Characteristics of patients with melanoma with non-melanoma skin cancer comorbidity: Practical implications based on a retrospective study

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Abstract. The co-occurrence of melanoma and non-melanoma skin cancer (NMSC) can lead to increased morbidity. However, there has been limited research into the dermoscopic characteristics of melanomas and clinical factors during co-occurrence. A total of 264 patients with melanoma, including 63 with NMSC comorbidity, were enrolled in the present study to retrospectively analyse the coexistence of melanoma morphology, as determined by dermoscopic examination, pathological report, tumour location and clinically manifested risk factors. The frequency of solar lentiginosis (SL) was compared between 264 patients with melanoma and 233 patients with NMSC without melanoma. In 83.4% of cases, skin cancer occurred before or concomitantly with the melanoma. The leading indicators of comorbidity were age (median 70 years; P<0.0001) and SL on the trunk and arms (P<0.0001). Melanomas in patients with NMSC comorbidity were significantly more frequently located on the head and neck [P<0.001; Bonferroni adjusted P-value (P-adj.)<0.01], then on the trunk, but less frequently occurred on the lower limbs (P<0.05). The dermoscopic multi-component asymmetric pattern was the predominant pattern in both groups. The most characteristic pattern in the NMSC group was facial melanoma (P<0.005; P-adj.<0.05); the spitzoid pattern (P<0.001; P-adj.<0.01) was rare. Dermoscopic regression was more common (P<0.001) in the NMSC group. Regression and the number of nevi were independent of age. Differences in the incidence of SL were evaluated based on the presence of melanoma (P<0.01) and in patients without melanoma based on the presence of squamous cell carcinoma (SCC; P<0.01), multiple basal cell carcinoma (P<0.0001) and multiple SCC (P<0.005). Patients with melanoma were 10 years younger on average compared with patients with NMSC (P<0.0001). The differentiation factors identified in the present study may improve the precision of dermoscopic examinations and potentially lead to modifications in the diagnostic workflow for patients with multiple NMSCs with comorbid melanoma.

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Abbreviations: NMSC, non-melanoma skin cancer; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; P, P-value; CI, confidence interval; HR, hazard ratio; OR, odds ratio; SD, standard deviation; NS, not statistically significant; SL, solar lentiginosis; LM, lentigo maligna; LMM, LM melanoma; TNM, tumour-node-metastasis; ANS, atypical nevus syndrome; NAN, numerous acquired nevi

Key words: melanoma, non-melanoma skin cancer, dermoscopy, basal cell carcinoma, solar lentiginosis, comorbidity

Introduction

The worldwide incidence of skin neoplasms has notably increased over the past few decades, particularly among white individuals (1,2). It is estimated that globally the incidence of melanoma will increase by ~50% and melanoma-associated mortalities will increase by 68% by the year 2040 (1). The number of new non-melanoma skin cancer (NMSC) cases is projected to increase ~20-fold for men and 15-fold for women over the next 25 years (2). Despite the high global incidence of non-melanocytic neoplasms, their comorbidity with melanomas is uncommon. A study by Neale *et al* (3) reported a 7% prevalence of NMSC in melanoma settings. By contrast, several patients with melanoma never experience NMSC, even basal cell carcinoma (BCC), which shares an analogous pattern of ultraviolet exposure (non-occupational or recreational). Currently, skin cancer comorbidity also results from rapidly

increasing host susceptibility factors, such as sun-sensitive skin phenotype caused by migration, older age (extended lifespan), a growing number of chronically immunosuppressed patients (of iatrogenic or haematological origin) and infection with human papillomavirus or human immunodeficiency virus (4). Melanoma with NMSC comorbidity affects not only individuals at general population-level risk, but also those with the highest risk of developing multiple skin neoplasms caused by germline mutations [such as cyclin-dependent kinase inhibitor 2A, melanocyte inducing transcription factor (MITF-E318K variant), BRAC1-associated protein, p53], red hair colour phenotype (melanocortin-1 receptor polymorphism), chronic immunosuppression, chronic lymphocytic leucaemia, allogeneic hematopoietic stem cell transplant proceeded by total-body irradiation or solid organ transplantation (5-24). Common features among these high-risk patients are the difficulty of skin examination and multistep treatment approach when the dermoscopic surveillance was not implemented (23,24).

Therefore, it is essential to characterize patients with melanoma and NMSC comorbidity to facilitate clinical practitioners performing the dermoscopic total skin examination. Publications including patients with both types of these tumours have described the epidemiological aspects of this comorbidity (3,4). The dermoscopic patterns of melanoma in this setting of patients were not evaluated in the studies. Therefore, the aim of the present study was to analyse the association between the dermoscopic features of melanomas and the presence of clinically expressed risk factors in patients with NMSC comorbidity to identify simple and fast practical implications for screening and follow-up.

Materials and methods

The present study enrolled consecutive adult patients (≥18 years of age) who were referred for a dermoscopic skin examination to a dermatology clinic of the Military Institute of Medicine-National Research Institute (Warsaw, Poland) between January 2015 and October 2023. The Bioethics Commission at the Military Institute of Medicine (Warsaw, Poland) approved the study protocol (#21/WIM/2021, May 2021; no. 65/24, Dec 2024). Patients signed consent permitting the publication of anonymised photographs.

The retrospective analysis of the patient's medical records consisted of epidemiological data, including previous diagnoses of melanoma (personal and/or among close relatives), NMSC (personal) and melanoma pathological report, including the topology, histological subtype and invasiveness according to the tumour-node-metastasis (TNM) staging system upon 8th American Joint Committee on Cancer classification (25). Patients diagnosed with lesions of uncertain malignant potential (melanocytic tumour of uncertain malignant potential, superficial atypical melanocytic proliferations of unknown significance or atypical spitzoid tumour) were also identified. Patient age was regarded as that on the pathological report; where there were multiple melanomas, the age at first diagnosis was considered.

The evaluated melanoma risk factors included those manifested clinically. The atypical nevus syndrome (ANS) or numerous acquired nevi (NAN; defined as >50 lesions on the body surface), skin phototype (I or II), solar lentiginosis (SL) located on the trunk and upper arms and previous/concomitant/subsequent basal or squamous cell carcinoma (SCC; described as NMSC) were evaluated as the most common risk factors. Patients with genodermatoses and associated types of skin cancer, such as Gorlin-Goltz syndrome (GGS), were considered eligible.

The dermoscopic features of melanoma, particularly the characteristic pattern and presence of regression structures, were evaluated based on the videodermoscopic documentation that was captured in polarised light and at 20-fold magnification. The images were captured using Fotofinder HD 800 or Medicam 1000 (FotoFinder Systems GmbH) or Mole Max (Derma Medical Systems Handels u. Entwicklungs GmbH).

The exclusion criteria were as follows: i) Lack of videodermoscopic images of primary cutaneous melanoma or clinically manifested melanoma risk factors such as number of nevi, SL, types of skin cancer and skin phototype; ii) lack or incomplete pathological report of primary melanoma and NMSC; and iii) recurrent melanomas, metastatic melanomas after skin tumour excision, melanomas of unknown primary location or melanomas unable to be examined with videodermoscopy due to technical reasons.

The control group consisted of adult patients (≥18 years of age) who were referred for a dermoscopic skin examination to a dermatology clinic of the Military Institute of Medicine-National Research Institute (Warsaw, Poland) between January 2015 and October 2023, and were diagnosed with NMSC, whose detailed medical documentation was available, including anamnesis proving the absence of previous/concomitant/subsequent melanoma, a histopathological report confirming the diagnosis of BCC and/or SCC, videodermoscopic images of NMSC and trunk and/or arms skin area that allowed for the assessment of SL and melanocytic nevi. NMSC lesions were regarded as multiple when ≥2 BCC and/or SCC lesions were diagnosed.

Statistical analysis. Statistical analysis was performed using the R software (version 4.3.1; RStudio, version 2023.09.1+494; R software, version 4.4.1; RStudio, version 2024.04.2+764; Posit Software, PBC) and R packages (26).

The frequencies of count data were determined using cross tables. Fisher's exact test was employed to assess differences in frequencies as the expected counts in certain groups were <5. Meanwhile, differences in the means of continuous numerical data were evaluated using the Kruskal-Wallis rank test due to the non-normal distribution of the numerical data in both the entire dataset and the subgroups. The normality of distribution was evaluated with Shapiro-Wilk test. The statistical analysis involved computing the differences in the means between multiple groups using Dunn's test and Bonferroni's P-value correction [adjusted P-value (P-adj.)]. For detailed count data statistics for tables >2x2, row-wise Fisher's test and Bonferroni's P-adj. were used. In addition, crude odds ratios (OR) were computed with 95% confidence intervals (CIs) for pairs of binomial variables in groups using conditional maximum likelihood estimation. Furthermore, ORs adjusted for age and sex with 95% CIs were calculated

using multivariable logistic regression. P<0.05 was considered to indicate a statistically significant difference.

Results

Population characteristics. Data from consecutive dermoscopic examinations of patients admitted between January 2015 and October 2023 to the dermatological clinic were analysed, identifying 295 melanomas in 264 patients (63.3% women and 36.7% men), aged 18-90 years. The mean age of patients with melanoma was 52.2 and the median age was 49 years. A total of 63 patients with an NMSC comorbidity exhibited 69 melanomas. The mean age of these patients was 67.3 and the median age was 70.0 years (P<0.0001). BCC was present in all cases; SCC was also present in 10/63 (15.9%) patients. In 53/63 (84.1%) patients, NMSC was diagnosed before or concomitantly with melanoma and in 10/63 (15.9%) patients it was diagnosed as a second primary tumour. Thin melanomas [lentigo maligna (LM), LM melanoma (LMM), pTis and pT1] comprised 257/295 (87.1%) lesions and 57/69 (82.6%) melanomas coexisting with NMSC. A total of 37/264 patients (14.0%) were diagnosed with ≥2 melanomas, and 4/264 (1.5%) had 3 melanomas. In 24/264 (9.0%) patients, melanoma occurred in an immediate family member. Among the 63 patients with an NMSC comorbidity, 6 (9.5%) were diagnosed with ≥2 melanomas and 8 (12.7%) reported a familial melanoma. Non-cutaneous types of cancer were found sporadically; mainly prostate cancer (6 cases in total, 3 coexisting with NMSC), breast cancer (3 cases in total, no coexisting with NMSC) and chronic lymphocytic leukaemia (2 cases in total, both coexisting with NMSC). No genetic syndromes and organ transplant recipients were detected among the patients. Out of the 264 patients, 249 (94.3%) had II skin phototype, 9 (3.4%) had phototype I and 6 (2.3%) had phototype III. The recapitulation of the analysed data is presented in Table I.

Analysis of differences between groups of patients with melanoma depending on NMSC comorbidity. The median age of patients with melanoma with NMSC was ~25 years higher compared with that of patients with melanoma without NMSC comorbidity (P<0.0001) (Fig. 1). No difference in sex was observed. Among the analysed melanoma risk factors, ANS/NAN were observed significantly more often in patients with melanoma without NMSC comorbidity (127 patients vs. 30 patients; 63.2% vs. 47.6%, respectively; P<0.05). By contrast, SL was a characteristic risk factor in patients with NMSC comorbidity (54 patients vs. 79 patients; 85.7% vs. 39.3%, respectively; P<0.0001).

The comparison of melanoma locations revealed statistically significant differences (P<0.005) in the group NMSC comorbidity compared with that of the melanoma without NMSC group; melanomas were detected significantly more frequently within the head and neck region (P<0.05; P-adj.<0.01) and less frequently on lower limbs (P<0.05; P-adj.>0.05). Despite the similar predominance of thin melanomas in both groups, the histological report in the NMSC group showed an increased incidence of LM (in facial and extra-facial locations) and LMM (P<0.05) compared with that of melanoma patients without NMSC.

The aforementioned findings were also complemented by data regarding the dermoscopic pattern of melanoma (P<0.0005; Table I). The asymmetric multicomponent pattern was the most frequent dermoscopic pattern of melanoma among those identified during dermoscopic examination in patients with melanoma without NMSC and with NMSC comorbidity (39.8 and 33.3%, respectively). This finding was associated with the most commonly identified type of melanoma in pathological reports, the superficial spreading melanoma in patients with melanoma without NMSC and with NMSC comorbidity (79.2 and 69.6%, respectively). The second in frequency was the dermoscopic melanoma on face, when NMSC was present (21.7%; P<0.005; P-adj.<0.05) or the spitzoid pattern when NMSC was absent (21.2%; P<0.001; P-adj.<0.01). The melanoma on chronically sun-damaged skin was more frequently presented with NMSC coexistence (18.8% vs. 11.9%), though the difference was statistically insignificant. The dermoscopic regression structures within melanomas were characteristic of NMSC (49.3% vs. 26.1%; P<0.001). Common dermoscopic patterns of melanoma in this setting of patients are shown in Fig. 2.

In the case of patients with field cancerisation, the enhanced regression of melanoma, particularly within the scalp area, might be responsible for the delayed diagnosis due to difficulties in recognising the melanoma extension despite its already advanced stage. For example, the case of an elderly patient (85 years old) included in the present study demonstrated the complexity of skin examination in this setting (Fig. 3) as the diagnosis and margins of advanced melanoma (pT3b) on the scalp (Fig. 3B-D) were obtained after detailed, multistep and profound non-invasive examinations with videodermoscopy and reflectance confocal microscopy (RCM). In addition, this workflow enabled revealing the collision tumour - the overlap with pigmented BCC and lentigo maligna melanoma (pT1) within the forehead (Fig. 3A-C) in this patient. Among younger (<65 years) patients with NMSC comorbidity, the diagnosis of melanoma remains challenging, particularly when numerous melanocytic nevi are present. Fig. 4A presents images of a 43-year-old patient who exhibited 3 melanomas (Fig. 4D) within 1 year after >12 excisions of BCCs. Though GGS was excluded, some of the BCCs were pigmented (Fig. 4C) with dermoscopic features similar to those observed in GGS. Numerous melanocytic nevi were not clinically atypical, but many simulated patterns of melanoma on sun-damaged skin under dermoscopy (Fig. 4B). Therefore, RCM was also performed for both aforementioned patients (presented in Figs. 3 and 4), leading to the identification of melanoma and reducing unnecessary excisions of benign lesions. This had an additional positive impact on the second patient, who was heavily surgically pretreated, and implementation of the two-step diagnostics, videodermoscopic and RCM, enabled us to achieve more precise qualification of lesions for excision or videodermoscopic monitoring.

OR of groups depending on NMSC comorbidity. Table II and Fig. 5 summarise the ORs (crude and adjusted for age and sex), 95% CIs and P-values for the clinical, dermoscopic and epidemiological characteristics of the patients with melanoma depending on NMSC comorbidity.

Table I. Epidemiological, clinical, histopathologic, topographic and dermoscopic data of patients diagnosed with melanoma stratified by NMSC comorbidity.

Factor	Melanoma, n (%)	Melanoma without NMSC, n (%)	Melanoma with NMSC comorbidity, n (%)	P-value	P-value, within the group	Bonferroni adjusted P-value
Sex						
Female	167 (63.3)	127 (63.2)	40 (63.5)	NS		
Male	97 (36.7)	74 (36.8)	23 (36.5)			
Age						
Range	18-90	18-88	19-90			
Mean	52.2	47.5	67.3			
Median	49.0	45.0	70.0	<0.0001		
Standard deviation	16.5	13.9	14.9			
History of personal/familial melanoma						
Yes	38 (14.4)	27 (13.4)	11 (17.5)	NS		
No	226 (85.6)	174 (86.6)	52 (82.5)			
NAN/ANS						
Yes	157 (59.5)	127 (63.2)	30 (47.6)	<0.05		
No	107 (40.5)	74 (36.8)	33 (52.4)			
Solar lentiginosis						
Yes	133 (50.4)	79 (39.3)	54 (85.7)	<0.0001		
No	131 (49.6)	122 (60.7)	9 (14.3)			
Melanoma location				<0.01	<0.01	
Head and neck	40 (13.5)	22 (9.7)	18 (26.1)		0.001	<0.01
Trunk	106 (35.9)	84 (37.2)	22 (31.8)		NS	NS
Upper limb	48 (16.3)	34 (15.0)	14 (20.3)		NS	NS
Lower limb	94 (31.9)	79 (35.0)	15 (21.7)		<0.05	NS
Nail apparatus	1 (0.3)	1 (0.4)	0 (0.0)		NS	NS
Mucous membrane	6 (2.0)	6 (2.6)	0 (0.0)		NS	NS
Histopathological type				NS	NS	
LM	35 (11.9)	22 (9.7)	13 (18.9)			
LMM	17 (5.8)	10 (4.4)	7 (10.1)			
Superficial spreading	227 (76.9)	179 (79.2)	48 (69.6)			
Spitzoid	4 (1.3)	4 (1.8)	0 (0.0)			
Nevoid	2 (0.7)	2 (0.9)	0 (0.0)			
Desmoplastic	0 (0.0)	0 (0.0)	0 (0.0)			
Acral lentiginous	2 (0.7)	2 (0.9)	0 (0.0)			
MELTUMP	8 (2.7)	7 (3.1)	1 (1.4)			
Histopathological report						NS
LM (facial/extra-facial)	35 (11.8)	22 (9.7)	13 (18.8)	<0.05	<0.05	
LMM (facial)	17 (5.7)	10 (4.4)	7 (10.1)			
pTis	76 (25.7)	64 (28.3)	12 (17.4)			
pT1	129 (43.7)	104 (46.0)	25 (36.2)			
pT2	17 (5.7)	10 (4.4)	7 (10.1)			
pT3	7 (2.4)	5 (2.2)	2 (2.9)			
pT4	6 (2.0)	4 (1.7)	2 (2.9)			
MELTUMP/SAMPUS	8 (2.7)	7 (3.1)	1 (1.4)			
Dermoscopic pattern of melanoma				<0.0005	<0.005	
Multicomponent asymmetric	113 (38.3)	90 (39.8)	23 (33.3)		NS	NS
Spitzoid	51 (17.3)	48 (21.2)	3 (4.3)		<0.001	<0.01
Melanoma on sun damaged skin	40 (13.6)	27 (11.9)	13 (18.8)		NS	NS
Hypomelanotic/amelanotic	16 (5.4)	13 (5.7)	3 (4.3)		NS	NS

Table I. Continued.

Factor	Melanoma, n (%)	Melanoma without NMSC, n (%)	Melanoma with NMSC comorbidity, n (%)	P-value	P-value, within the group	Bonferroni adjusted P-value
Dermoscopic pattern of melanoma				<0.0005	<0.005	
Homogenous	7 (2.4)	6 (2.6)	1 (1.4)		NS	NS
Reticular	10 (3.4)	8 (3.5)	2 (2.9)		NS	NS
Nodular	17 (5.8)	9 (4.0)	8 (11.6)		<0.05	NS
Melanoma on face	34 (11.5)	19 (8.4)	15 (21.7)		<0.005	<0.05
Melanoma in special location (nail apparatus/acral/ mucous membranes)	7 (2.4)	6 (2.6)	1 (1.4)		NS	NS
Dermoscopic structures of regression						
Yes	93 (31.5)	59 (26.1)	34 (49.3)	<0.001		
No	202 (68.5)	167 (73.9)	35 (50.7)			

Fisher's exact test utilised for count data with simulated P-value. P<0.05 was considered statistically significant. NMSC, non-melanoma skin cancer; NS, not statistically significant; ANS, atypical nevus syndrome; NAN, numerous acquired nevi; MELTUMP, melanocytic tumour of uncertain malignant potential; SAMPUS, superficial atypical melanocytic proliferations of unknown significance.

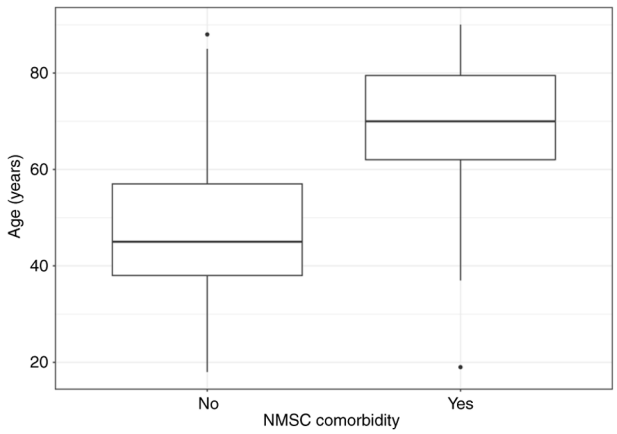

Figure 1. Differences in the median age of patients with melanoma with or without NMSC comorbidity. Among 264 patients with melanoma aged 18-90 years, the median age of patients without NMSC comorbidity was 47 years. Among 63 patients (23.8%) diagnosed with melanomas and NSMC, the median age was 70 years (P<0.000001). NMSC, non-melanoma skin cancer. Horizontal lines represent median values, boxes indicate the first and third quartiles, whiskers indicate the 1.5 interquartile range, and dots indicate outliers.

The unadjusted ORs of investigated factors in the group of patients with NMSC comorbidity demonstrated a high risk for occurrence of SL (OR, 9.07; 95% CI, 4.42-20.75; P<0.0001), regression structures in melanoma under dermoscopy (OR, 2.74; 95% CI, 1.56-4.81; P<0.001) and with absence of ANS or NAN (OR, 0.53; 95% CI, 0.3-0.94, P<0.05). The crude ORs for sex (P>0.05) and age (OR, 1.09; 95% CI, 1.07- 1.12, P<0.0001) of patients with NMSC comorbidity are shown in Fig. 5A.

The ORs adjusted for age and sex of investigated factors in a group of patients with NMSC comorbidity demonstrated a statistically significant risk for occurrence only for SL (OR, 3.83; 95% CI, 1.71-9.25; P<0.001; Fig. 5B).

Analysis of differences in NMSC comorbidity group depending on age. Differences in investigated factors were analysed between younger (age, <65 years) and older (age ≥65 years) patients with NMSC comorbidity (Table III). The clinical findings in the younger subgroup demonstrated a significantly lower frequency of SL (68.4% vs. 93.2%; P<0.05), although it was still found to be ~30% more common compared with that of patients with melanoma without NMSC comorbidity (39.3%). Another clinical factor, NAN/ANS, was observed notably less frequently in older patients (P>0.05). The analysis of differences in the topography of melanoma with NMSC comorbidity demonstrated a statistically significant trend in the occurrence of melanoma in the head and neck area in the elderly group (34.7% vs. 5%; P<0.05; P-adj.>0.05). In the analysis of dermoscopic factors, regression features were present independently of the patients' age and the pattern of facial melanoma was predominant in the elderly patients (28.5% vs. 5.0%; P<0.05; P-adj.>0.05), but the multicomponent asymmetric pattern was more frequent in younger patients (60.0% vs. 22.4%; P<0.005; P-adj.<0.05).

Analysis of SL comorbidity differences between patients with melanoma and patients with NMSC without melanoma. The control group containing 233 patients with NMSC without melanoma comorbidity was included in the present study to evaluate the impact of SL. The control group consisted of 209 patients with BCC, 51 patients with SCC, 27 patients with BCC and SCC, and 3 patients with multiple BCC and SCC (Table IV). The comparison of SL comorbidity between patients with melanoma and the control group demonstrated statistically significant differences in the mean and median age;

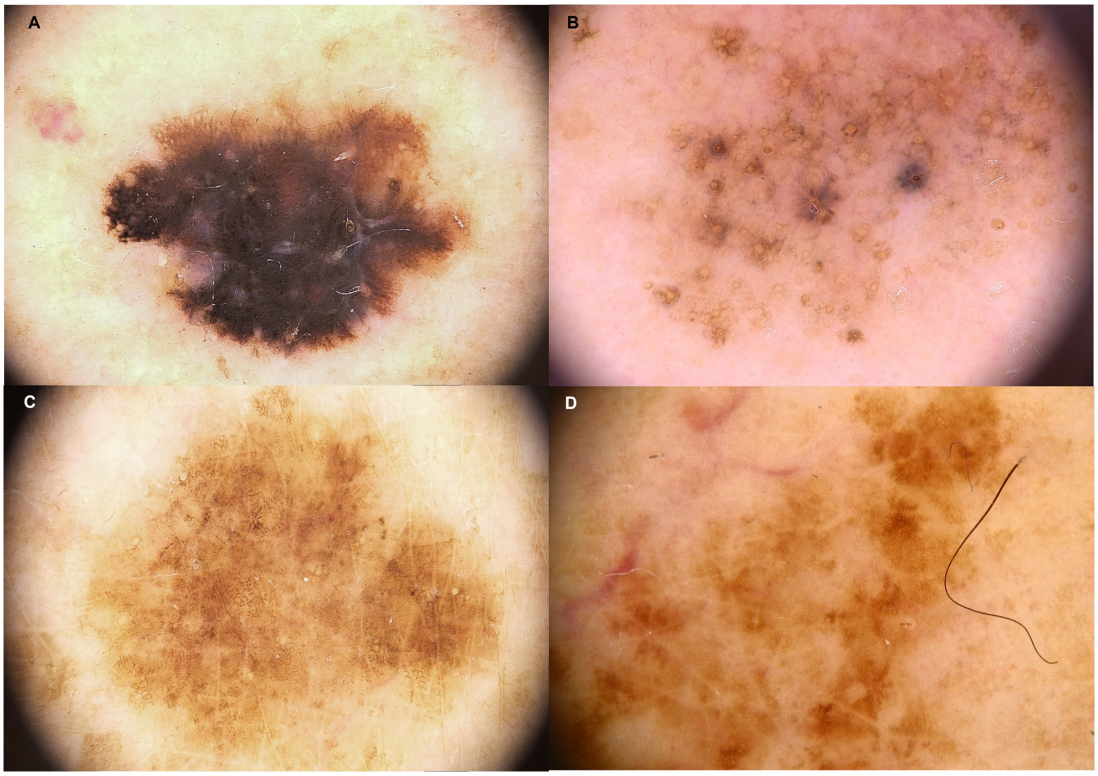

Figure 2. Characteristic dermoscopic patterns of patients with melanoma with NMSC co-occurrence. The most commonly found dermoscopic patterns of melanoma in patients with non-melanoma skin cancer comorbidity were (A) multicomponent asymmetric melanomas, (B) melanomas on the face and (C and D) melanomas on chronically sun-damaged skin.

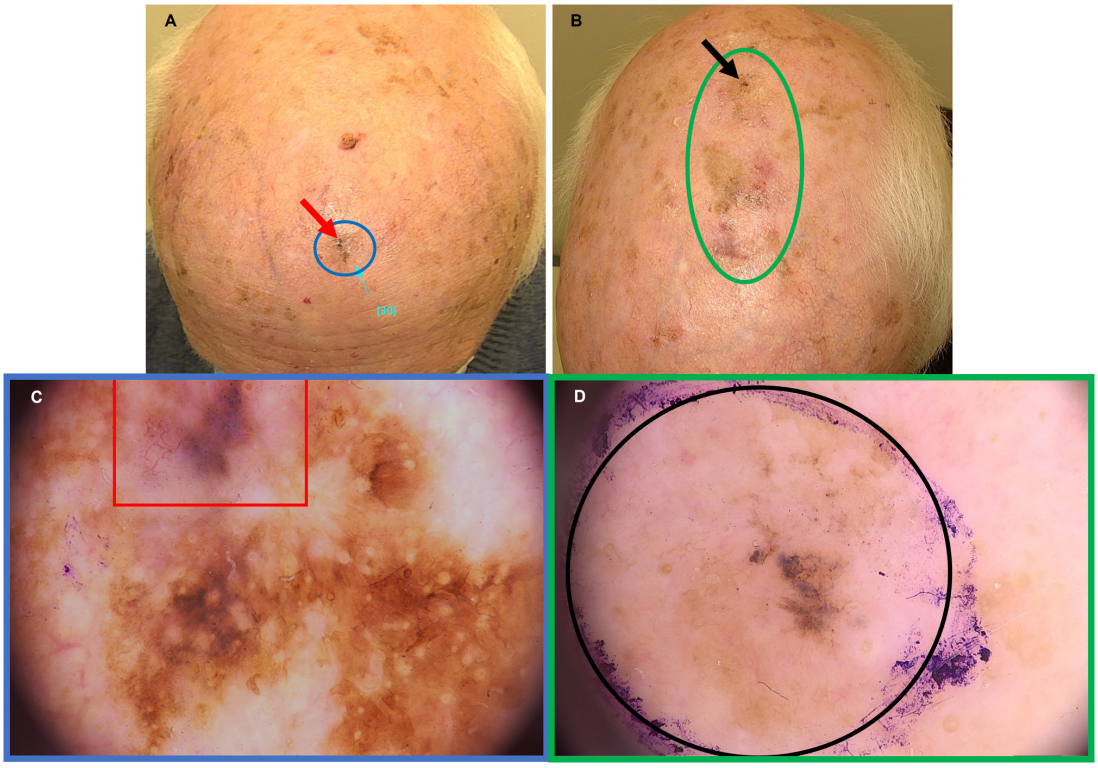

Figure 3. Representative case demonstrating the difficulties in diagnosing melanoma in elderly (≥65 years) patients with NMSC comorbidity. The subgroup of elderly patients with non-melanoma skin cancer comorbidity commonly demonstrates severe photodamaged skin, field cancerisation and multiple solar lentiginosis. (A) Clinical presentation of lentigo maligna melanoma pT1 (borders marked with blue circle) in collision with pigmented BCC (red arrow). (B) Concomitant scalp melanoma stage pT3b with borders (green circle) marked upon RCM examination and further confirmed following excision with the Mohs microsurgery method (black arrow, most pigmented part of this melanoma). (C) Representative images of dermoscopy results demonstrating the facial melanoma pattern (blue frame) and pigmented BCC (red square). (D) The black circle highlights an area of suspected melanoma detected by dermoscopy, which implied a further need for RCM-led diagnosis. NMSC, non-melanoma skin cancer; BCC, basal cell carcinoma; RCM, reflectance confocal microscopy.

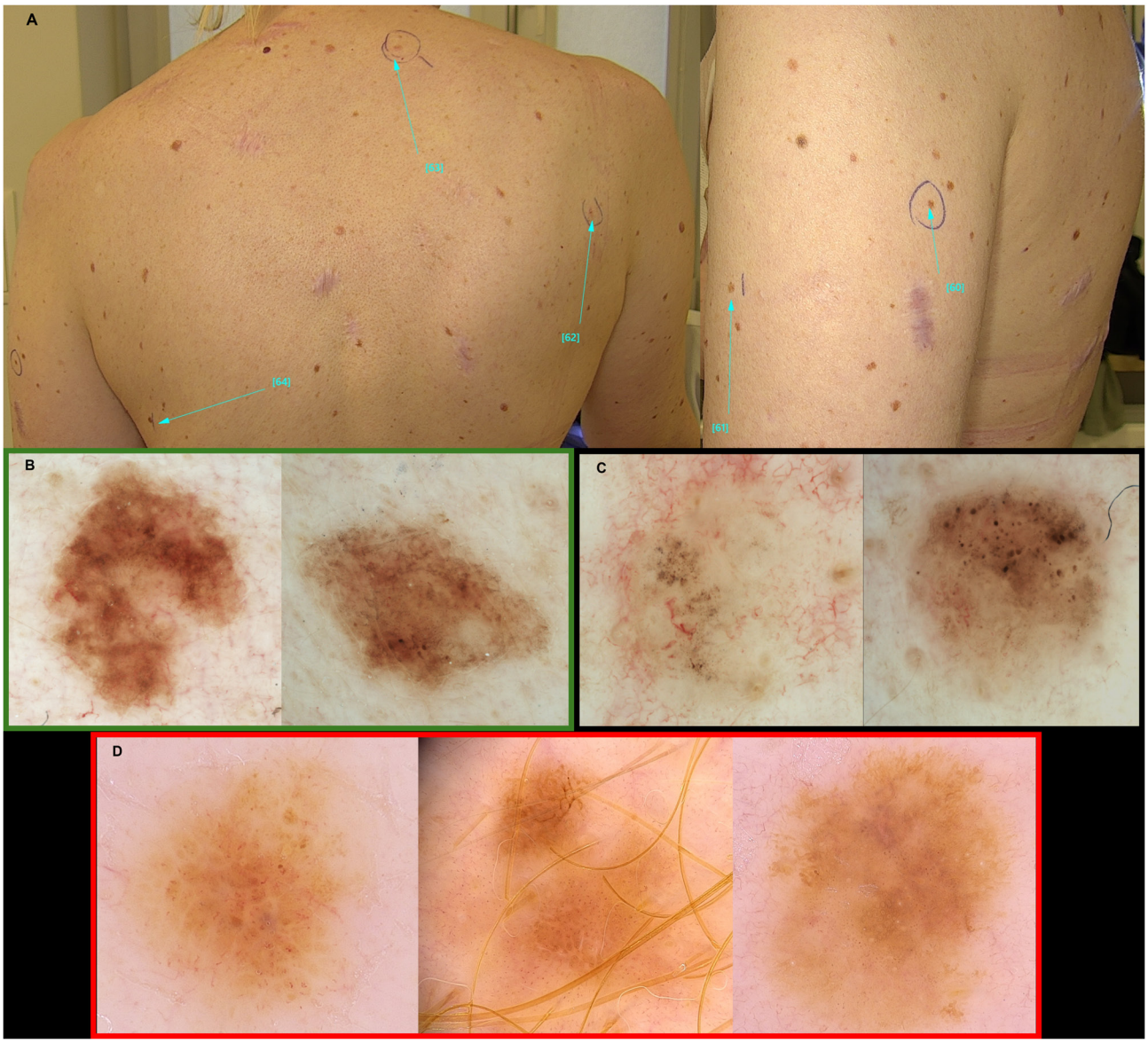

Figure 4. Representative case demonstrating the dermoscopic difficulties of diagnosing melanoma in young (<65 years) patients with non-melanoma skin cancer comorbidity. (A) Clinical presentation of trunk and arm revealing multiple melanocytic nevi and scars following the excision of a dozen BCC and a few nevi. (B-D) Representative dermoscopy images of (B) Melanocytic nevi resembling melanoma on sun-damaged skin pattern (green frame); (C) pigmented and non-pigmented BCC (black frame); (D) lower row, three melanomas (one of pTis, and two of pT1a invasiveness according to tumour-node-metastasis classification, two located on the trunk and one on the lower limb) identified within 1 year, presenting a multi-component asymmetric pattern, a light brown pigmentation and atypical vessels (red frame). BCC, basal cell carcinoma.

the patients with melanoma with SL were younger compared with the patients with NMSC (mean, 52.2 years vs. 64.2 years; median, 49.0 years vs. 66.0 years; P<0.0001; Table V). SL was found more frequently among patients with melanoma (P<0.01) and in selected subcategories of patients with NMSC: i) with multiple BCC (P<0.0001); ii) multiple SCC (P<0.005) or single SCC (P<0.01); and iii) the comorbidity of BCC and SCC (P<0.0001). No statistically significant differences in the sex distribution between patients with and without melanoma, were observed, regardless of the diagnosed skin cancer.

Discussion

While the prevalence of NMSC in patients with melanoma has been previously reported as 7% by Neale *et al* (3), the incidence reached 23.8% in the present study. Based on results of multivariable logistic regression presented in Table II the likelihood of patients with melanoma developing NMSC increased by 9% for each year of life (OR 1.09). Furthermore, while BCC was found in every patient, 83.4% of patients with melanoma exhibited NMSC mainly before, rather than concomitantly with, the diagnosis of melanoma, which offers insights into the comorbidity of NMSC. To the best of our knowledge, this finding has not been reported thus far.

The present study demonstrated a significant (P<0.0001) association between SL in the trunk and upper limbs, and NMSC in patients who presented with melanoma concurrently or after the initial presentation. Further analysis of the presence of SL demonstrated an independent association both with melanoma and multiple NMSC in the control group.

Table II. Summary of OR, 95% CI and P-value results for clinical, dermoscopic and epidemiologic characteristics of patients with melanoma with NMSC comorbidity.

A, Characteristics of patients with melanoma with NMSC comorbidity (unadjusted)

Factor	OR	95% CI	P-value
Male	0.99	0.54-1.77	NS
Median age	1.09	1.07-1.10	<0.0001
Melanoma (previous/concomitant or in family history)	1.37	0.61-2.9	NS
ANS/NAN	0.53	0.30-0.94	<0.05
Regression under dermoscopy	2.74	1.56-4.81	<0.001
Solar lentiginosis	9.07	4.42-20.75	<0.0001

B, Characteristics of patients with melanoma with NMSC comorbidity adjusted for age and sex

Factor	OR	95% CI	P-value
Melanoma (previous/concomitant or in family history)	1.71	0.70-4.09	NS
ANS/NAN	1.48	0.72-3.17	NS
Regression under dermoscopy	1.46	0.74-2.85	NS
Solar lentiginosis	3.83	1.71-9.25	<0.001
Melanoma thickness	1.62	0.66-3.88	NS

ORs adjusted for age and sex with 95% CIs were calculated using multivariable logistic regression. P<0.05 was considered statistically significant. NMSC, non-melanoma skin cancer; OR, odds ratio; CI, confidence interval; NS, not statistically significant; ANS, atypical nevus syndrome; NAN, numerous acquired nevi.

The differentiation factor was the mean and median age, as the patients with melanoma with SL were >10 years younger compared with that of the non-melanoma group. The SL comorbidity was insignificant among patients with a diagnosis of BCC, but BCC was found in all patients with melanoma with NMSC comorbidity. By contrast, SCC was associated with SL irrespectively of their burden (single or multiple) but was present only in 15.9% of patients with melanoma with NMSC comorbidity. Therefore, SL may potentially be used as a marker of comorbidity in different types of skin cancer, as well as an indicator of their multiplicity.

Drawing the clinicians' attention to the presence of lentiginosis may be valuable, as it could affect the risk assessment of patients during clinical/dermoscopic skin examination. Lentiginosis also indicates the possibility of comorbid melanoma, which is difficult to identify due to excessive regression or its similarity to SL on the face (27-29). Previous studies have provided evidence linking SL to sun exposure in various types (intense and intermittent or chronic-occupational and everyday solar irradiation) and photodamage to the skin (30-33). Certain studies have made distinctions within SL, classifying those on the face as associated with cumulative lifetime sun exposure (30-33). By contrast, those on the trunk and arms were considered to be associated with cumulative sun exposure and a history of sunburns before the age of 20 (33). Thus, in light of these findings, the present study focused on evaluating the presence of SL on the upper arms and trunk, considering that the presence of SL only on the face and dorsum of hands may be age-related. By applying this approach, the present study identified and described a subgroup of patients who are likely to demonstrate NMSC before melanoma, without the need to conduct complex sun exposure calculations or rely on potentially unreliable questionnaires. A number of patients may not accurately recall their sun exposure history or the number of sunburns experienced, making it challenging to obtain accurate information through self-reports. Therefore, the present approach allowed for a more straightforward and practical method of identifying patients at higher risk. At the same time, it should be considered that dermatologists or healthcare providers performing routine screening visits should ask patients about their sun exposure history and number of sunburn episodes.

Considering the median age of patients with NMSC comorbidity (70 years), it was found that individual factors associated with those melanomas differ from the previously described characteristics of melanomas in older patients (34-37). Though facial melanoma is commonly found in the elderly population, melanomas occurring in 'special locations' were not found in the group of patients with NMSC, except for 1 case of acral melanoma. Due to the mean age of onset for acral (63.1 years) or mucosal (64±15 years) melanomas more cases might be expected, especially considering that the NMSC comorbidity group was ~25 years older compared with that of the comparator group (38,39). Despite the rarity of acral and mucosal melanomas, the small sample size of the present study could be a possible explanation. In addition, a previous study proved that the most common dermoscopic patterns among individuals aged >60 years were melanomas on chronically sun-damaged skin, including the extra-facial LM type, and multicomponent asymmetric or

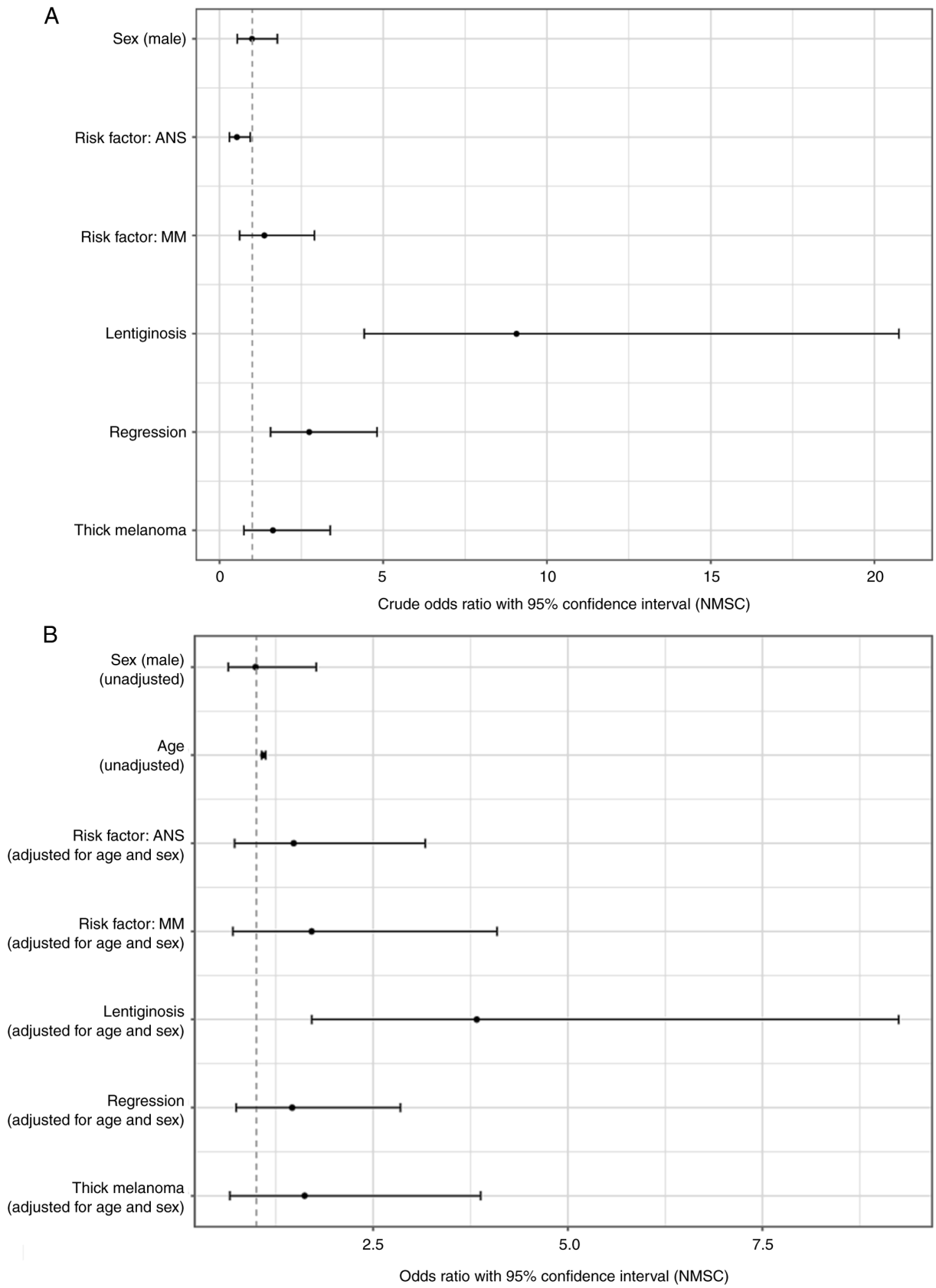

Figure 5. Characteristics of patients with melanoma with NMSC comorbidity demonstrated by (A) crude odds ratios and (B) odds ratios adjusted for age and sex. MM, melanoma; NMSC, non-melanoma skin cancer; ANS, atypical nevus syndrome.

homogenous melanomas (37). Those results were consistent with previous observations (37,40-42). In the present study the distinguishing patterns of the NMSC comorbidity appeared to be other dermoscopic patterns, predominantly melanoma on the face and nodular melanomas, while spitzoid melanomas were rare.

Table III. Clinical, topographic and dermoscopic data of patients diagnosed with melanoma and NMSC comorbidity comparing younger (<65 years) and older (≥65 years) patients.

Factor	NMSC, comorbidity n (%)	NMSC comorbidity aged <65 years, n (%)	NMSC comorbidity aged ≥65 years, n (%)	P-value	P-value within the group	Bonferroni adjusted P-value
Total patients	63 (100.0)	19 (30.1)	44 (69.9)			
Total melanoma	69 (100.0)	20 (29.0)	49 (71.0)			
Solar lentiginosis				<0.05		
Yes	54 (85.7)	13 (68.4)	41 (93.2)			
No	9 (14.3)	6 (31.6)	3 (6.8)			
NAN/ANS				NS		
Yes	30 (47.6)	13 (68.4)	17 (38.6)			
No	33 (52.4)	6 (31.6)	27 (61.4)			
Melanoma location				<0.05		
Head and neck	18 (26.1)	1 (5.0)	17 (34.7)		<0.05	NS
Trunk	22 (31.8)	9 (45.0)	13 (26.5)		NS	NS
Upper limb	14 (20.3)	3 (15.0)	11 (22.4)		NS	NS
Lower limb	15 (21.7)	7 (35.0)	8 (16.3)		NS	NS
Nail apparatus	0 (0.0)	0 (0.0)	0 (0.0)		NS	NS
Mucous membrane	0 (0.0)	0 (0.0)	0 (0.0)		NS	NS
Dermoscopic pattern of melanoma				<0.05		
Multicomponent asymmetric	23 (33.3)	12 (60.0)	11 (22.4)		<0.005	<0.05
Spitzoid	3 (4.3)	2 (10.0)	1 (2.0)		NS	NS
Melanoma on sun-damaged skin	13 (18.8)	1 (5.0)	12 (24.5)		NS	NS
Hypomelanotic/amelanotic	3 (4.3)	1 (5.0)	2 (4.0)		NS	NS
Homogenous	1 (1.4)	0 (0.0)	1 (2.0)		NS	NS
Reticular	2 (2.9)	0 (0.0)	2 (4.0)		NS	NS
Nodular	8 (11.6)	2 (10.0)	6 (12.2)		NS	NS
Melanoma on face	15 (21.7)	1 (5.0)	14 (28.5)		<0.05	NS
Melanoma in a special location (nail apparatus/acral/mucous membranes)	1 (1.4)	1 (5.0)	0 (0.0)		NS	NS
Dermoscopic structures of regression				NS		
Yes	34 (49.3)	8 (40.0)	26 (53.0)			
No	35 (50.7)	12 (60.0)	23 (47.0)			

Fisher's exact test utilised for count data with simulated P-value. P<0.05 was considered statistically significant. NMSC, non-melanoma skin cancer; NS, not statistically significant; ANS, atypical nevus syndrome; NAN, numerous acquired nevi.

Therefore, to investigate whether the patients' age affected the characteristics of the melanoma with NMSC comorbidity setting, patients were compared between two subgroups: younger (age <65), and older (age ≥65 years). Among the clinical aspects, the younger subgroup demonstrated a significantly lower frequency of SL compared with that of the elderly group, but SL frequency was still more common compared with that in patients with melanoma without NMSC comorbidity (68.4% vs. 39.3%). The analysis of differences in the topography of melanoma with NMSC comorbidity demonstrated a trend in the predominance of melanoma in the head and neck region in the elderly group (34.7% vs. 5%; P<0.05; P-adj.>0.05). The topography of melanoma in the younger group was similar to that of patients without NMSC. The dermoscopic regression structures of melanoma were present independently of the patient's age, and therefore can be regarded as the characteristic feature of NMSC comorbidity. The dermoscopic pattern of facial melanoma was predominant in elderly patients (28.5% vs. 5.0%; P<0.05); however, this was insignificant due to the small sample size following Bonferroni's correction. The multicomponent asymmetric pattern was the most frequently described in younger patients (60% vs. 22.4%; P<0.005; P-adj. <0.05), similar to patients without NMSC.

Melanomas on the face and scalp often pose notable diagnostic difficulties under dermoscopy, particularly in amelanotic/hypomelanotic LMM, and regressed or recurrent LMM (27,28,43-46). In such situations, RCM may indicate an adequately representative area for biopsy and suggest the primary diagnosis. Furthermore, LM can cause diagnostic problems for

Table IV. Summary of data analysed in patients diagnosed with melanoma or NMSC without melanoma with division into lentiginosis comorbidity.

Factor	Total patients, n (%)	Patients with lentiginosis, n (%)	Patients without lentiginosis, n (%)	P-value	OR (95% CI)
Melanoma				<0.02	1.58
No	233 (46.9)	91 (40.6)	142 (52.0)		(1.11-2.67)
Yes	264 (53.1)	133 (59.4)	131(48.0)		
Total	497 (100.0)	224 (100.0)	273 (100.0)		
BCC				NS	0.73
No	24 (10.3)	11 (12.1)	13 (9.2)		(0.31-1.76)
Yes	209 (89.7)	80 (87.9)	129 (90.9)		
Total	233 (100.0)	91 (100.0)	142 (100.0)		
SCC				<0.01	2.28
No	182 (78.1)	63 (69.2)	119 (83.8)		(1.22-4.34)
Yes	51 (21.9)	28 (30.8)	23 (16.2)		
Total	233 (100.0)	91 (100.0)	142 (100.0)		
Multiple BCC				<0.0001	3.98
No	166 (71.2)	49 (53.9)	117 (82.4)		(2.20-7.32)
Yes	67 (28.8)	42 (46.1)	25 (17.6)		
Total	233 (100.0)	91 (100.0)	142 (100.0)		
Multiple SCC				<0.01	10.41
No	225 (96.6)	84 (92.3)	141 (99.3)		(1.76-268.44)
Yes	8 (3.4)	7 (7.7)	1 (0.7)		
Total	233 (100.0)	91 (100.0)	142 (100.0)		
Multiple NMSC				<0.0001	3.96
No	164 (70.4)	48 (52.8)	116 (82.7)		(2.20-7.25)
Yes	69 (29.6)	43 (47.2)	26 (18.3)		
Total	233 (100.0)	91 (100.0)	142 (100.0)		

Fisher's exact test utilised for count data with simulated P-value and OR with 95% CI. The Kruskal-Wallis rank test was used to calculate differences in the means of continuous numerical data due to the non-normal distribution of the numerical data. P<0.05 was considered statistically significant. NMSC, non-melanoma skin cancer; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval; NS, not statistically significant.

Table V. Summary of age and sex data analysed in patients diagnosed with melanoma or NMSC without melanoma with stratified by lentiginosis comorbidity.

Factor	Total patients	Patients with melanoma	Patients with NMSC without melanoma	P-value	OR (95% CI)
Sex, n (%)					
Female	299 (60.2)	167.0 (55.9)	132.0 (44.1)	NS	0.76 (0.53-1.09)
Male	198 (39.8)	97.0 (49.0)	101.0 (51.0)		
Total	491 (100.0)	264.0 (100.0)	2330 (100.0)		
Age, years					
Mean		52.2	64.2	<0.0001	
Median		49.0	66.0		
Standard deviation		16.5	15.6		
Range		18.0-90.0	18.0-96.0		

Fisher's exact test utilised for count data with simulated P-value and OR with 95% CI. The Kruskal-Wallis rank test was used to calculate differences in the means of continuous numerical data due to the non-normal distribution of the numerical data. P<0.05 was considered statistically significant. NMSC, non-melanoma skin cancer; OR, odds ratio; CI, confidence interval; NS, not statistically significant.

pathologists; LM is often misdiagnosed as junctional melanocytic nevi, which may result in a delay of diagnosis for years (29).

The present study demonstrated no statistically significant differences between the groups regarding NMSC comorbidity in the histological type or stage of melanomas. A possible explanation is that the comparator group (patients with melanoma without NMSC; median age, 45.0 years) undergo dermoscopic screening tests more often, which results in a higher frequency of early-stage or micro-melanomas diagnoses (47). Among patients with NMSC comorbidity, melanomas arising within the photodamaged skin are most often characterised by the primary horizontal type of growth (LM, LMM, extra facial LM and superficial spreading melanoma) (27,36,40-42,48).

The differences between the aforementioned individual patient groups partly indicate clinicians' possible difficulties during the skin screening. Hence, to reflect real clinical situations based on two cases, the present study described different features of melanomas in patients with NMSC comorbidity, independent of their age, which influenced the diagnostic workflow. Elderly patients usually exhibit enhanced SL, which can overlap with pigmented actinic keratosis or LM lesions, particularly in the head area. The presence of melanoma simulators such as pigmented BCC or pigmented actinic keratosis, collision tumours (that consist of NMSC and melanoma tissue overlap) and features of wide regression can make these melanomas go unnoticed despite their large size or may lead to false-negative results. This, in turn, may result in the delayed diagnosis of advanced melanomas. Younger patients with NMSC comorbidity will present different diagnostic difficulties, mainly due to the common presence of the ANS/NAN (63.2%) and the multicomponent asymmetric pattern of melanomas (60%) with features of regression (40%), which are also present in dysplastic nevi of ANS. As a result, patients with NMSC comorbidity require detailed dermoscopic skin examinations, preferably accompanied by complementary RCM, and multiple punch biopsies to enhance the specificity of the presurgical diagnostic process. Therefore, simple descriptive features of unique patients' characteristics might help physicians identify patients with NMSC who may present or already have a difficult-to-diagnose melanoma, thus preventing potential diagnostic pitfalls in clinical practice.

For future exploration of the characteristics of melanoma and NMSC comorbidity, haematological patients or organ transplant recipients may provide data regarding the role of the patient-related risk factors such as ANS, NAN, SL and degree of skin photodamage, as these patients are known to be at a high risk of developing multiple skin neoplasms (11-23). For organ transplant recipients, Rizvi *et al* (17) reported standardised incidence ratios of 51.9 for SCC (95% CI, 48.4-55.5), 54.9 for Kaposi sarcoma (95% CI, 27.4-98.2) and 2.4 for melanoma (95% CI, 1.9-3.0). A study by Omland *et al* (18) on allogeneic hematopoietic stem cell transplant (HSCT) recipients demonstrated an increased risk (hazard ratio, HR) of BCC (HR, 3.1; 95% CI, 1.9-5.2), SCC (HR, 18.3; 95% CI, 4.1-81.8) and melanoma (HR, 5.5; 95% CI, 1.7-17.7). Morbidity varied depending on the type of transplant, with SCC being most common in renal transplant recipients (RTRs) and allogeneic HSCT recipients having a higher risk of melanoma. The risk of BCC following allogeneic HSCT has only been reported in patients treated with total-body irradiation (HR, 3.9; 95% CI, 2.6-6.8), where it was found to be similar to that of RTRs (18). A complex and not fully explored group is that of patients who underwent hematopoietic stem cell or solid organ transplantation in childhood or have been under chronic immunosuppressive treatment since then (20). It is crucial to address several aspects related to their ongoing care, such as the longevity of follow-ups, adherence to screening, education on photoprotection and the importance of self-examination of the skin (21). Silverberg and Ratner (22) reported that patients with a history of NMSC and melanoma are at an increased risk of developing extra-cutaneous cancer (single or multiple), particularly at a younger age (18-49 years), with a smoking history or of Caucasian origin ($P<0.0001$). A possible explanation of melanoma and NMSC comorbidity is polymorphisms of genes involved in DNA repair or T-lymphocyte pathways observed in subsets of patients prone to develop multiple types of cancer (22). Zheng *et al* (49) reported an increased risk of types of cancer associated with CTLA-4 +49G>A variant genotypes (OR, 1.24; 95% CI, 1.18-1.32; $P<0.05$). These findings were also consistent with those of other studies with common types of skin cancer such as melanoma, BCC and SCC (OR, 1.30; 95% CI, 1.10-1.52; $P=0.001$) and were more predominant in Caucasian patients (OR, 1.29; 95% CI, 1.13-1.47; $P<0.005$) (49-51).

A limitation of the present study was its retrospective nature. The analysis of melanoma risk factors was primarily based on empirical data gathered from medical procedures. The differential analysis of the NMSC comorbidity group depending on age (<65 years vs. ≥65 years) may have been influenced by the small sample size of the younger population (the Bonferroni correction was applied). Based on the retrospective analysis of the medical records data regarding patient history and number of sunburn episodes, and patient compliance with the rules of photoprotection could not be obtained; hence, SL was considered as the objective marker of sunburns.

In conclusion, the present study highlighted the importance of closely monitoring patients who show signs of SL on their trunk and upper arms, in terms of the high-risk of developing multiple NMSC and melanoma comorbidity. Understanding the differentiation features may increase the precision of dermoscopic examination of difficult-to-diagnose melanomas by modifying the diagnostic workflow, such as performing RCM rather than multiple biopsies, and more detailed skin examination in this setting.

Given the expected global increase of skin neoplasm and an increasing population of chronically immunosuppressed and hemato-oncological patients in the coming decades, the diagnostic difficulties described in the present study may become increasingly common in everyday practice. The present study highlights the importance of performing skin examinations to avoid an increase in mortality due to late-diagnosed melanomas developing with time in an increasingly younger population of patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MS contributed to the conceptualization, methodology, writing and original draft preparation and project administration. RC performed software handling. MS and RC performed data visualisation and formal analysis. MS, IC and ANG performed data validation. MS, IC, PT, ANG, ML, JK and WO undertook the study investigation. MS and IC acquired resources. MS, IC and PT performed data curation. MS, IC, RC and WO participated in manuscript writing, review and editing. MS and WO were responsible for supervision. MS was responsible for funding acquisition. All authors read and agreed the final version of the manuscript. MS and IC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The Bioethics Commission at the Military Institute of Medicine (Warsaw, Poland) approved the study protocol (#21/WIM/2021, 19 May 2021; No. 65/24, 18 Dec 2024).

Patient consent for publication

Patients signed consent permitting the publication of anonymised photographs.

Competing interests

The authors declare that they have no competing interests.

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