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Dermoscopy and digital dermoscopy analysis of palmo-plantar equivocal pigmented skin lesions in Caucasians.

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Key Words: Acral lentiginous melanoma, Dermoscopy, Digital dermoscopy analysis

Abstract

Background/Aim: The diagnosis of palmoplantar melanoma is often delayed and misdiagnosis is common, due to frequently unusual clinical presentation. We used a digital dermoscopy analyzer with a series of palmoplantar pigmented skin lesions (PP-PSL), and we compared sensitivity, specificity and diagnostic accuracy obtained with digital dermoscopy analysis (DDA) and classical dermoscopy. Methods: Digital dermoscopy images of 107 PP-PSL were retrospectively obtained from the database of images of 3 Italian centers. The lesions (25 melanomas and 82 nevi) were all removed because of the presence of clinical and/or dermoscopic suspicious features. All digital images were analyzed using appropriate algorithms, and the diagnostic accuracy of the model was calculated. For comparison, dermoscopic images were clinically evaluated by two dermatologists and the Cohen κ concordance with DDA was calculated. Results: The stepwise logistic regression analysis selected only 5 parameters out of 49. The logistic model achieved a sensitivity of 96% and a specificity of 87.8%. The Cohen κ concordance, evaluated by the Landis and Koch scale, supplied a substantial agreement between dermoscopy and DDA. Conclusions: DDA might be a useful diagnostic instrument in the evaluation of preselected PP-PSL. However, these findings should be confirmed in a formal clinical trial.

Introduction

Acral lentiginous melanoma (ALM) is a subtype of melanoma that was identified as a distinct entity about 30 years ago [1]. As the name implies, ALM occurs on acral surfaces, specifically the palms, soles and nails [2,3,4,5]. It is the most prevalent type of melanoma in non-Caucasian populations. However, since the incidence of ALM in different races is quite similar, the prevailing belief is that ALM occurs at the same rate in all races [6,7,8,9,10]. ALM has a worse prognosis than other subtypes of melanoma, specifically superficial spreading melanoma and lentigo maligna melanoma [11,12]. This is primarily due to the fact that ALM is usually diagnosed at a later stage [13]. Many factors seem to contribute to the delay in diagnosis: advanced age of patients, difficulty in exploring plantar sites and unusual presentation, not infrequently without pigmentation [11,12,13,14].

Epiluminescence light microscopy (ELM) or dermoscopy is a noninvasive technique that enables clinicians to differentiate nevi from melanomas in an early stage [15,16,17,18]. Specific dermoscopic patterns of nevi and melanomas located on the palms and soles were initially described in Japanese studies and showed that dermoscopic examination can increase accuracy in the diagnosis of pigmented acral melanocytic skin lesions [19,20]. Despite the use of dermoscopy, diagnosis is nevertheless subjective and the accuracy of expert dermatologists in diagnosing melanoma is estimated to be 75–84% [21,22,23]. This is why several groups have developed automated analysis procedures (digital dermoscopy analysis, DDA) with high levels of diagnostic accuracy in preselected lesions. However, pigmented lesions in acral sites do not show the classical pigment network pattern and/or other classical dermoscopic features typical of other skin areas [24,25,26,27,28,29,30,31,32,33]. Almost all studies applying DDA to pigmented skin lesions (PSL) have therefore excluded palmoplantar PSL (PP-PSL).

On this basis and because of the limited data available on melanoma in acral locations, especially in Caucasian populations, the aims of this study were to evaluate a significant number of equivocal PP-PSL, to develop a diagnostic classifier using numerical variables obtained by DDA and to compare sensitivity, specificity and diagnostic accuracy obtained with DDA and classical dermoscopy (pattern analysis and 3-step algorithm for PP-PSL).

Materials and Methods

Digital dermoscopy images of PP-PSL were retrospectively obtained from the database of images of 3 Italian centers: the Istituto Dermopatico dell'Immacolata in Rome, the Department of Biomedical Sciences and Human Oncology – Dermatology Section, First Dermatology Division, University of Turin, and the Department of Clinical Medicine and Immunological Sciences – Dermatology Section, University of Siena, Italy. The images were acquired with identical digital dermoscopy devices (DB-Mips System: Biomips Engineering SRL, Siena, Italy). The study population included all PP-PSL observed and removed in the cancer prevention and early diagnosis outpatient sections of the 3 centers in the years 2008–2010. Histopathological diagnosis was based on the criteria of the National Institute of Health Consensus Conference. We had a total of 107 images of malignant and benign PSL excised from palmoplantar regions. Lesions included in our study were located in the palmoplantar areas provided with dermatoglyphics. PP-PSL were excluded when located on the volar skin of the folds near toes. Elevated, ulcerated and/or lesions with a diameter larger than 26 mm (device maximum opening) were excluded from the study too.

Patients

All the PP-PSL were removed because of the presence of clinical and/or dermoscopic suspicious features and in the absence of any clear benignity pattern (parallel furrow pattern, lattice-like pattern or fibrillar pattern). The 107 PP-PSL were from 107 Caucasian subjects [44 females (41.12%), mean age, 49.8 years; 63 males (58.88%), mean age, 44.9 years], ranging in age from 19 to 73 years. The 25 acral melanomas (22 on soles and 3 on palms) were from 25 patients (14 men and 11 women; age range, 32–81 years; mean age, 48 years). Twelve out of 25 malignant PP-PSL were clinically/dermoscopically clear-cut melanomas. The dermoscopic images of the 25 acral melanomas constituted 3% of our digital database of 966 dermoscopic images of cutaneous melanomas (all sites) recorded from January 2008 to December 2010 at the Siena, Turin and Roman centers. The 82 acral nevi (56 on soles and 16 on palms), were from 82 patients (49 men and 33 women; age range, 21–75 years; mean age, 43 years).

All PSL were examined by 3 experienced dermopathologists (C.M., R.B. and M.F.) and identified as nevi (82) and melanomas (25). Histopathological examination of melanomas showed a Breslow thickness of 0.75 mm or less in 9/25 lesions (4 out of 9 were in situ melanomas), between 0.76 and 1.5 mm in 11/25 lesions, and greater than 1.51 mm in the remaining 5 lesions.

Digital Dermoscopy Analysis

The lesions were imaged (magnification ×16), recorded as a digital signal and analyzed by 3 DB-Mips System devices. This computerized system provides a visual database and objective evaluations of pigmented skin lesions. The lesions were removed surgically (by P.R., M.B., P.Q. and R.B.), and a histological examination was performed. All digital images were analyzed using appropriate algorithms as previously reported.

Equipment

The DB-Mips System consists of a firewire/USB digital camera with 1,024 × 768 or 1,280 × 1,024 pixels. The camera was connected to a hand-held optical system enabling a horizontal field of view of 16.5 mm. The camera was calibrated weekly using special paper for white balance. Illumination was provided by a 150-watt light source at 3,200K. The components of the video signal were connected to a frame grabber interfaced with a Pentium III 500-MHz personal computer having a magneto-optical drive for image storage. The system ran under Microsoft Windows, and all the software was written in language C/C++.

Digitization and Parameterization

The choice of the most useful features to extract from digital images depends on the results of epiluminescence pattern analysis. The variables we chose were dermoscopic parameters currently used in the diagnosis of PSL. Although the system saves microscope magnifications along with texture analysis, offering an objective evaluation, the different magnifications could confuse clinicians wanting to make subjective comparisons of lesions. In this paper we only discuss images with a magnification of ×16. The system used a procedure for digital image processing based on a Laplacian filter for segmentation and a zero-crossing algorithm for border automatic outline. It then evaluated 48 parameters for discriminating power. A reproducibility study included multiple captures of one lesion with the same and different devices and with different operators. As second step it was tested on digitized images of 30 PP-PSL (5 malignant melanomas and 25 nevi) randomly chosen and belonging to 30 subjects acquired with the 3 instruments. Absolute differences between single measurements and means of a given lesion or parameter never

exceeded 5% of the mean value. The parameters, as previously described, belonged to 4 categories: geometries, colors, textures and islands of color (i.e. color clusters inside lesions) [27]. Briefly, the geometric variables were: area, perimeter, maximum and minimum diameters, radius, variance of contour symmetry, circularity, fractality of borders and ellipsoidality. Color variables were: mean values of blue, green and red inside the lesion, quartiles and deciles of red, green and blue inside the lesion, red, green and blue of healthy skin around the lesion, mean skin-lesion gradient, variance of border gradient, border homogeneity and border interruptions. Texture variables were: mean contrast and entropy of lesion, contrast and entropy fractality. Islands of color variables were: peripheral dark regions, dark area, imbalance of dark region, total imbalance, green area, light red area, dominant green region imbalance, blue-gray area, blue-gray regions, transition area, transition region imbalance, background area, background region imbalance, red, green and blue multicomponent, number of red, green and blue percentiles inside lesion.

ELM Evaluation (Pattern Analysis and Saida Algorithm)

For comparison, ELM images achieved with the DB-Mips System were studied by two dermatologists with 20 years' experience in dermoscopy. The first dermatologist (G.A.) suggested the diagnosis (melanoma or not melanoma) on the basis of classical pattern analysis [23]. The second dermatologist (T.S.) assessed the lesions using the diagnostic algorithm most widely used for this type of PP-PSL [34]. The algorithm offers 3 options: removal, follow-up or no follow-up. For the present study, the last two options were pooled under the term 'no melanoma'.

Statistical Analysis

All cases were diagnosed histopathologically, and these results were used as the training data for the classifier. Descriptive statistics including mean and standard deviation were obtained for each variable for the two groups (palmoplantar melanoma and palmoplantar nevi). Univariate differences between groups were tested by F statistics. The corresponding probability of error p was also calculated.

Stepwise Logistic Discriminant Analysis

A logistic classifier was used as third diagnostic strategy. Logistic discrimination is generally preferable to linear discrimination in small samples, especially when distributions are suspected to be nonnormal [35]. Stepwise logistic discriminant analysis was then carried out to identify a statistically significant minimum subset of variables with the highest possible discriminant power from all the variables of the digital images processed by our system (independent variables) [36]. The binary dependent variable of the logistic model was coded to 0 and 1 to represent benign and malignant palmoplantar lesions, respectively, and the posterior probability of melanoma was expressed as:

$$P = \frac{e^V}{1 + e^V}$$

where V is a linear function of 1 or more independent DDA variables selected in a stepwise manner. At each step, 1 independent variable was added to or removed from the model according to the statistical criterion of maximum likelihood ratio. The leave-one-out cross-validation technique was used to evaluate the predictive performance of logistic classification rules, step by step [37]. This technique is particularly useful when little data is available, because it uses all the n available data (studied lesions) to build the classifier and to test its predictive performance on new data. It computes the posterior probabilities of each case, 1

at a time, without using that case in the identification of a current model constructed on the other cases. In other words, n models were trained on n – 1 cases, leaving out 1 different case at a time. All the n cases left out, 1 at a time in each training session, were used for testing the model capacity to correctly recognize new lesions. We compared the model-predicted probability with a decision probability threshold chosen to produce a classification matrix giving a sensitivity value as close as possible to those provided by the other two diagnostic methods. The diagnostic agreement between pairs of diagnostic methods was studied using the Cohen coefficient κ which was interpreted using the Landis and Koch scale [38]. Computer analysis was performed using SPSS statistical software and the MATLAB package [39,40].

Results

Digital Dermoscopy Analysis

The DDA-Mips system produced high-quality images in real time, making it possible to examine all the features revealed by ELM. Image resolution was 45 pixels/mm at a magnification of ×16. Objective evaluations were performed automatically in real time, and no modification by the operator was necessary. Graphic windows showed the objective results (which were readily understood). The operators were able to use the program without any special training.

Logistic Classifier

Table 1 shows the results of the univariate F test for group comparison. The DDA parameters are listed in descending order of separation power, that is in order of decreasing values of F. Seventeen parameters had a statistical significance of at least 95% ($p < 0.05$).

Table 1. Univariate F test of differences of DDA parameters between palmoplantar melanomas and nevi

DDA parameters	F statistics	p value
Area	51.0	0.000
Maximum diameter	50.7	0.000
Minimum diameter	48.4	0.000
Blue multicomponent	39.2	0.000
Green multicomponent	30.3	0.000
Red multicomponent	29.2	0.000
Entropy	26.0	0.000
Perimeter	17.8	0.000
Imbalance of dark region	17.7	0.000
Contrast	15.0	0.000
Total imbalance	11.1	0.001
Variance of border gradient	10.0	0.002
Green average inside the lesion	8.78	0.003
Border homogeneity	7.94	0.005
Light red area	5.00	0.025
Border interruptions	4.54	0.033
Red average inside the lesion	3.70	0.044

Differences with a probability of error p less than 0.05 were considered not statistically significant.

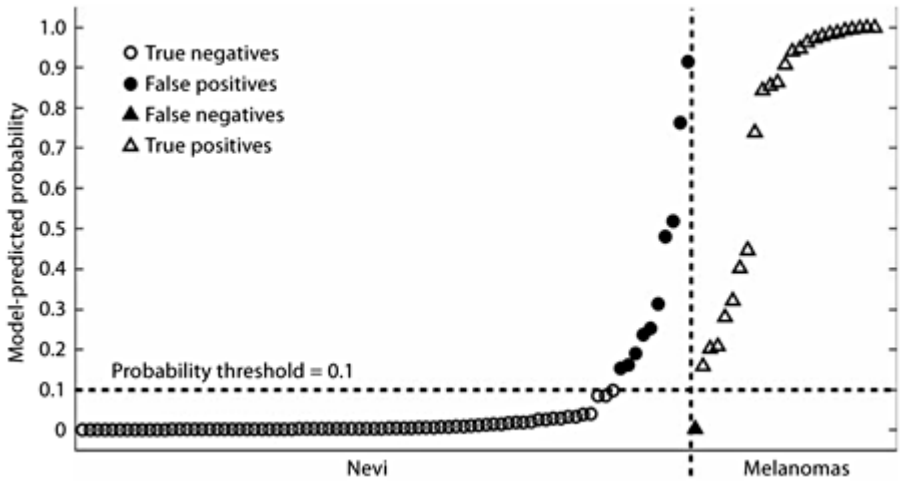
The stepwise logistic regression analysis selected only 5 parameters. In order of inclusion they were: blue multicomponent, blue of healthy skin around the lesion, green area, dominant green region imbalance and mean skin-lesion gradient. The logistic model gave a sensitivity (96%) equal to the other two diagnostic methods by setting a probability threshold pt = 0.1. This means that cases having a model posterior probabilities p > pt were classified as melanomas. Figure 1 shows the whole distribution of risk probabilities predicted by the logistic model both for benign PP-PSL (circles) and for melanomas (triangles). It is to underline that model identified only 1 false-negative lesion, out of 25 melanomas, whereas it recognized 10 benign lesions, out of 82, as melanomas (false positives), that is a specificity equal to 87.8% (table 2). The false-negative lesion was 0.6 mm in diameter and showed an irregular border and variegated color, ranging from light brown to black. Histopathology demonstrated an increase in basal melanocytes and hyperpigmentation with focally uniform cytological atypia of melanocytes, which was consistent with in situ melanoma. Dermoscopy revealed a parallel ridge pattern, abrupt ending of pigmentation and irregular diffuse pigmentation with focal depigmentation.

Table 2. Sensitivity (SE), specificity (SP) and accuracy (ACC) percentages and related 95% confidence intervals (in parentheses) obtained with pattern analysis, diagnostic algorithm and logistic model classifier applied to DDA data

	SE with CCM/TM	SP with CCN/TN	ACC with CCL/TL
Pattern analysis	96.0 (81.3–99.8) [24/25]	92.7 (88.2–93.8) [76/82]	93.5 (86.6–95.2) [100/107]
Saida algorithm	96.0 (81.1–99.8) [24/25]	91.5 (86.9–92.6) [75/82]	92.5 (85.5–94.3) [99/107]
Logistic model with DDA	96.0 (80.6–99.8) [24/25]	87.8 (83.1–89.0) [72/82]	89.7 (82.5–91.5) [96/107]

In square brackets the correctly classified melanomas (CCM), nevi (CCN) and lesions (CCL) with respect to total melanomas (TM), nevi (TN) and lesions (TL), respectively.

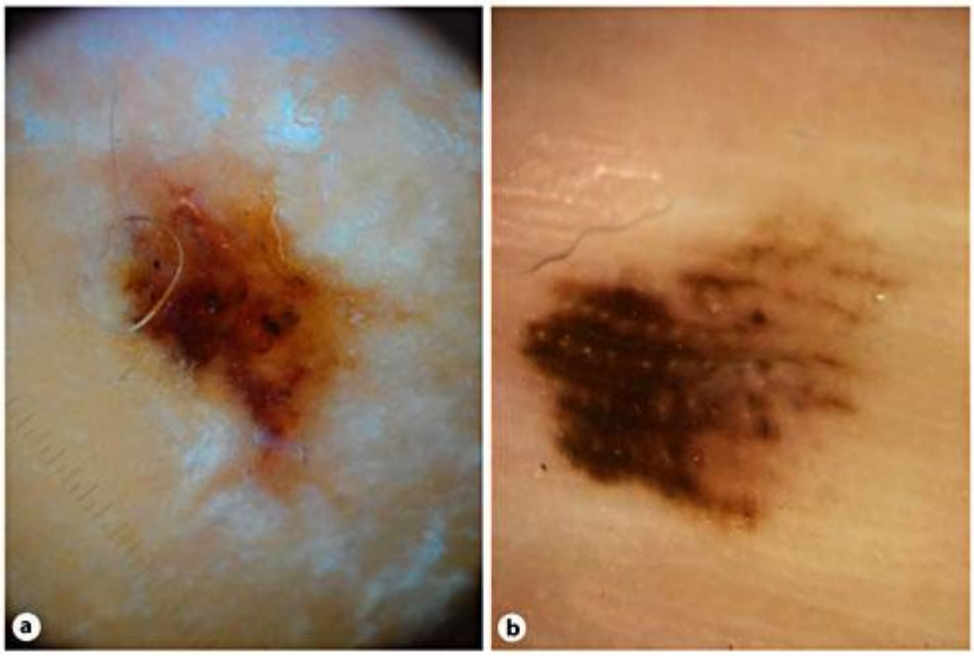
Fig. 1. Distribution functions of risk probabilities predicted from the logistic model for the classification of palmoplantar lesions by DDA: nevi (circles) and melanomas (triangles).



Traditional ELM Methods

Table 2 shows the classification of traditional ELM findings. The percentage of cases classified correctly by pattern analysis (accuracy) was 93.5%. Specifically, 24/25 palmoplantar melanomas (sensitivity 96%) and 76/82 palmoplantar nevi (specificity 92.7%) were correctly classified. The false-negative lesion was a melanoma in the middle of a large area of hyperkeratosis in a patient with Siemens keratosis palmoplantaris striata et areata (fig. 2). The percentage of cases correctly classified by the Saida algorithm (accuracy) was 92.5%, namely 24/25 palmoplantar melanomas (sensitivity = 96%) and 75/82 palmoplantar nevi (specificity = 91.4%). In this case, the false-negative lesion was a melanoma in situ about which the pathologists were unable to agree: two diagnosed melanoma in situ and the third dysplastic nevus (fig. 2). Moreover the suggestion by the clinician was follow-up.

Fig. 2. The 2 false-negative cases assessed by pattern analysis (a) and Saida algorithm (b). a Melanoma in a patient with Siemens keratosis palmoplantaris striata et areata: the lesion was about 10 × 10 mm in diameter, brown yellow in color and surmounted by a squamous crust, at the site of a preexisting islet-shaped hyperkeratotic skin area on the right heel. Dermoscopy revealed an irregular and asymmetric rhombus-shaped structure with a yellow to brown pigmentation and small black areas arranged irregularly within the lesion. Histological examination of the nodule showed small nevocytic epithelioid cells typical of ALM in vertical growth phase (0.9 mm thick). b Saida algorithm: the in situ melanoma was clinically 9 mm in diameter, irregularly shaped with asymmetric hyperpigmentation. Dermoscopy revealed asymmetrically arranged colors (from brown to black). In a small portion of the lesion, pigmentation was present both on the furrows and on the ridges. Histopathology revealed a proliferation of solitary, slightly atypical melanocytes, mainly detected in the crista profunda intermedia.



Comparison of DDA, Pattern Analysis and Saida Algorithm

The Cohen κ concordance, reported in table 3, evaluated by the Landis and Koch scale, supplied a substantial agreement between each pair of the 3 diagnostic approaches [38].

Table 3. Analysis of concordance between different diagnostic approaches: estimated k of Cohen and its standard error SE

	Pattern analysis	Saida algorithm	Logistic model with DDA
Pattern analysis		κ = 0.748 (SE = 0.072)	κ = 0.688 (SE = 0.077)
Saida algorithm	κ = 0.748 (SE = 0.072)		κ = 0.713 (SE = 0.074)
Logistic model with DDA	κ = 0.688 (SE = 0.077)	κ = 0.713 (SE = 0.074)	

Discussion

Univariate analysis enabled us to identify certain numerical variables, which were significant for differentiating palmoplantar melanomas from palmoplantar nevi. We observed that the melanomas were geometrically different from nevi. In particular, the area, perimeter and diameters (maximum and minimum) were larger. This correlated well with reports in the literature [41,42]. Indeed, in the Saida algorithm, a diameter of PP-PSL greater or less than 7 mm is considered an important cut-off in deciding whether to follow up or remove equivocal lesions [34]. We also found that 5 variables related to 'internal confusion' (blue, red and green multicomponent, contrast and entropy) were also significantly different between the two groups of lesions. In this regard, it is worth recalling that many authors have reported a combination of many elements and disorganization in their disposition within a PSL as a dermoscopic feature peculiar to melanoma [20,21,22,23,43,44]. The shape of the edges is undoubtedly another factor that has proved crucial in the differentiation of palmoplantar nevi and palmoplantar melanomas [19,20,41,45]. In fact, the variables related to boundary evenness (variance of border gradient, border homogeneity and border interruptions) showed statistically significant differences between palmoplantar melanoma and nevi. This finding is also sustained by many dermoscopy studies that have demonstrated the significance of border morphology for the differential diagnosis of benign and malignant PSL [22,23,46,47]. It is, however, to underline that in acral sites the borders of in situ and thin melanomas may be poorly pigmented with no demarcated limits. The imbalance of pigment in the lesion was also significantly higher in melanomas than in nevi (imbalance of dark regions and total imbalance). Finally, the amount of red in a lesion was statistically different in benign and malignant lesions (red average inside the lesion and light red area). This is in line with reports in the literature. Amelanotic ALM may mimic vascular tumors and other nonmelanocytic lesions [48,49,50]. The stepwise logistic regression analysis selected only 5 parameters. When these variables were used in multivariate analysis to evaluate the percentage of correct classifications between palmoplantar melanomas and palmoplantar nevi, the results were very interesting, showing 96% sensitivity and 87% specificity.

Pattern analysis and the Saida algorithm gave better overall results than the DDA logistic classifier in terms of specificity. However, both clinical methods produced a false negative. Combining the two clinical methods to increase the sensitivity could avoid this (sensitivity = 100%). However, this would lead to a

significant increase in false positives (12 out of 82 nevi, specificity = 85.4%). Moreover, we must always remember that these methods are subjective and dependent on the experience of the clinician. On the other hand, the advantage of DDA is to be a more objective methodology. On this basis it would be interesting to combine DDA with the Saida algorithm, since the latter is based on a semiquantitative analysis (quasi-objective) and therefore less linked to the experience of the clinician. This would provide the benefits to avoid false negatives, to lower false positives and make the assessment rather independent from the examiner. However, we must emphasize that the clinician remains fundamental for the preselection of the PP-PSL to be examined.

False negatives could be avoided (melanoma regarded as nevus) with an increase in false positives (nevi regarded as melanomas). Even combining pattern analysis with DDA, false negatives were zeroed. This indicates an important role for DDA as a formidable auxiliary for correct clinical decision-making combined with more traditional methods. Of course, using only the logistic classifier it is possible to avoid false negatives, simply by lowering the probability threshold, although at the cost of a marked increase in false positives. However, in our analysis, appropriate lowering of the threshold (data not shown) to obtain 100% sensitivity, led to 21 false positives or a reduction in specificity to 74.4%. In practice, when the 25 melanomas were included, the classifier considered more than 40% of the lesions studied to be at risk. According to the results it is clear that DDA cannot be used alone without preselection of the lesions and that the combination with clinical and dermoscopic evaluation is needed. The DDA analysis might be useful to allow the detection of some false-negative ALM but in which lesions and the real utility of the system should be demonstrated in further clinical studies. Moreover, the use of this technique together with other noninvasive diagnostic methods (scanning electron microscopy, confocal microscopy etc.) could further improve the diagnostic accuracy of PP-PSL [50,51,52].

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