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An Updated Algorithm Integrated With Patient Data for the Differentiation of Atypical Nevi From Early Melanomas: the idScore 2021

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ABSTRACT

Introduction: It is well known that multiple patient-related risk factors contribute to the development of cutaneous melanoma, including demographic, phenotypic and anamnestic factors.

Objectives: We aimed to investigate which MM risk factors were relevant to be incorporated in a risk scoring-classifier based clinico-dermoscopic algorithm.

Methods: This retrospective study was performed on a monocentric dataset of 374 atypical melanocytic skin lesions sharing equivocal dermoscopic features, excised in the suspicion of malignancy. Dermoscopic standardized images of 258 atypical nevi (aN) and 116 early melanomas (eMM) were collected along with objective lesional data (i.e., maximum diameter, specific body site and body area) and 7 dermoscopic data. All cases were combined with a series of 10 MM risk factors, including demographic (2), phenotypic (5) and anamnestic (3) ones.

Results: The proposed iDScore 2021 algorithm is composed by 9 variables (age, skin phototype I/II, personal/familiar history of MM, maximum diameter, location on the lower extremities (thighs/legs/ankles/back of the feet) and 4 dermoscopic features (irregular dots and globules, irregular streaks, blue gray peppering, blue white veil). The algorithm assigned to each lesion a score from 0 to 18, reached an area under the ROC curve of 92% and, with a score threshold ≥ 6, a sensitivity (SE) of 98.2% and a specificity (SP) of 50.4%, surpassing the experts in SE (+13%) and SP (+9%).

Conclusions: An integrated checklist combining multiple anamnestic data with selected relevant dermoscopic features can be useful in the differential diagnosis and management of eMM and aN exhibiting with equivocal features.

Introduction

An adequate dermoscopic differentiation between atypical melanocytic skin lesions (aMSLs), ie, atypical nevi (aN) and early melanomas (eMM) can represent a challenge in daily practice, especially for less experienced dermatoscopists. Dermoscopy alone cannot be accurate enough to adequately recognize aN exhibiting equivocal dermosocpic feature or, of converse, can fail to identify those eMM that do not exhibit clear-cut dermoscopic features suggestive for malignancy [1-6]. In addition, we also debate whether a certain degree of overdiagnosis of in situ MM might have took place in the last decade worldwide [7-10]. In this context, a reasonable way out seems to be to follow a global approach to the patient integrating dermoscopic imaging with multiple risk assessment tools and personal plus lesional data [7,11-18].

Objectives

We previously demonstrated the efficacy of integrating 3 relevant clinical parameters (ie, age, maximum diameter and body location) into a dermoscopic algorithm (the iDScore 2018*)* [1], which reached high diagnostic accuracy on both a monocentric dataset of 435 aMSLs and on a multicentric dataset of 980 aMSLs. We then aimed to extend the list of clinical parameters to the most relevant potential melanoma risk factors and to investigate which were the most significant independent association with a MM histologic diagnosis. Secondly, we aimed to select through stepwise logistic regression analysis a series of interdependently significant data, useful to develop a new iDScore 2021 checklist, able to provide a differential score to distinguish eMM from aN with equivocal features.

Methods

This retrospective study was realized in accordance with the Declaration of Helsinki and approved by the local ethical committee (ID16801); all data were de-identified before use.

Data Collection

A total of 410 aMSLs were consecutively excised from January 2018 to May 2021 in Siena University Hospital in the suspicion of malignancy. All aMSLs localized on the face, palms, and soles were excluded a priori due to their specific dermoscopic pattern. Histological diagnoses were retrospectively collected, including dermoscopic standardized polarized images (OM 20X) have been prospectively collected along with lesional data (maximum diameter and body location based on a sun-exposure classification), as previously described [14]. In addition, patients personal data concerning 8 MM risk factors were collected, ie: personal/familiar history of MM; sunburns before 14 years, phototype, pheomelanin, blond hairs, blue/green eyes, >11 nevi on the right arm (Table 1). The presence of pheomelanin phenotype was assessed when the patient had red/carroty/straw red/brown-reddish hair, pale skin, freckles and high tendency to sunburn and/or inability to tan.

Dermoscopic-reader Study

Dermoscopic evaluations were independently performed by 4 experts in dermoscopy, blinded for histopathological diagnosis (EC, MB, AL, PR). They were asked to recognize a dermoscopic feature among a series of 7, previously selected for the iDScore 2018 checklist (Tables 1 and 4), including: Atypical Network (AN), Irregular Streaks (IS), Blue White Veil (BWV), Blue Gray Peppering (BGP), White Scar-like Areas (WSA), Shiny White Streaks (SWS) and Irregular Dots Globules (IDG) (Figures 1 and 2). Then, they were asked to express an intuitive diagnosis of eMM/aN. The presence of one or more dermoscopic features inside each lesion and the final diagnosis was assessed based on the agreement of 3 out of 4.

Integrated dataset

After selection (MG, LT, AC) for image quality, availability of patient data and agreement of 2 out of 3 pathologists on histopathological diagnosis, the final database consisted of 374 standardized dermoscopic pictures, 258 and 116 eMM. Each lesion was paired with 19 objective parameters, including: 8 MM risk factors, 2 patient demographic data, 2 aMSL objective data and 7 dermoscopic features (Table 1).

Statistical analysis

Descriptive analysis was carried out using absolute frequencies and percentages for qualitative variables, mean and standard deviation for age and diameter, median and minimum-maximum range for the iDScore. Age and diameter were then categorized for the score model purpose, merging classes with same risk. The association of gender, risk

factor and clinical features with histology were evaluated by chi-squared test. The difference of age and diameter between aN and eMM by t test, instead, the iDScore by Mann-Whitney test. Kolmogorov-Smirnov test was used to evaluate the normality distribution of quantitative variables. Bivariate analysis was performed by logistic regression, the Odds Ratios (OR) and their 95% confidence interval (CI) were estimated, too. In particular, eight bivariate logistic regression were carried out, each one with iDScore plus one risk factor. After that, an integer score model was developed based on logistic regression. Leave-one-out procedure was used for testing the model. ROC curves and their areas (AUROC) were also estimated to compare the model performances. A $P < 0.05$ was considered statistically significant. The analyses were carried out with R version 4.10.

Results

Case study

In Table 1 is reported the distribution of all patienst demographic data (2), the melanoma risk factors (8) and the aMSLs morphologic data (2). Concerning the eMM, they affected males in 53% versus females in 46% of cases, mean age was 58.9 years, the predominant body area was the upper trunk (49% of cases) and the average diameter was 9.5mm. Histologic stages included: Tis (50), Ia (37), Ib (20) and IIa (9 cases) [19].

Table 1. Distribution of patient demographic data, melanoma risk factors and lesional data in the case study iDScore database 2018-2020 of 374 atypical melanocytic skin lesions. The results of univariate analysis for significant association with MM histologic diagnosis are also reported with corresponding P-values.

	Atypical nevi (aN) *N=258*	Early melanomas (eMM) *N=116*	P
Demographic data			
1. Age (years)	48.0±14.2	58.9±15.0	< 0.001
2. Gender			
Female	106 (41.1%)	54 (46.6%)	0.366
Male	152 (58.9%)	62 (53.4%)	
Anamnestic risk factors			
1. History of melanoma (personal / 1st relative)	72 (28.2%)	50 (43.1%)	0.007
2. Sunburns before 14 (yes/no)	173 (68.7%)	82 (71.9%)	0.542
3. Smoke (>5 cigarettes/day) (yes/no)	66 (26.3%)	19 (22.1%)	0.475
Phenotypic risk factors			
4. Skin phototype			
I+II	66 (25.8%)	60 (51.7%)	0.005
III+IV	190 (74.2%)	56 48.3%)	
5. Pheomelanin phenotype (yes/no)	23 (9.0%)	21 (18%)	0.005
6. Blonde hair (yes/no)	42 (16.4%)	28 (24.3%)	0.05
7. Green/light-blue/blue eyes (yes/no)	86 (33.7%)	43 (37.4%)	0.556
8. >11 nevi/right arm (yes/no)	128 (50.4%)	66 (57.4%)	0.005
aMSLs data			
1. Maximum diameter (mm)	6.4±2.5	9.5±3.2	<0.001
2. Body area / anatomical site			
Upper Extremities - chronically photoexposed [head/neck/arms/hands]	18 (7.0%)	14 (12.1%)	0.113
Upper Trunk - seldom photoexposed [shoulders/back/chest/breast]	146 (56.6%)	57 (49.1%)	0.217
Lower Extremities - frequently photoexposed [thighs/legs/ankles/back of the feet]	26 (10.1%)	18 (15.5%)	0.164
Lower Trunk - rarely photoexposed [side/bottom/abdomen]	68 (26.4%)	27 (23.3%)	0.608

Table1 continues

Table 1. Distribution of patient demographic data, melanoma risk factors and lesional data in the case study iDScore database 2018-2020 of 374 atypical melanocytic skin lesions. The results of univariate analysis for significant association with MM histologic diagnosis are also reported with corresponding P-values. (*Continued*)

	Atypical nevi (aN) *N=258*	Early melanomas (eMM) *N=116*	P
aMSLs Dermoscopic features			
1. Atypical Network (yes/no)	230 (89.1%)	104 (89.7%)	1.000
2. Irregular Streaks (yes/no)	29 (11.2%)	49 (39.7%)	<0.001
3. Blue White Veil (yes/no)	18 (7.0%)	29 (25.0%)	<0.001
4. Blue Gray Peppering (yes/no)	21 (8.1%)	28 (24.1%)	<0.001
5. White Scar-like Areas (yes/no)	6 (2.3%)	18 (15.5%)	<0.001
6. Shiny White Streaks (yes/no)	1 (0.4%)	4 (3.4%)	0.034
7. Irregular Dots Globules (yes/no)	71 (27.5%)	60 (51.7%)	<0.001
iDScore 2018	6 [2-11]	9 [4-14]	<0.001

Table 2. Bivariate analysis of the 8 variables/melanoma risk factors combined with the iDscore 2018 checklist and association with MM histologic diagnosis.

8 variables/melanoma risk factors	iDScore 2018 checklist + new variable	
	OR (95% CI)	P
>11 nevi/right arm	1.1 (0.6-2.3)	0.801
History of MM (personal/1st relative)	2.8 (1.4-5.4)	< 0.001
Sunburns	1.0 (0.5-2.0)	0.928
Skin phototype (I+II vs III+IV)	2.9 (1.5-5.6)	< 0.001
Pheomelanin phenotype	1.5 (0.7-3.6)	0.333
Green/light-blue/blue eyes	1.0 (0.6-2.0)	0.913
Blonde hair	1.3 (0.6-2.7)	0.546
Smoke (>5 cigarettes/day)	1.1 (0.5-2.4)	0.803

CI = Confidence Interval; OR Odds ratio.

Dermoscopic-reader study

The presence of 7 dermosocpic variables in the 2 groups of aN and eMM according to experts consensus (ie, number of positive observation, %) is also reported in Table 1. The 4 experts in dermoscopy obtained, on average, a sensitivity (SE) and specificity (SP) of 85.2% and 41.5%, respectively, on the present dataset of difficult aMSLs.

Univariate analysis

A total of 12 variables resulted more frequently associated with a eMM diagnosis rather than with aN diagnosis, and to significantly discriminate ($P < 0.05$) the 2entities, namely: "age", "history of MM (personal / 1st relative)", "skin phototype I/II", "pheomelanin phenotype", ">11 nevi/right arm", "maximum diameter" and the presence of IS, BWV, BGP, WSA, SWS and IDG (Table 1).

Bivariate analysis

Each one of the 8 variables assumed as possible MM risk factors was tested in combination with the iDscore 2018 checklist for the association with MM histologic diagnosis: according to the bivariate analysis results (Table 2), it appeared that only 2 variables added a significant increase in accuracy when incorporated into the previous checklist iDScore 2018, namely the "skin phototype I/II" and the "history of MM" (personal or regarding the 1st degree relative).

Logistic regression

According to the stepwise analysis of the logistic regression (Table 3), the new iDScore 2021 checklist would be composed by only 9 parameters, including the "age ranges 31-60 years" and ≥ 61 years, the "skin phototype I/II", the "history of MM", the "maximum diameter" ranges 6-10mm

and ≥11mm, the "body location on the lower Extremities (including thighs/legs/ankles/back of the feet), and presence of 4 dermoscopic variables such as IDG, IS, BWV and BGP.

Performance analysis of the integrated model

Table 4 illustrates the composition of the iDScore 2018 and the new iDScore 2021 model, the partial scores (coefficients) assigned to each variable and the total score (S range) which could be assigned to a given aMSL (from S = 0 to S = 18). In addition, the preferred score threshold (St) for both model is reported, along with the corresponding SE and SP values, while the global performance is expressed as area under the ROC curve with 95% confidence interval. In detail, the iDScore 2021 showed: with St ≥ 6, SE = 98.2%, SP = 50.4 (+0.6% SE and +2.3% SP compared with 2018 model); with St ≥ 5, SE = 100%, SP = 30%; with St ≥ 7, SE = 96.4% and SP=31.7.

In Figures 1 and 2 are reported 6 exemplificative cases, namely 3 aMSL of the back (Figure 1) and 3 aMSLs of the

Table 3. Results of the stepwise multivariate logistic regression analysis performed over all variables (2 patient anagraphic data + 8 melanomas risk factors + 2 lesion data + 7 dermoscopic data) for the association with a histologic diagnosis.

9 selected variables (iDScore 2021)	OR (95% CI)	P
Age 31-60 years	16.9 (3.0-54.4)	0.004
Age ≥ 61 years	89.5 (14.4-889.4))	< 0.001
Maximum Diameter 6-10mm	7.4 (3.1-20.2)	< 0.001
Maximum Diameter ≥11mm	36.7 (12.1-126.3)	< 0.001
Lower Extremities	3.1 (1.1-8.7)	0.027
IDG	2.6 (1.4-5.1)	0.004
IS	5.1 (2.4-11.3)	< 0.001
BWV	6.7 (2.5-19.1)	< 0.001
BGP	3.7 (1.5-9.3)	0.005
Phototype (I+II vs III+IV)	3.2 (1.7-6.2)	< 0.001
History of melanoma (personal /1st relative)	3.2 (1.6-6.5)	< 0.001

BGP = Blue Gray Peppering; BWV = Blue White Veil; CI = Confidence Interval; IDG = Irregular Dots Globules; IS = Irregular Streaks; OR Odds ratio.

Table 4. Comparison of the two models of 2 models of integrated iDScore checklist: composition and performances obtained over 324 atypical melanocytic skin lesions of the body.

iDScore 2018		iDScore 2021	
composition	coefficient	composition	coefficient
1. Atypical Network	1	1. Blue white veil	2
2.Irregular Streaks	1	2.Irregular Streaks	2
3.Blue White Veil	1	3.Irregular dots and globules	1
4.Blue Gray Peppering	1	4. Blue Gray Peppering	1
5.White Scar-like Areas	1	5. Maximum Diameter	
6.Shiny White Streaks	1	6–10 mm	2
7.Irregular Dots Globules	1	≥ 11mm	4
8.Maximum diameter	1	6. Age	
6–10 mm	3	31-60 years	3
≥11 mm	4	≥ 61 years	5
9.Age		7. Lower Extremities frequently photo-exposed [thighs / legs / ankles / back of the feet]	1
30-40 years	1		
41-60 years	2		
≥61 years	3		

Table4 continues

Table 4. Comparison of the two models of 2 models of integrated iDScore checklist: composition and performances obtained over 324 atypical melanocytic skin lesions of the body. (*Continued*)

iDScore 2018		iDScore 2021	
composition	**coefficient**	**composition**	**coefficient**
10.Body area		8. Fair phototype (I/II)	1
Upper extremities - chronically photo-exposed	2	9. History of melanoma (personal/ 1st degree relative)	1
Lower extremities - frequently photo-exposed	2		
Upper trunk - seldom photo-exposed	1		
ROC area (CI 95%)	0.904 (0.872-0.935)	ROC area (CI 95%)	0.917 (0.887-0.944)
Score Range	0-16	Score Range	0-18
Score threshold	St ≥6 (SE = 97.4%; SP = 48.1%)	Score threshold	St≥ 6 (SE = 98.2%; SP = 50.4%)

CI = confidence interval; SE = sensitivity; SP = specificity; st = core threshold

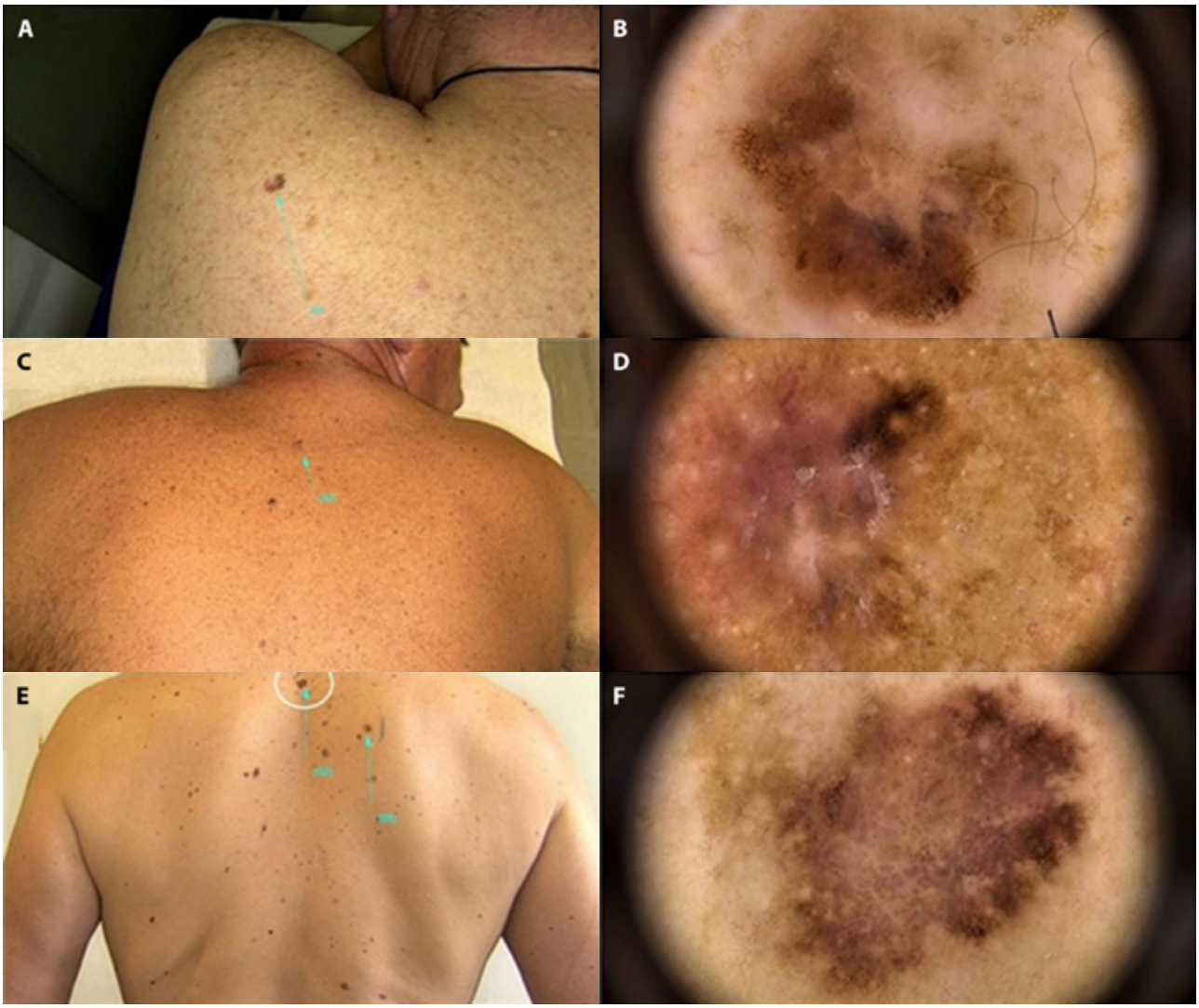

Figure 1. Examples of atypical melanocytic skin lesions (aMSLs) on the upper back from the case study. A 71 years-old male, phototype II, personal history of melanoma, with a 11 mm aMSL, iDScore 2021 = 15 (iDScore 2018 = 9): histological examination revealed an early melanoma (MM T1aN0M0, thickness 0.7mm) (aA and B). A 61 years-old male, phototype II, with 7mm aMSL: the iDScore 2021 was 9 (iDScore 2018 = 7) and the histological examination revealed a nevus with moderate atypia (C and D). A 50 years-old male, 11 mm, phototype II, > 11 nevi/right arm, 1st relative history of MM, sunburns before the age of 14, with a 10mm aMSL: the iDScore 2021 was 10 (iDScore 2018 = 8) and the histological examination revealed a nevus with severe atypia (E and F).

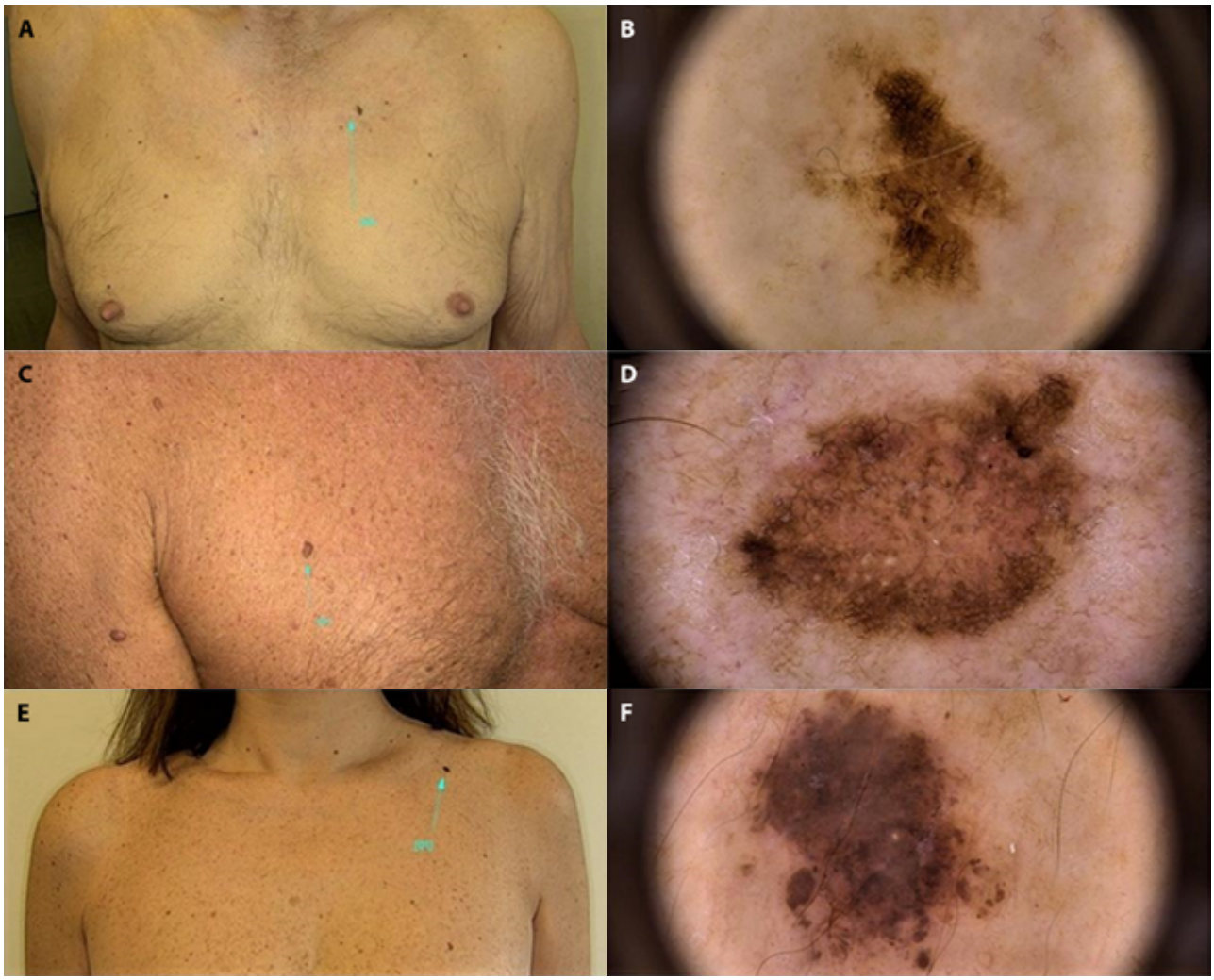

Figure 2. Examples of atypical melanocytic skin lesions (aMSLs) of the chest from the case study. A 80 years-old male, phototype III, familiar history of melanoma, with a 7 mm aMSL: iDScore 2021 was 12 (iDScore 2018 = 8) and the histological analysis revealed an in situ melanoma (A and B). A 66 years-old male, phototype II, familiar history of MM, with a 10mm aMSL: the iDScore 2021 was 10 (iDScore 2018 = 8); the histological analysis revealed a nevus with moderate atypia (C and D). A 47 years-old female, phototype III, with a 7.7 mm aMSL, the iDScore 2021 was 6 (iDScore 2018 = 5) and the histological examination revealed a compound nevus (E and F).

chest (Figure 2) with the corresponding total scores obtained iDScore 2021; for comparison, the iDScore 2018 total scores are also reported in brackets.

Finally, according to the ROC curve analysis comparison (Figure 3) the new algorithm demonstrates to surpass the previous one by +1.3%.

Conclusions

The debate about the relative impact of modifiable and non-modifiable risk factors on melanoma development is still ongoing [20-22]. However, some demographic data related to the patient and some characteristics of the lesion itself have currently acquired a considerable body of evidence and deserve to be investigated as possible additional risk score coefficients along with the dermoscopic parameters [1,2,11,13,14].

When taking into account the patient demographic data, age confirmed to be a significant independent risk factors for discriminating aN from eMM, with a flexing point of the S-shaped curve for malignancy incidence at 50 years [23-25]. The statistical analyses here conducted on a large dataset of aMSLs were restricted to two crucial cut-offs at 31 and 60years and allowed to identify three range groups with increasing risk for malignancy (Table 4). Concerning sex, we here observed that sex variable is not a variable to be considered for an algorithm, because aN and eMM are similarly distributed among males and females, in line with recent studies confirming no significancy, but only in association with the UV-exposure habits and/or hormonal changes (ie female sex) [26-28]. Among the patient anamnestic data, the positive history for MM-personal or in a 1st degree relative-is still a considered a nonmodifiable risk for the incidence of a new MM [20-23,27,28]. Here in this dataset, this variable

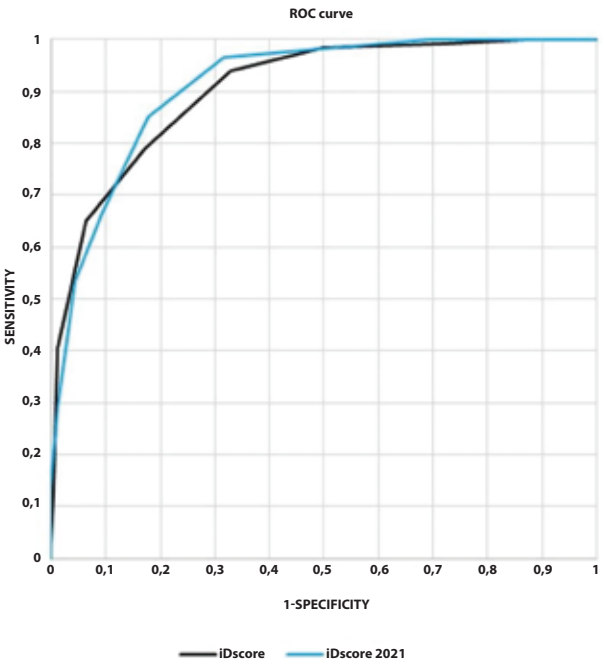

Figure 3. Receiver operating characteristic (ROC) of the 3 integrated algorithms: iDScore 2018 (black) and iDScore 2021 (blue) obtained on the iDScore database 2018-2020 of 324 atypical melanocytic skin lesions. The segments of the curves represent cases obtaining the same score.

appeared to have a significant discrimination power in the univariate (Table1) and bivariate (Table 2) analysis and was one of the predictive variable of the score model classifier (Tables 3 and 4), in line with previous studies on data from a multivariate analysis of predictors of eMM diagnosis [29-31]. The parameter "positive history of sunburns in childhood" is well known to be primary inciting event in the development of acquired melanocytic nevi in adults [30-32]. On the other hand, recent ecological and case-control studies highlighted that is the total cumulative ambient sun exposure during childhood to correlate with melanoma risk development, more than the parameter "positive history of sunburns in childhood" [33-35]. In line with these literature data, here in this study we found similar distribution of the infancy sunburn parameter when comparing the population of patient with dysplastic nevus syndrome/multiple atypical nevi (69%) and eMM (70%), which resulted not significant in discriminating among the two entities (Tables 2 and 3). Renown as a risk factor for several types of human cancer, cigarette smoke was correlated with premature skin aging, squamous cell carcinoma of the skin, psoriasis and impaired wound healing [36]. Many studies have been carried out in the last decades for testing the association with MM too, but results were not univocal or clear-cut due to residual statistical confounders or inadequate sample size [36-38]. In a recent case-control study carried out over 1,157 patients diagnosed with MM and 5,595 controls in the Netherlands, cigarette smoking was found not to increase the risk of MM development, as well as in a large cohort study on US white women [39,40]. Similarly, here in this study we find the smoke habit to involve 26% of patients from the aN group and 21% of patients from the eMM group (Table 1) and not to impact significantly on the differential diagnosis among these two entities (Tables 2 and 3).

In the last decade, the parameter "total nevi number" was investigated in adult European and American population as possible MM risk factor, both independently or in association with other parameters (MM body site distribution, patient height, etc.) [37,39-43]: the high nevus count > 50 of the whole body appeared to be independently associated with MM incidence, and high nevus count on the extremities (ie photo-exposed areas) appeared to bring more risk than high nevus count on the trunk [37,40,42,44]. Then, several investigations were carried out to find a valid esteem of the total body count taking into account the nevi count on the 4 extremities, on the upper extremities (> 20), on the lower extremities (> 10) or on the right arm (> 11) [37,40-42,44]. To facilitate the risk factors collection in clinical practice, we decided to adopt the cut-off of > 11 nevi on the right arm as predictor of the total nevi count, based on current literature knowledge. When investigating this parameter in our adult population of patients with aMSLs, similar rates of high nevus count in both the eM (53%) and the aN (50%) group (Table 1), and it was not selected by multiple regression analysis. Indeed, our aN group population hosts a considerable quote of patients with multiple Clark nevus phenotype, as occur in many second level referring ambulatories for screening and follow-up. There are however data suggesting that the MM incidence is higher in patients with multiple aN/Clark nevi in addition to a family history of melanoma among relatives with the same phenotype, but low among people with sporadic phenotype of multiple Clark nevi [45,46]. Consequently, the nevus count is not a discriminant variable for distinguishing aN form EMs, but should be evaluated along with the nevi characteristics, such as the stability/change during follow-up and additional patient data (eg the "Clark phenotype").

Finally, we took into account the impact of all physical characteristics related to melanin type, including the skin phototype of the patient, its hair color, the eye color and the presence/absence of a pheomelanin phenotype. The presence of blond hair and of blue/light-blue or green color were traditionally investigated as risk factor for skin cancer [46-48]. First studies in northern Europe population-based studies, the light eye color emerged as independently associated risk factor for MM development (~1.6-fold higher risk for MM compared with dark eyes), while the blond hair color had moderate risk [45-48]; more recently, Spanish population-based study revealed that hair and eye color did

not show any significant effects even after adjustments for confounders [44].

Here in this study based on a southern European population, the univariate analysis (Table 1) demonstrated that the discriminant independent power of the variables "fair phenotype", "blonde hair" and "green/light-blue/blue eyes" is similar. Moreover, a significant discrimination is obtained when comparing phenotypes I+II versus phenotypes III+IV, in line with literature data that assigned a 3-fold higher risk for MM as compared with phenotypes V+VI [45]. However, the multivariate logistic regression analysis selected the variable fair skin phenotype (I-II) (Table 4) instead of the two variables "blonde hair" and "light-colored eyes": these two were likely to be statistically "absorbed" by the fair phototype variable, which is nevertheless considered an including category.

Of converse, the "pheomelanin phototype" is assessed in a patient exhibiting when red/carroty/reddish hair, pale skin and freckles in combination with the high tendency to sunburn and/or inability to tan [45-50]. Recent molecular studies in vitro and in vivo on mouse models (including inactivated mutation of the MC1R gene and BRAFV600E mutation) suggest that the pheomelanin phenotype may facilitate skin carcinogenesis through either an UV-dependent (ie accumulation of DNA damage through oxidative stress) and an UV-independent pathway [49-50]. It is understood that this parameter should be regarded as a body-site and sun-exposure independent risk factor for MM, with reported with rates between 1.4 and 3 [45-48]. We indeed observed a discriminant power for this parameter in the dd between aN and EMs (P = 0.005) according to univariate analysis (Table 1).

When comparing the new iDScore 2021 checklist with its precursor iDScore 2018 (Table 4), some differences can be highlighted.

First, the training phase was based on a total of 19 parameters (3 anamnestic risk factors + 5 phenotypic risk factors + 2 anagraphic data + 2 aMSL data + 7 aMSLs dermoscopic features) instead of the 10 parameters (2 anagraphic data + 2 aMSL data + 7 aMSLs dermoscopic features) of the iDScore 2018.

Second, some modifications were applied in order to simplify the checklist final use: estimation of 3 age groups with different coefficient instead of using 4 age groups; selection of one body area with the high discriminant power, instead of using 3 body areas; reduction of dermoscopic variables from 7 to 4. Concerning this final selection of 4 inter-dependently significant dermoscopic variables, the 3 left out were: White Scar-like Areas, Shiny White Streaks and Atypical network. White Scar-like Areas and Shiny White Streaks were significant in the univariate analysis, but not in the multivariate analysis, as they did not reached significant numerosity in the whole dataset. Importantly, the atypical network was similarly observed in both the aN and the eMM groups (89.1% and 89.7% of cases, respectively) (Table 1) thus cannot be considered a discriminant factor. Thus, the differential diagnosis of aN and eMM equivocal images, concerning this monocentric dataset, relies essentially on the combination of 4 dermoscopic variables: "Blue white veil", "Irregular Streaks, Irregular dots and globules" and "Blue Gray Peppering" (Table 4).

Third, for the final checklist composition, the selection based on multivariate analysis was restricted to the most relevant interdependent 9 integrated variables, to respect the feasibility requirement for using the checklist in daily practice without reducing the accuracy [1,13].

Fourth, the total score range of iDScore 2021 is wider, from 0 to 18, while for iDScore 2018 was 0-16 (Table 4, Figures 1 and 2).

Concerning the performance comparison of the two models, when tested on the same monocentric dataset of 324 aMSL, the new iDScore 2021 appeared to be more accurate (ROC area=92%, SE=98%, SP=50%) then the iDScore 2018 (ROC area = 90%, SE = 97%, SP = 48%) (Table 4, Figure 3), and to surpass the experts in terms of SE (+13%) and SP (+9%).

The present study has some limitations. First, although the number of eMM lesions selected was enough to obtain an adequate discriminant power, the whole sample size was limited. Secondly, the evaluators were forced to use a series of selected dermoscopic parameters (ie iDScore checklist 2018) in the dermoscopic pattern analysis: this selection of 7 dermoscopic criteria has a practical value but could also be regarded as a bias in the sense that some recent additional terminology/dermoscopic features of aN and eMM is preventively excluded.

Taken together, the present findings suggest the following consideration. First, the investigation approach of developing a scoring checklist based on an integrated dataset of patients demographic, phenotypic and anamnestic risk factors integrated with objective clinical and dermoscopic data could help dermatologists in early identification of the patient with high risk of MM in routinary medical consultations. Second, using an integrated risk score algorithm such as the new 2021 iDScore checklist with 9 parameters, each one associated with a peculiar partial score, could be proposed as a rapid and easy tool to screen patients with multiple aMSLs and assign them a progressive predictive score ranging from an aN to an eMM diagnosis based on statistical probability. Third, managing these patients according to the peculiar aMSL risk score could help not only in reducing the rate of inappropriate excision for benign lesions but also in organizing the proper follow-up timing (3/6/9/12 months) during daily practice.

Further studies on larger integrated datasets from multiple centers are required to confirm the validity of the present approach and proceed to the testing phase of the proposed integrated checklist.

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