAF are shown in Figure 3. The pooled sensitivity and specificity of SAF were 0.79 (95% CI: 0.72–0.88; $p = 0.759$) and 0.54 (95% CI: 0.32–0.92; $p = 0.0001$), respectively. The pooled PLR was 2.17 (95% CI: 0.62–7.64; $p = 0.923$) and the pooled NLR was 0.27 (95% CI: 0.07–1.03; $p = 0.730$). The heterogeneity for specificity was considerable ($I^2 = 97.0\%$), but for sensitivity was not important ($I^2 = 0.0\%$).

The area under the HSROC that estimates the discrimination accuracy of PAS for identifying DR is shown in Figure 4. The 95% confidence region for the point that summarised the overall test performance included all studies. This HSROC indicates that the cut-off points for the diagnosis of the included studies range between 1.82 and 4.83 AU.

3.4 | Sensitivity analysis for the effect of individual studies

When the impact of individual studies was examined, the effect was not modified after removing any of the studies from the analysis.

3.5 | Publication bias

The asymmetry test, using the Deeks method, did not suggest publication bias for SAF ($p = 0.22$) (Figure S2).

4 | DISCUSSION

This systematic review and meta-analysis was conducted to evaluate the accuracy of SAF as a screening method of DR. Our data indicate that the use of DR has sufficient diagnostic accuracy for clinical

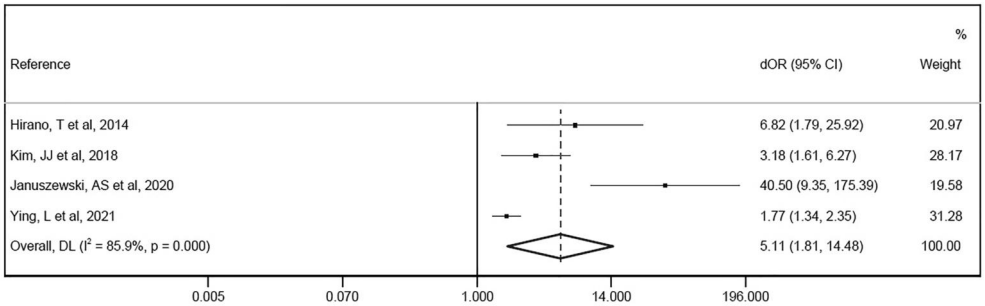

FIGURE 2 Forest plot of the diagnostic odds ratio (dOR) of the skin autofluorescence (SAF) test in the studies included.

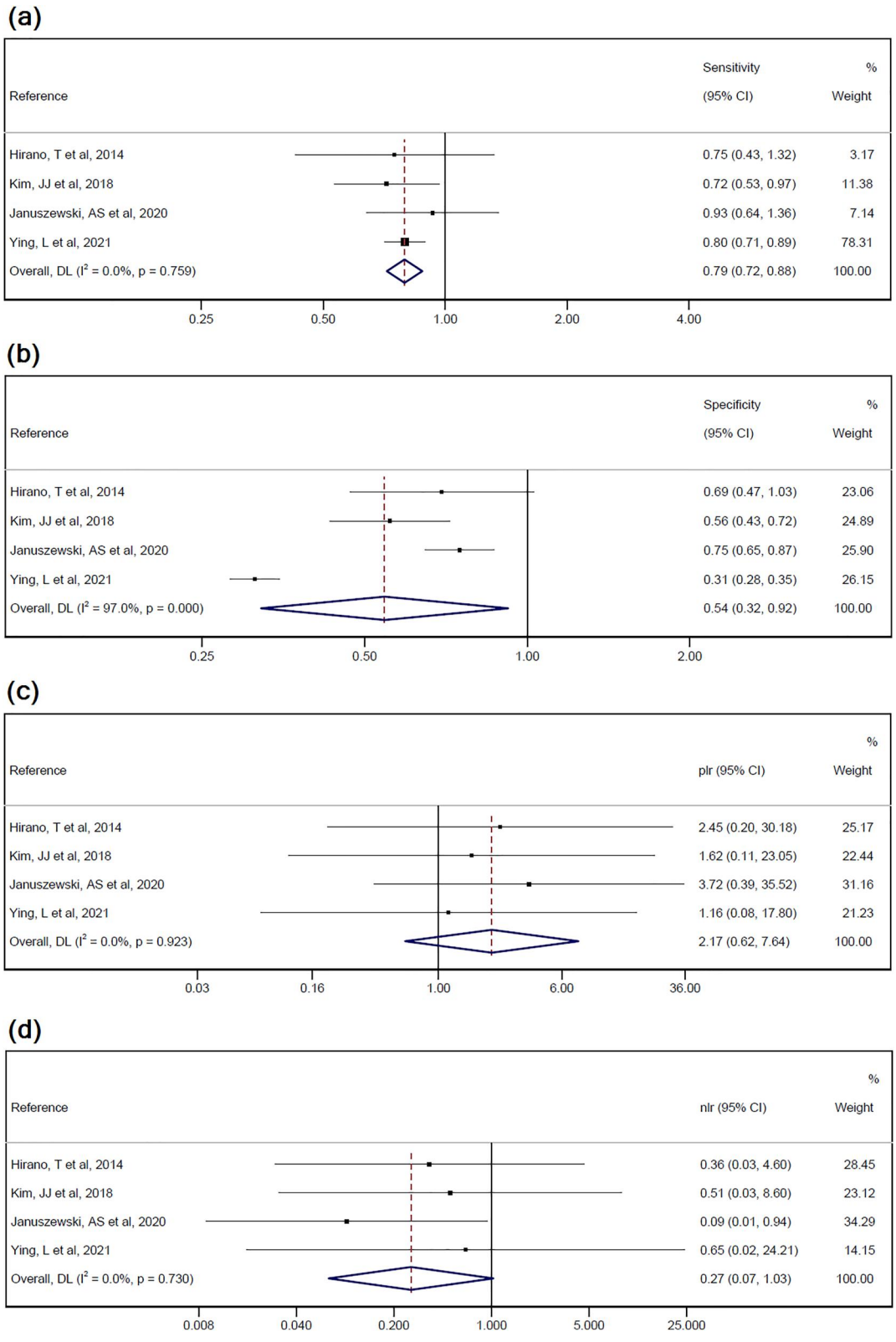

FIGURE 3 Diagrams with parameters of total sensitivity (A), total specificity (B), positive likelihood ratio (PLR) (C) and negative likelihood ratio (NLR) (D), by studies for the diagnosis of diabetic retinopathy (DR) using the skin autofluorescence (SAF) test.

practice, supporting the pre-existing information on the SAF test for the detection of diabetic complications in settings such as primary care centres.

The reviewed studies showed that SAF can predict DR severity by distinguishing between nonproliferative and proliferative retinopathy. Since SAF reflects longer-term glycaemic control,[47] it may

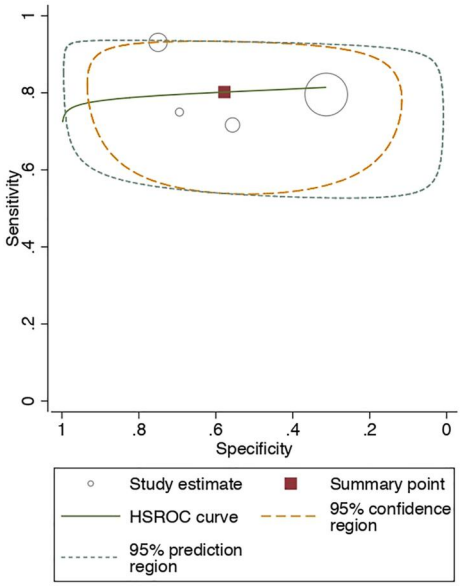

FIGURE 4 Hierarchical summary receiver operating characteristic curves (HSROC) summarising the ability of skin autofluorescence (SAF) to identify diabetic retinopathy (DR).

serve as a surrogate marker for the development of DR,[42] since the development of microvascular complications begins as soon as diabetes is detected and even during prediabetes.[48,49] This characteristic of SAF is an advantage over HbA1c, which has been previously proposed as an alternative to the use of fundus diagnostic test as the gold standard in the diagnosis of DR.[22,42] In addition, SAF is a rapid, simple, noninvasive test and it is assumed that could lead to reduce costs in health systems; therefore, a future study on the cost-utility of this test would be necessary. However, there are more sophisticated models for assessing DR severity, such as the use of deep learning-based lesion detection and staging, which have shown better diagnostic values than SAF and other systems without this automated model.[50]

The patient skin colour could influence SAF results since the current performance of the device is insufficient in dark-skinned patients.[51,52] However, most of the studies in the meta-analysis are performed in a Caucasian population, so it is assumed that the patients are light skinned even though some studies do not refer to this fact. Furthermore, in one of the studies, SAF was measured in the first dorsal interosseous muscle of the hand, creating an alternative measurement point with good results in subjects with dark skin.[44] Noteworthy, diet and some behaviours during cooking can influence AGEs. In this regard, a diet rich in simple sugars,[53] especially free fructose[54], could be a source of endogenous and exogenous AGEs.[55] In addition, the process of prolonged cooking of food at high temperatures (mainly foods rich in fat and proteins) influences the intake of exogenous AGEs.[56] Finally, non-fluorescent skin AGEs, such as carboxymethyl-lysine (CML), cannot be measured by SAF.[46]

It should be noted that SAF may be difficult to interpret in patients suffering from certain pathologies, including patients with renal failure among whom elevated AGEs measured by SAF may not correlate with DR.[28] In addition, the age and sex of subjects influence the measurement of AGEs. However, with reference to age, most of the studies included in this meta-analysis were performed in an adult population around 60 years of age.[45] Furthermore, the device that showed better PLR and NLR data is the AGE Reader, that incorporates an age-related correction factor.[24] For this device, an algorithm has been designed to correct the values by some factors, making the measurement of AGEs with SAF more applicable in the general population[57] and reference values based on age, sex and smoking in healthy persons have been established.[58]

Since the measurement of AGEs is a non-invasive method and can be performed in a matter of minutes in the outpatient clinic, it could be used as an effective screening method for DR or asymptomatic diabetes.[42] According to our study, the abnormal value of AGE measured through SAF from which DR should be suspected, and consequently the patient should be referred to the ophthalmologist for a definitive diagnosis, would be from 1.82 AU. However, it is necessary to consider the age of the patient as SAF is age-dependent, which is why our results show a range between 1.82 and 4.83 AU.[58] Although, the measurement of AGEs by SAF has shown to be a significant predictor of diabetes complications,[25] there are still no clear reference values established for the diagnosis of DR by SAF. Further research is needed considering all the factors that could influence the test and establish reference cut-offs.

Among the limitations of our study, we found a small sample size due to the lack of studies, in addition to variability between studies and cut-off points. In addition, some studies categorised DR by severity and missed information of patients with severe DR. The considerable heterogeneity in the analyses may be due to the measurement of AGEs using different devices, including a portable fluorescence hyperspectral imaging system based on a MEMS scanner,[59] a recently developed noninvasive optical transmission geometry system,[44] or the AGE Reader.[42,45] This situation may explain the PLR and NLR data, as studies that did not measure SAF with the AGE Reader showed worse accuracy data. The heterogeneity could also be influenced by the inclusion of one of the studies including children and young people since this age group does not have a high prevalence of DR as a disease resulting from the complications of diabetes. There is a paucity of information on test analysis and one of the studies does not show SAF test specificity data for DR, so we decided to use the data for microvascular complications in general.[44] There are unreported data in the studies, so it is not possible to assess whether some factors were considered.

5 | CONCLUSIONS

The SAF test as a diagnostic test for DR shows sufficient accuracy for its use in clinical settings. Due to the drawbacks of the fundus test (gold standard), SAF could be an appropriate method for the screening of DR as it is a quick, accessible test for the patient and is inexpensive for the health systems; however, this test cannot replace the gold standard diagnostic test and new technologies, such as AI,

due to its limitations. However, appropriate use of this test requires a patient evaluation to try to correct for the variability of this test, and more research is needed in this area to increase the sample size and establish appropriate reference values for SAF.

AUTHOR CONTRIBUTIONS

Conceptualisation: Irene Martínez-García and Iván Cavero-Redondo. Methodology: Irene Martínez-García, Alicia Saz-Lara and Iván Cavero-Redondo. Software: Iván Cavero-Redondo and Celia Álvarez-Bueno. Validation: Carlos Pascual-Morena and María Dolores Gómez-Guijarro. Formal analysis: Irene Martínez-García and Iván Cavero-Redondo. Investigation: Irene Martínez-García and Iván Cavero-Redondo. Resources: Irene Martínez-García, Alicia Saz-Lara and María Dolores Gómez-Guijarro. Data curation: Iván Cavero-Redondo and Irene Martínez-García. Writing – original draft preparation: Irene Martínez-García and Iván Cavero-Redondo. Writing – review and editing: Alicia Saz-Lara. Visualisation: Carlos Pascual-Morena and Celia Álvarez-Bueno. Supervision: Iván Cavero-Redondo. All the authors revised and approved the final version of the article.

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CONFLICT OF INTEREST STATEMENT

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 analysed in this study. The original contributions presented in the study are included in the article/supplementary material; further enquiries can be directed to the corresponding author.

ETHICS STATEMENT

Not applicable.

PEER REVIEW

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