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SYSTEMATIC REVIEW

Melanoma in children: A systematic review and individual patient meta-analysis

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Abstract

The current evidence on paediatric melanoma is heterogeneous, especially regarding the prognosis of different histological subtypes. We sought to systematically review the evidence on paediatric melanoma, highlighting the major sources of heterogeneity and focusing on available data on single patients. A systematic search was performed from 1948 to 25 January 2021. Only studies reporting at least one case of cutaneous melanoma in patients aged ≤18 years were included. Unknown primary and uncertain malignant melanomas were excluded. Three couples of authors independently performed title/abstract screening and two different authors reviewed all the relevant full texts. The selected articles were manually cross-checked for overlapping data for qualitative synthesis. Subsequently data on single patients were extracted to perform a patient-level meta-analysis. PROSPERO registration number: CRD42021233248. The main outcomes were melanoma-specific survival (MSS) and progression-free survival (PFS) outcomes. Separate analyses were done of cases with complete information on histologic subtype, focusing on superficial spreading (SSM), nodular (NM) and spitzoid melanomas, as well as of those classified as *de-novo* (DNM) and acquired or congenital nevus-associated melanomas (NAM). The qualitative synthesis covered 266 studies; however, data on single patients were available from 213 studies including 1002 patients. Among histologic subtypes, NM had a lower MSS than both SSM and spitzoid melanoma, and a lower PFS than SSM. Spitzoid melanoma had a significantly higher progression risk than SSM and trended toward lower mortality. Focusing on nevus-associated status, DNM demonstrated better MSS after progression than congenital NAM, and no differences were highlighted in PFS. Our findings describe the existence of different biological patterns in paediatric melanoma. Specifically, spitzoid melanomas demonstrated intermediate behaviour between SSM and NM and showed a high risk of nodal progression but low mortality. This raises the question of whether spitzoid lesions are being overdiagnosed as melanoma in childhood.

Riccardo Pampena and Vincenzo Piccolo contributed equally.

INTRODUCTION

Cutaneous melanoma is rare in childhood, accounting for about 1% of all paediatric malignancies and a global incidence of 2–5 new cases per million of people per year (in children, 0.7–0.8/million; in adolescents, 10/million).[1–4] In addition to its rarity, melanoma in children frequently displays peculiar features, such as the association with a pre-existing large/giant congenital nevus or the presence of spitzoid features at histopathological examination,[1,5–7] and this suggests a different biological behaviour of paediatric melanoma from the adult counterpart.[3,8,9]

Greater confusion about the prevalence, management and prognosis of melanoma in children has arisen over the years because (i) paediatric melanoma is rare,[1–4] (ii) biologically benign tumours that mimic melanoma morphologically exists in this age group,[1,10–14] and (iii) there is biological and morphological heterogeneity between nevus-associated and *de-novo* melanoma.[15–18]

In detail, the benign proliferations which could mimic melanoma in morphology are Spitz nevi and atypical Spitz nevi. They are primarily called 'juvenile melanoma' by Sophie Spitz.[10–14]

The aim of our systematic review was to offer a comprehensive overview of the current evidence on paediatric melanoma, focusing on specific histopathological features, that is, spitzoid features and nevus-associated status, and their prognostic implications to better identify and try to solve the controversies associated with melanoma in this special age group.

METHODS

Search strategy and data selection

We performed a systematic review and individual patient meta-analysis by searching the PubMed, Embase and Cochrane Central databases for cases of paediatric melanoma from inception to 25 January 2021 using the following search terms: melanoma AND (child OR childhood OR children OR infan* OR pediatr* OR puber*). We included all studies that reported at least one case of histopathologically confirmed primary cutaneous melanoma in patients aged ≤18 years. All article types were included. The cut-off age was not chosen a priori, as we were aware of the high heterogeneity in the definition of paediatric melanoma in the literature.[19–24] The final age cut-off of 18 years was defined by a panel of experts (G.A., C.L., E.M.) on the basis of the most relevant references selected after initial screening.[1,25] Another cut-off was set at 10 years (≤10 vs. >10 years) to differentiate prepubertal from postpubertal patients. The main outcomes were melanoma-specific survival (MSS) and progression-free survival (PFS) outcomes. Separate analyses were done of cases with complete information on histologic subtype, focusing on superficial spreading (SSM), nodular (NM) and spitzoid melanomas, as well as of those classified as *de-novo* (DNM) and acquired or congenital nevus-associated melanomas (NAM).

The same panel of experts decided to exclude cases diagnosed prior to 1948, unless they were undergoing histological review thereafter, because in that year Spitz et al.[11] laid the foundation for paediatric melanoma terminology. Non-cutaneous, transplacental and unknown primary melanomas were also excluded and only articles in the English language were selected. The reference sections of included studies were perused, and experts on the topic were contacted in order to identify all relevant studies and unpublished data.

In order to calculate the total number of paediatric patients with melanoma, all the articles selected for qualitative synthesis were screened for overlapping cases and manually cross-checked for demographic and melanoma-related data, as well as the enrolment period and data on geographic areas. A summary of these data is reported in Table S1, together with the number of paediatric melanoma patients included in each study. When the exact number of patients aged ≤18 years was not available, we reported the number of the nearest age subgroup.

Given the high heterogeneity of data on paediatric melanoma prognosis, we decided to perform a patient level meta-analysis by extracting information on individual cases of paediatric melanoma from the selected studies. Records not reporting data on single patients were excluded at this stage. In patients with multiple synchronous or metachronous melanomas, we included only the cases at the highest stage, because primarily influencing the prognosis. The following information was included into an electronic database (database of individual melanoma cases): study data (type, year of publication, enrolment period, country, number of centres involved), patients (age, gender, syndromes) and melanoma (location, histologic subtype, nevus-associated status, Breslow thickness, ulceration, mitosis, Clark level, sentinel node biopsy [SLNB], metastasis, deaths, therapy administered, time of progression and follow up).

All the individual cases were manually checked for duplicates. Melanocytic lesions of uncertain malignant potential, including atypical Spitz tumours, melanocytic and spitzoid tumours of uncertain malignant potential (MelTUMP and STUMP) were excluded.[10,14,26,27] Three sets of authors (V.P. and T.R., G.B. and E.V.D.B., G.C. and S.P.) independently performed the search and title and abstract screenings. Full texts of relevant papers were subsequently retrieved and independently reviewed by two authors with expertise in conducting systematic reviews and meta-analysis (M.M. and R.P.).

This systematic review was performed in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) proposal and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines where feasible.[28,29] Figure 1 summarizes the search strategy.

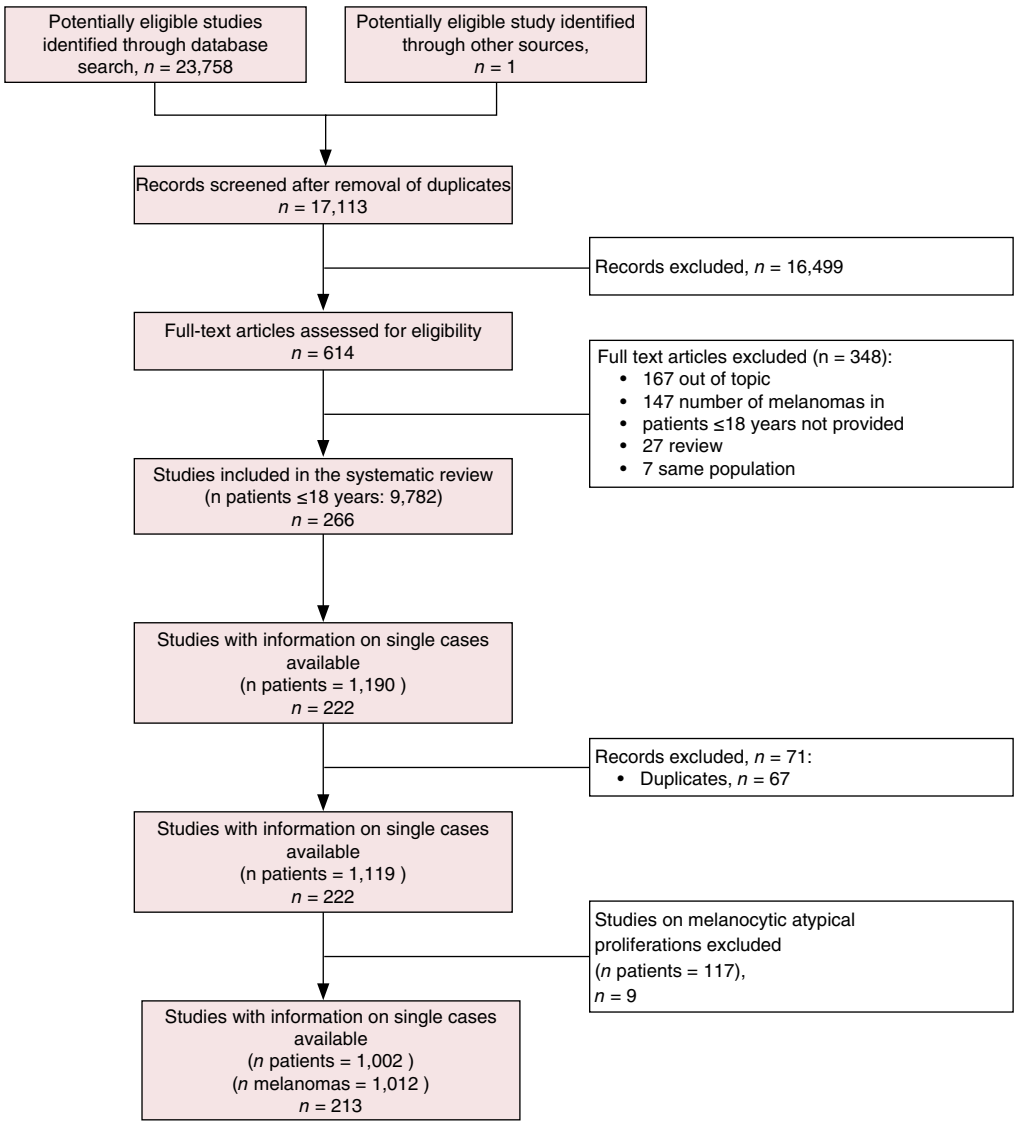

FIGURE 1 Study flowchart of search results and study selection.

The review protocol was registered in PROSPERO (registration No. CRD42021233248).

Two investigators (M.L. and R.P.) assessed the quality of reporting for the included records based on previously published guidelines.[30]

A separate systematic search was performed by two investigators (M.L. and R.P.) on the PubMed, Embase and Cochrane Central electronic databases for cases of transplacental melanoma, using the following keywords: (transplacent* OR placent*) AND melanoma. The flowchart of search results and study selection is reported in Figure S1. These results were combined with the cases detected by the search on paediatric melanoma and previously excluded. Only records describing transplacental transmission from mother to newborn with histopathologically verified melanoma in the English language were included.

Please refer to Appendix S1 for statistical analysis.

RESULTS

Study selection

After the removal of duplicates, a total of 17,113 articles were identified in the initial search. Subsequently, 16,499 records were excluded based on title/abstract and language screening and 614 full-text studies were assessed for eligibility. Upon full-text examination, 341 articles were excluded: 167 due to irrelevance; 147 because the number of melanomas

in patients aged ≤18 years was not provided; 27 because they were reviews without original data; and seven because they included the same cases of other studies.

Of the 266 selected records, a total of 22,408 patients with melanoma were reported, with 9782 patients definitively identified as aged ≤18 years (Figure 1).[2–4,6–12,14,19,21–25,31–279] However, most of the included studies had potential overlaps (60.2%, *n*: 160), making data combination impossible (Table S1). Data on individual cases were available for 222/266 (83.5%) studies, accounting for 1190 patients. At this stage, 67 cases were excluded because of duplicates and another four because of too little data.

Finally, 117 patients with atypical melanocytic tumours with uncertain malignant potential were excluded. The result was a total number of 1002 patients with paediatric melanoma from 213 studies that were included in the database of individual cases. Of them, eight had a total of 10 synchronous or metachronous melanomas. The clinical and histologic features of the excluded tumours with uncertain malignant potential are summarized in Table S2.

Study population

Studies

The 213 selected studies were published from 1954 to 2020 and included cases from 42 different countries in five continents, with a predominance of patients from the United States (369 patients; 36.8%). The number of patients included per study ranged from 1 to 60 (Table S3). The majority of the selected studies were case reports including one (98 articles) or two patients (11 articles), followed by observational studies with retrospective and retrospective-prospective patient enrolment (98 and 2, respectively). Two observational prospective studies and two clinical trials were also included. In 61 out of 100 retrospective studies, expert pathologists reassessed histologic slides.

Among the retrospective studies, seven retrieved cases from national cancer registries (Sweden, Finland, Denmark, Ireland, Slovenia and Puerto Rico)[71,177,206,216,227,231,242]; one was a multicentric study promoted by the European Organisation for Research and Treatment of Cancer (EORTC)-Melanoma Cooperative Group, including the Netherlands national cancer registry[22]; two included cases from the provincial cancer registry of Alberta[39,253]; five studies retrieved cases from large population-based databases from Wales,[34] Scotland,[167] British Columbia,[85] Olmsted County and South Korea; and two studies were from the Division of Cancer Epidemiology and Genetics at the National Cancer Institute (United States).[115,174,196,274] Moreover, 11 retrospective studies were multicentric, while 72 were monocentric (Table S1).

Patients

Table 1 summarizes demographic, clinical and melanoma-related features of the 1002 patients with melanoma

TABLE 1 Demographics, clinical and melanoma-related characteristics of the study population (1002 patients from 213 studies).

Variables	*N* (total: 1002)
Median age—years (IQR) (*n*: 992)	12 (6–15)
Sex (*n*: 967)	
M	443 (45.8%)
F	524 (54.2%)
Location (*n*: 940)	
HN	259 (27.6%)
Trunk	254 (27%)
Limbs	365 (38.8%)
Multiple sites	6 (0.6%)
Other (genital, Acral, ungueal)	56 (6%)
Histotype (*n*: 544)	
Spitzoid/spindle cells	108 (19.9%)
SSM	231 (42.5%)
NM	148 (27.2%)
ALM	16 (2.9%)
LMM	1 (0.2%)
Nevoid	9 (1.7%)
Animal-type	7 (1.3%)
Desmoplastic	6 (1.1%)
PEM	5 (0.9%)
Malignant blue nevus	5 (0.9%)
Small cell variant	5 (0.9%)
Polypoid	3 (0.6%)
Nevus-association status (*n*: 691)	
DNM	418 (60.5%)
NAM acquired	84 (12.1%)
NAM congenital	189 (27.4%)
Not specified	60 (31.7%)
Small	35 (18.5%)
Medium	10 (5.3%)
Large/giant	84 (44.4%)
Median Breslow's thickness—mm (IQR) (*n*: 656)	2.3 (1–4.2)
In situ (*n*: 844)	
No	787 (93.2%)
Yes	57 (6.8%)
Ulceration (*n*: 367)	154 (42.0%)
Mitosis (*n*: 263)	229 (87.1%)
Median FUP time (months) to death or latest alive (IQR) (*n*: 829)	36 (14–84)
Death for melanoma (*n*: 916)	
Yes	261 (26.0%)
Lost to follow up	18 (1.8%)
Median time (months) to any progression (IQR) (*n*: 157)	12 (5–24)
Metastasis (*n*: 855)	474 (55.4%)
Mets at diagnosis (*n*: 855)	188 (22.0%)
Metastasis location (*N*: 474)	

TABLE 1 (Continued)

Variables	*N* (total: 1002)
Local	19 (4%)
Nodal	214 (45.1%)
Distant	69 (14.6%)
Local + nodal	12 (2.5%)
Local + distant	6 (1.3%)
Nodal + distant	75 (15.8%)
Local + nodal + distant	15 (3.2%)
Not reported	64 (13.5%)
SLNB (*n*: 229)	
Positive	134 (58.5%)
Not reported	4 (1.7%)
CLND (*n*: 134)	
Not performed	5 (3.7%)
Yes	101 (75.4%)
Refused	1 (0.7%)
Not specified	27 (20.1%)
Medical treatment (*n*: 613)	247 (40.3%)

Abbreviations: CLND, complete lymph node dissection; FUP, follow up; IQR, interquartile range; SLNB, sentinel lymph node biopsy.

included in the quantitative synthesis. The median age was 12 years (interquartile range [IQR]: 6–15), with a slight predominance of girls (54.2%). Melanomas were mainly located on the limbs (38.8%), followed by head and neck and trunk in similar proportions; only 6.8% were in situ, and the median Breslow thickness of invasive cases was 2.3 mm (IQR: 1–4.2). Histologic subtypes were reported in 54.3% (*n*: 544) of cases, with a predominance of SSM (42.5%), followed by NM (27.2%) and spitzoid/spindle cells melanomas (19.9%).

Information on nevus-associated status was available in 69% (*n*: 692) of cases: NAM was 39.5%, with a cNAM prevalence (27.4%). The sizes of cNAMs were reported in 129 cases and there was a predominance of large/giant nevi (44.4%). The majority of spitzoid melanomas with known nevus-associated status were DNMs (81.0%; 51/63), and no spitzoid melanomas were associated with medium to giant cNAMs. The proportions of nevus-associated SSMs and NMs were similar (43%; 74/172 and 40.2%; 47/117, respectively). However, SSMs were associated more with acquired nevi (25%, *n*: 43) and NMs with congenital nevi (33.3%, *n*: 39).

Interestingly, the proportion of both spitzoid melanomas and NAMs decreased with age. More precisely, cNAMs decreased while aNAMs slightly increased. In particular, in patients aged ≤10 years, melanomas were spitzoid in 38.7% of cases, SSMs in 29.4%, NMs in 32.0% and NAMs were 48.3%, with a cNAM prevalence of (39.5%). Patients aged >10 years, however, had a predominance of SSMs (59.0%), followed by NMs (29.7%) and spitzoid melanomas (11.4%). NAM was 31.6%, with similar proportions of aNAMs (15.4%) and cNAMs (16.2%; Figure S2).

Concerning prognosis, 188/855 (22.0%) patients were diagnosed with local, nodal or distant metastasis and 286 (33.4%) developed metastasis during follow up. The median follow-up time was 36 months (IQR: 14–84), with progression occurring after a median time of 12 months (IQR: 5–24). Metastases were only nodal in the majority of cases (214/474; 45.1%), including 134/229 (58.5%) positive SLNBs. In all, 261/916 (26.0%) patients died of melanoma, and 18 (1.8%) were lost to follow up.

Therapy

Data on therapy were available on 613 patients, of which 249 (40.6%) received medical or radiation therapy for curative, neoadjuvant, adjuvant or palliative purposes. Only 35 (5.7%) received immune or targeted therapy, of which 14 were treated with BRAF inhibitors (BRAFi), 18 with immune checkpoint inhibitors (ICI) and three with both BRAFi and ICI. Data on targeted therapy are reported in Table S4.

Regarding other therapies, chemotherapy and IFNα2b were the most frequently administered therapies (112 and 111 patients, respectively), followed by radiotherapy (47), a minority of cases received IL-2 (10), bacillus Calmette-Guerin (6), palliative treatment (2), granulocyte-macrophage colony-stimulating factor (1) or vaccine (peptide vaccine with IL-2) (1). Out of 233 for whom data on therapy were available, 110 died of melanoma.

Spitzoid melanoma

Complete data on melanoma histologic subtypes were available for 54.3% (*n*: 544) of cases. We focused on the three most reported subtypes (SSM, NM and spitzoid melanoma) that accounted for the majority of cases (*n*: 487; 89.5%). When comparing these groups, we found significant differences in age, location and Breslow thickness. Patients with spitzoid melanomas were indeed younger, and tumours were more frequently located on the limbs than the other subtypes. Breslow thickness of spitzoid melanoma was higher than SSM but lower than NM. Moreover, with the exception of one spitzoid case, all the NMs and spitzoid melanomas were invasive, while 18.2% (*n*: 41) of SSMs were in situ.

Histologic ulceration was more frequently seen among spitzoid melanomas and NMs than in SSMs. The same trend was also registered for metastases, with spitzoid melanomas harbouring the highest risk of progression followed by NMs and SSMs. Notably, most of the spitzoid melanomas underwent only nodal progression (72.6%). No differences in time progression were observed between spitzoid and non-spitzoid melanomas, but a significantly lower follow-up time was reported for spitzoid melanomas than the other two subtypes.

A lower number of patients died from melanoma in the spitzoid and SSM groups as compared to NM (Table 2). A survival analysis was performed to assess the influence of follow-up time on melanoma-related deaths for spitzoid and non-spitzoid melanomas (Figure 2; Table 3).

TABLE 2 Demographics, clinical and melanoma-related characteristics of spitzoid versus non-spitzoid melanomas.

	Histologic subtypes (*N*: 488)					
		Non-spitzoid				
Variables	**Spitzoid (*n*: 108)**	**SSM + NM (379)**	**SSM (*n*: 231)**	**NM (*n*: 148)**	**#*p* value***	**#*p* value****
Median age—years (IQR)	8 (4.3–11.9); 108	13 (9–16); 376	13.8 (10.1–16); 228	12.8 (6–15); 148	<0.001	<0.001
Sex						
M	60 (57.1%)	171 (45.2%)	102 (44.2%)	69 (46.9%)	0.102	0.031
F	45 (42.9%)	207 (54.8%)	129 (55.8%)	78 (53.1%)		
Location						
HN	33 (32.0%)	85 (23.5%)	43 (19.7%)	42 (29.4%)	0.001	0.001
Trunk	11 (10.7%)	109 (30.2%)	61 (28%)	48 (33.6%)		
Limbs	51 (49.5%)	149 (41.3%)	100 (45.9%)	49 (34.3%)		
Multiple sites	0 (0%)	2 (0.6%)	1 (0.5%)	1 (0.7%)		
Other (genital. acral. ungueal)	8 (7.8%)	16 (4.4%)	13 (6%)	3 (2.1%)		
Median Breslow's thickness—mm (IQR)	3.3 (1.9–4.5); 74	1.9 (0.9–4); 297	1 (0.6–1.9); 166	3.5 (2.2–5.5); 131	<0.001	<0.001
In situ						
No	99 (99%)	330 (88.9%)	184 (81.8%)	146 (100%)	<0.001	0.002
Yes	1 (1%)	41 (11.1%)	41 (18.2%)	0 (0%)		
Ulceration						
No	30 (56.6%)	92 (59%)	59 (72%)	33 (44.6%)	0.002	0.762
Yes	23 (43.4%)	64 (41%)	23 (28%)	41 (55.4%)		
Mitosis						
No	3 (7%)	14 (10.9%)	11 (15.9%)	3 (5%)	0.088	0.461
Yes	40 (93%)	115 (89.1%)	58 (84.1%)	57 (95%)		
Median FUP time (months) to death or latest alive (IQR)	26 (14.5–47.5); 93	48 (17–94.5); 321	60 (21.3–96); 192	39 (12–88); 129	<0.001	0.003
Death for melanoma						
No	88 (88.0%)	255 (73.1%)	178 (84.8%)	77 (55.4%)	<0.001	0.002
Yes	12 (12.0%)	94 (26.9%)	32 (15.2%)	62 (44.6%)		
Median time (months) to any progression (IQR)	10 (6–13); 15	7.6 (4.5–18.5); 46	10.5 (4.7–19.5); 24	6.6 (4.4–17.8); 22	0.582	0.788
SNB result						
Negative	21 (33.3%)	32 (42.7%)	18 (52.9%)	14 (34.1%)	0.122	0.261
Positive	42 (66.7%)	43 (57.3%)	16 (47.1%)	27 (65.9%)		
Metastasis						
No	28 (27.7%)	168 (55.8%)	129 (71.7%)	39 (32.2%)	<0.001	<0.001
Yes	73 (72.3%)	133 (44.2%)	51 (28.3%)	82 (67.8%)		
Metastasis at diagnosis						
No	15 (32.6%)	46 (44.7%)	24 (60%)	22 (34.9%)	0.014	0.167
Yes	31 (67.4%)	57 (55.3%)	16 (40%)	41 (65.1%)		
Metastasis location						
Local	2 (2.7%)	4 (3%)	3 (5.9%)	1 (1.2%)	0.02	0.03
Nodal	53 (72.6%)	62 (46.6%)	18 (35.3%)	44 (53.7%)		
Distant	2 (2.7%)	11 (8.3%)	6 (11.8%)	5 (6.1%)		
Nodal + local	3 (4.1%)	6 (4.5%)	2 (3.9%)	4 (4.9%)		
Distant + nodal	8 (11.0%)	23 (17.3%)	11 (21.6%)	12 (14.6%)		
Distant + local	0 (0%)	1 (0.8%)	1 (2%)	0 (0%)		
Distant + nodal + local	0 (0%)	5 (3.8%)	1 (2%)	4 (4.9%)		
Not reported	5 (6.8%)	21 (15.8%)	9 (17.6%)	12 (14.6%)		

TABLE 2 (Continued)

Variables	Histologic subtypes (*N*: 488)					
		Non-spitzoid				
	Spitzoid (*n*: 108)	SSM + NM (379)	SSM (*n*: 231)	NM (*n*: 148)	#*p* value*	#*p* value**
Clark level						
1	1 (2.7%)	41 (16.8%)	41 (26.8%)	0 (0%)	<0.001	<0.001
2	1 (2.7%)	41 (16.8%)	30 (19.6%)	11 (12.1%)		
3	4 (10.8%)	53 (21.7%)	40 (26.1%)	13 (14.3%)		
4	22 (59.5%)	83 (34%)	37 (24.2%)	46 (50.5%)		
5	9 (24.3%)	26 (10.7%)	5 (3.3%)	21 (23.1%)		

Abbreviations: FUP, follow up; IQR, interquartile range; SNB, sentinel lymph node biopsy.

#$p < 0.01$.

*Superficial spreading melanoma (SSM) versus nodular melanoma (NM) versus spitzoid melanoma.; **Non-spitzoid versus spitzoid.

distant metastases was found in congenital NAM (51.0%). The lowest number was seen in DNM; however, DNM had the highest proportion of nodal metastases (34.9%).

The proportion of melanoma deaths was higher in NAMs than in DMNs due to the higher mortality in cNAM (Table 4). Survival analysis failed to demonstrate significant differences between DNMs and NAMs in MSS, even when only metastatic cases were considered (Figure 3; Table 5). However, when comparing the three subgroups (DNM, aNAM and cNAM), significant differences were seen, with cNAM showing a higher mortality risk than both aNAM and DNM. The same scenario was observed when restricted to metastatic melanoma patients.

No significant differences in PFS were observed between DNMs and NAMs. When splitting aNAMs and cNAMs, a trend toward a higher progression risk for cNAM, followed by DNM and aNAM could be seen. However, any significant differences disappeared when adjusting for age and Breslow thickness in Cox regression analysis.

Transplacental melanoma

We selected 8 cases from 10 articles (two articles described the same cases) reporting transplacental transmission of melanoma, which are summarized in Table S5.[280–289] The mean age at diagnosis was 5.3 months (range: 0.37–10), six were males, most of them presenting multiple localisations of melanoma metastasis at diagnosis. The number of melanoma-related deaths was 5, and three patients underwent spontaneous regression.

DISCUSSION

In this systematic review on paediatric melanoma, we investigated and clarified several aspects of this peculiar entity. We performed a comprehensive analysis of the published literature on paediatric melanoma and included 266 articles in the qualitative synthesis that accounted for more than 22,000 patients. We were not able to define the real number of unique cases due to the tangled net of possible overlaps among studies, enrolling cases from the same geographic regions, registries or databases and because of the variability of definitions used for paediatric melanoma. After reviewing the most relevant studies on this topic, we decided to set the upper age limit at 18 years.[1,25] However, several studies placed the cut-off at either a younger or older age, making it nearly impossible to precisely estimate the number of enrolled patients aged ≤18 years.[19–24]

To perform a quantitative synthesis, we selected studies that reported data on single cases, focusing our analysis on spitzoid versus non-spitzoid melanomas and on DNMs versus NAMs. We found that spitzoid melanomas had a hybrid biological behaviour, with a risk of metastasis similar to NM and higher than SSM, even when adjusting for age and Breslow thickness. In contrast, the risk of death in spitzoid melanoma was similar to SSM and lower than NM.

These findings depict a blurred picture, in which the limits of spitzoid melanoma and atypical Spitz tumour appear less defined than expected.[1,10,26,82,290] Indeed, lesions classified as spitzoid melanoma showed a more indolent behaviour than non-spitzoid melanomas, despite harbouring higher Breslow thickness and more propensity to SLNB positivity and nodal metastasis in general. Together with the higher occurrence of spitzoid melanoma in children younger than 10 years, these findings suggest that a variable proportion of spitzoid melanomas of our series might be better classified as atypical spitzoid proliferations.

Nevus-associated melanoma accounted for 39.5% of paediatric melanomas, which is almost 10% more than those occurring in adults.[17,18,291,292] Interestingly, the proportion of NAMs was higher among patients ≤10 years, reaching almost a half of cases (48.3%), but after the age of 10 years it showed similar values as in adults (31.6%).[17,281] The observed differences are essentially due to the higher number of melanomas associated with congenital nevi in younger patients, and this confirms that congenital nevus is one of the major risk factors for melanoma in early childhood.[5]

In the survival analysis, after adjustment for Breslow thickness and age, DNM showed a similar metastatic profile as cNAM, but a lower mortality after progression. This might be

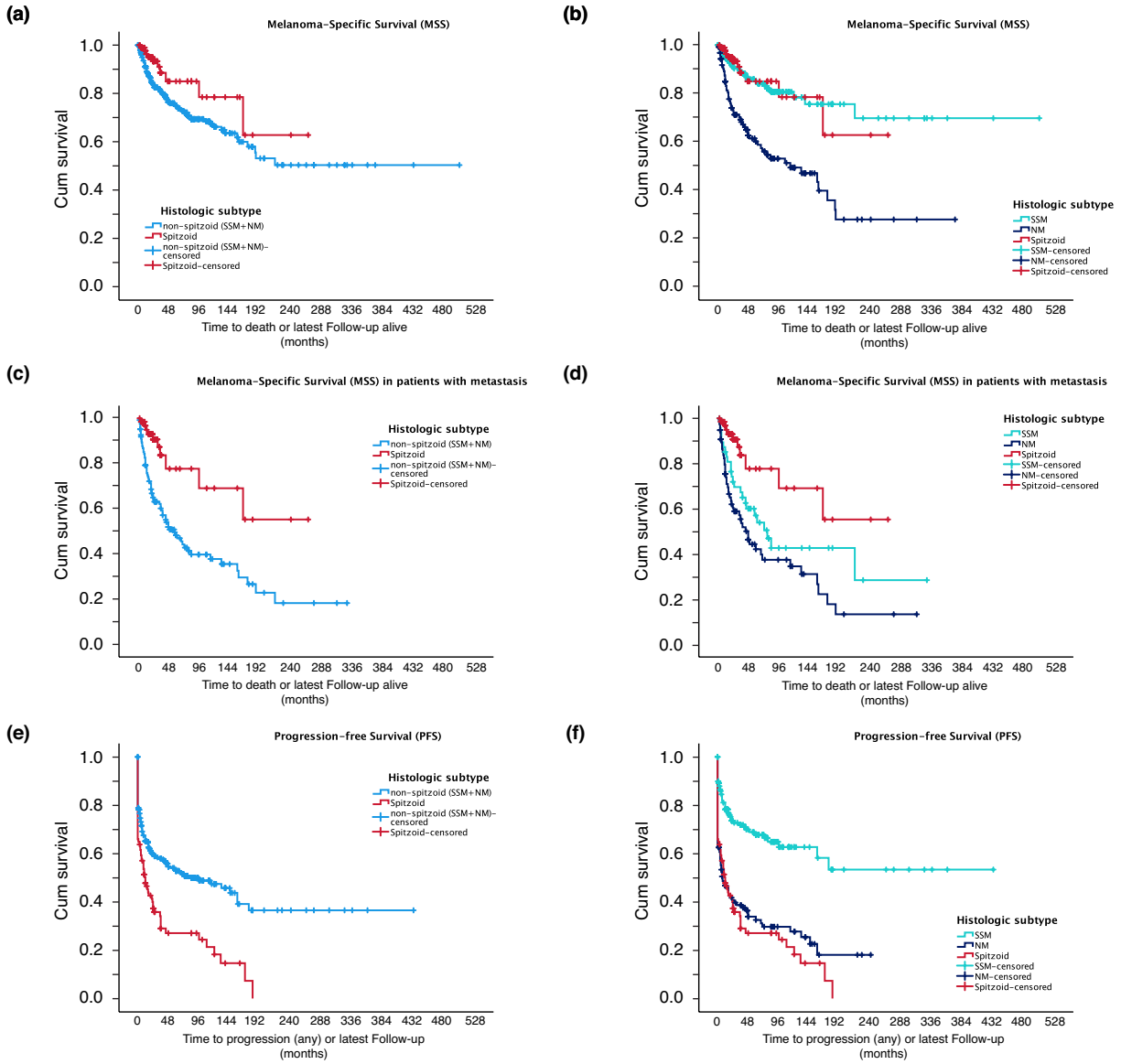

FIGURE 2 Kaplan–Meier curves for (a, b) MSS, (c, d) MSS in patients with metastasis and (e, f) PFS. (a, c, e) Comparison of spitzoid versus non-spitzoid melanoma and (b, d, f) spitzoid melanomas versus superficial spreading melanoma (SSM) and nodular melanoma (NM).

Kaplan–Meier and Cox regression analyses showed no significant differences between SSMs and spitzoid melanomas, but both of these subtypes had lower mortality than NMs.

In the subgroup of patients with metastases, the only group at risk for melanoma-related deaths, we were no longer able to detect significant differences between SSMs and NMs, while lower mortality for spitzoid melanomas as compared to NMs persisted, even when adjusting for age and Breslow thickness.

The PFS analysis demonstrated that spitzoid melanomas were significantly more at risk for metastasis than non-spitzoid lesions, as the tendency of SSMs to progress was lower than both spitzoid melanomas and NMs. The same results were observed after adjusting for age and Breslow thickness.

Nevus-associated melanoma

The nevus-associated status of melanomas was provided for 691 (69%) patients and classified as DNM, aNAM or cNAM. When comparing these three subtypes, we found significant differences in age, location and Breslow thickness. In particular, patients with cNAM were significantly younger than those with aNAM and DNM.

With regard to location, NAM was most often located on the trunk (35.1%), and DNM appeared more often on the limbs (42.0%). No differences were observed in median Breslow thickness between DNM and NAM; however, aNAMs appeared to be significantly thinner than both DNMs and cNAMs.

Concerning prognosis, no differences were observed between DNMs and NAMs according to the number of metastases and progression time. The highest proportion of

TABLE 3 MSS and PFS analysis for spitzoid versus non-spitzoid (SSM and NM) melanomas.

			Cox's regression analysis							
				99% CI for HR				99% CI for aHR		
Survival analysis	Variables	Log rank	HR	Lower	Upper	#*p* value	aHR	Lower	Upper	#*p* value
MSS	Histologic subtype (non-spitzoid vs. spitzoid)	0.043	0.85	0.68	1.05	0.047	0.77	0.53	1.11	0.064
	SSM		ref.				ref.			
	NM	<0.001	3.16	1.76	5.68	<0.001	3.18	1.68	6.01	<0.001
	Spitzoid	0.882	0.93	0.36	2.39	0.847	0.78	0.18	3.30	0.651
	Spitzoid		ref.				ref.			
	NM	<0.001	3.41	1.40	8.30	<0.001	4.10	1.05	15.97	0.008
MSS in patients with metastasis	Histologic subtype (non-spitzoid vs. spitzoid)	<0.001	0.75	0.60	0.93	<0.001	0.75	0.54	1.04	0.022
	SSM		ref.				ref.			
	NM	0.122	1.48	0.77	2.85	0.120	1.84	0.88	3.86	0.034
	Spitzoid	0.016	0.40	0.15	1.05	0.014	0.49	0.12	1.96	0.183
	Spitzoid		ref.				ref.			
	NM	<0.001	3.75	1.52	9.25	<0.001	3.78	1.05	13.69	0.008
PFS	Histologic subtype (non-spitzoid vs. spitzoid)	<0.001	1.18	1.07	1.30	<0.001	1.15	1.02	1.30	0.003
	SSM		ref.				ref.			
	NM	<0.001	2.85	1.78	4.56	<0.001	2.67	1.58	4.51	<0.001
	Spitzoid	<0.001	3.19	1.96	5.19	<0.001	3.06	1.70	5.51	<0.001
	Spitzoid		ref.				ref.			
	NM	0.425	0.89	0.58	1.37	0.498	0.87	0.53	1.44	0.478

Note: Log rank test and Cox regression analysis are reported; hazard ratios (HR) are adjusted for Breslow's thickness and age (aHR).

Abbreviations: CI, confidence interval; NM, nodular melanoma; SSM, superficial spreading melanoma.

#$p < 0.01$.

due to the fact that cNAM is known to have a worse prognosis than both aNAM and DNM, especially, when associated with a large-giant congenital nevus. Another reason might be related to a certain propensity to misclassify melanocytic lesions that morphologically resemble DNMs but are biologically benign. Indeed, the majority of spitzoid melanomas were classified as DNMs (81.0%). Based on these data, we were able to identify three biological patterns of paediatric melanoma.

The first includes SSM, that often arises after the age of 10 years, and that is associated with an acquired nevus in 25% of cases, showing biological behaviour similar to melanomas of adulthood.[9,111] The second includes NMs that in one-third of cases, arises in association with a congenital nevus in early childhood and harbours ab initio more aggressive behaviour.[65] The third pattern includes spitzoid melanoma, that arises as DNM in patients aged ≤10 years and harbours a higher Breslow thickness and a higher propensity for nodal involvement but shows a more indolent biological behaviour and a better prognosis.[7,53,124] Whether the latter subtype represents a true category of biologically more indolent melanomas or a mixed pot of benign and malignant melanocytic tumours remains to be fully elucidated.

Our systematic review has a number of limitations related to the difficulty in defining the true number of unique paediatric melanoma cases reported in the literature and to the variability of paediatric melanoma definitions, as previously discussed. To minimize this bias, we tried to draw an accurate and realistic picture of the current evidence on this topic by retrieving comprehensive data on a large sample of patients with paediatric melanoma and following proper methodology and a rigorous statistical approach. In addition, we excluded cases that fell in the spectrum of atypical melanocytic proliferations, and most of the included cases from retrospective studies were revised by expert pathologists. Despite the efforts above, the patients included in this study can hardly be considered as originating from the same population. As meta-analytical methods are tailored to using studies rather than patients as the unit of analysis, we elected to use 99% confidence intervals in order to be more conservative and reduce Type I error.

In conclusion, melanomas in children are rare, even more so in prepubertal age, and the histopathologic diagnosis of melanoma should be always discussed with a pathologist and a second opinion by an expert pathologist should be obtained. This is especially the case when dealing with lesions classified as spitzoid melanoma that still represent a grey-zone category of lesions where morphologic features do not always correlate with biologic behaviour.

TABLE 4 Demographics, clinical and melanoma-related characteristics of de-novo versus nevus-associated melanomas.

	Nevus-association status (692)					
		NAM				
Variables	**DNM (419)**	**aNAM+cNAM (273)**	**aNAM (84)**	**cNAM (189)**	**#p value***	**#p value****
Age	12 (7.8–14.9); 414	9.3 (3–14); 272	13 (10–16); 84	6 (2–13); 188	<0.001	<0.001
Sex						
M	188 (45.9%)	121 (46.5%)	37 (44%)	84 (47.7%)	0.839	0.862
F	222 (54.1%)	139 (53.5%)	47 (56%)	92 (52.3%)		
Location						
HN	111 (27.9%)	67 (25.9%)	16 (19.3%)	51 (29%)	<0.001	<0.001
Trunk	97 (24.4%)	91 (35.1%)	29 (34.9%)	62 (35.2%)		
Limbs	167 (42.0%)	73 (28.2%)	29 (34.9%)	44 (25%)		
Multiple sites	0 (0%)	6 (2.3%)	1 (1.2%)	5 (2.8%)		
Other (genital. acral. ungueal)	23 (5.8%)	22 (8.5%)	8 (9.6%)	14 (8%)		
Breslow	2.5 (1.2–4.4); 309	2 (0.9–4.6); 139	1.6 (0.65–2.6); 51	2.75 (1.05–6.905); 88	<0.001	0.172
In situ						
No	340 (95%)	180 (89.1%)	62 (82.7%)	118 (92.9%)	0.001	0.010
Yes	18 (5%)	22 (10.9%)	13 (17.3%)	9 (7.1%)		
Ulceration						
No	106 (61.3%)	42 (56.8%)	22 (73.3%)	20 (45.5%)	0.047	0.507
Yes	67 (38.7%)	32 (43.2%)	8 (26.7%)	24 (54.5%)		
Mitosis						
No	22 (17.3%)	0 (0%)	0 (0%)	0 (0%)	0.001	<0.001
Yes	105 (82.7%)	68 (100%)	20 (100%)	48 (100%)		
Time FUP (months) to death or latest alive	38.5 (17–93); 342	36 (12–84.5); 233	77 (21–157.5); 70	32 (12–78); 163	0.001	0.426
Death for melanoma						
No	270 (73.4%)	155 (62.5%)	62 (83.8%)	93 (53.4%)	<0.001	0.004
Yes	98 (26.6%)	93 (37.5%)	12 (16.2%)	81 (46.6%)		
Time to progression (any) (months)	12 (7–22.5); 53	8 (3–23.3); 38	21 (8–55.5); 9	7 (3–17.5); 29	0.027	0.189
SNB result						
Negative	26 (31.3%)	17 (42.5%)	6 (60%)	11 (36.7%)	0.334	0.265
Positive	54 (65.1%)	23 (57.5%)	4 (40%)	19 (63.3%)		
Not reported	3 (3.6%)	0 (0%)	0 (0%)	0 (0%)		
Metastasis						
No	165 (46.6%)	93 (41.7%)	44 (64.7%)	49 (31.6%)	<0.001	0.248
Yes	189 (53.4%)	130 (58.3%)	24 (35.3%)	106 (68.4%)		
Mets at diagnosis						
No	53 (37.9%)	38 (38.8%)	9 (45%)	29 (37.2%)	0.8	0.886
Yes	87 (62.1%)	60 (61.2%)	11 (55%)	49 (62.8%)		
Metastasis location						
Local	3 (1.6%)	5 (3.8%)	2 (8.3%)	3 (2.8%)	0.009	0.013
Nodal	104 (55.0%)	43 (33.1%)	10 (41.7%)	33 (31.1%)		
Distant	28 (14.8%)	24 (18.5%)	3 (12.5%)	21 (19.8%)		
Nodal + local	3 (1.6%)	2 (1.5%)	0 (0%)	2 (1.9%)		
Distant + nodal	30 (15.9%)	27 (20.8%)	2 (8.3%)	25 (23.6%)		
Distant + local	3 (1.6%)	3 (2.3%)	1 (4.2%)	2 (1.9%)		
Distant + nodal + local	5 (2.6%)	6 (4.6%)	0 (0%)	6 (5.7%)		
Not reported	13 (6.9%)	20 (15.4%)	6 (25%)	14 (13.2%)		

(Continues)

TABLE 4 (Continued)

Variables	Nevus-association status (692)					
		NAM				
	DNM (419)	aNAM+cNAM (273)	aNAM (84)	cNAM (189)	#*p* value*	#*p* value**
Clark level						
1	18 (7.6%)	22 (18.3%)	13 (27.1%)	9 (12.5%)	<0.001	<0.001
2	27 (11.4%)	22 (18.3%)	9 (18.8%)	13 (18.1%)		
3	46 (19.4%)	23 (19.2%)	12 (25%)	11 (15.3%)		
4	115 (48.5%)	29 (24.2%)	12 (25%)	17 (23.6%)		
5	31 (13.1%)	24 (20%)	2 (4.2%)	22 (30.6%)		

Abbreviations: FUP, follow up; SNB, sentinel node biopsy.

#$p < 0.01$.

*DNM versus acquired NAM (aNAM) versus congenital NAM (cNAM); **DNM versus NAM.

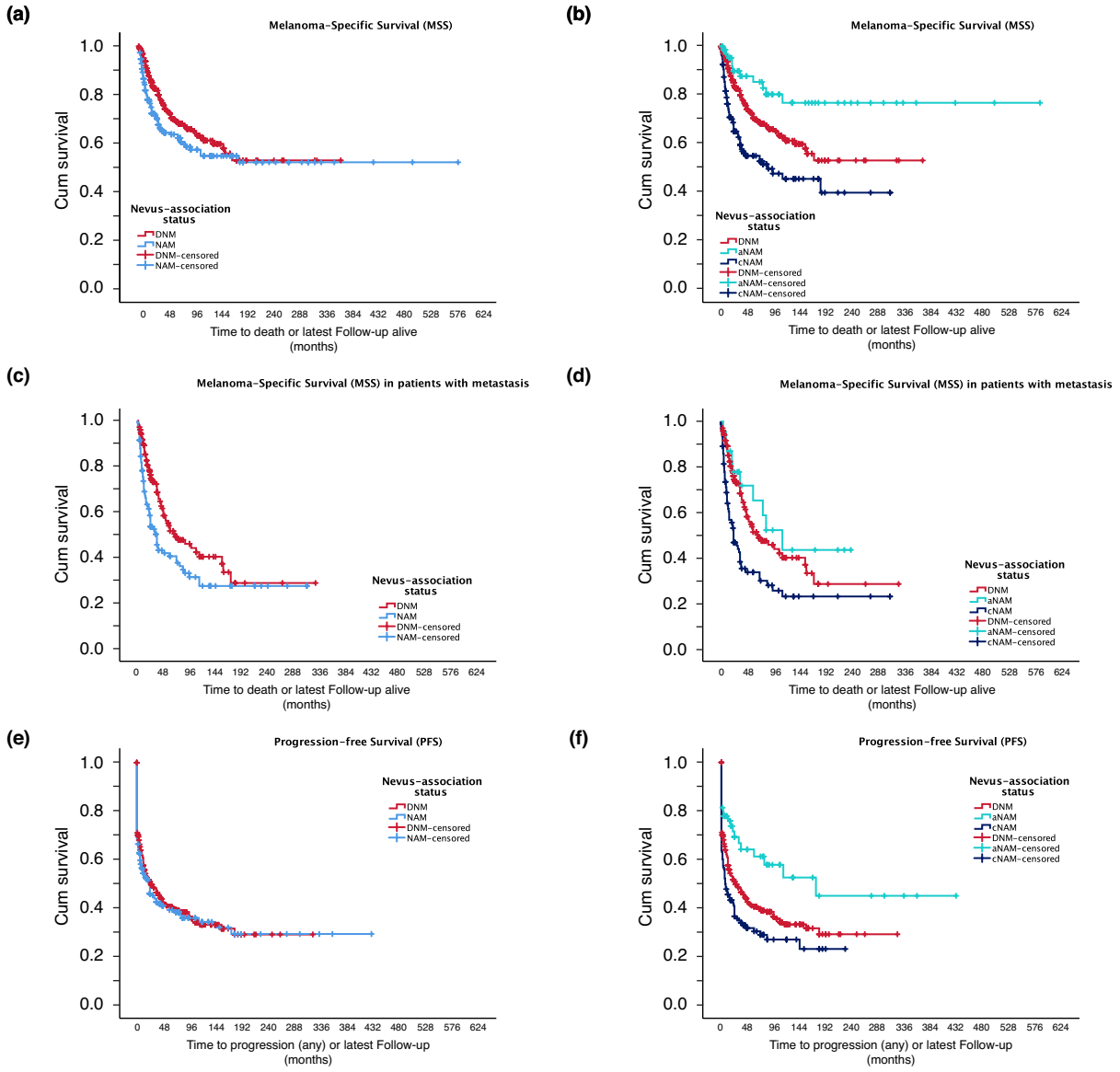

FIGURE 3 Kaplan–Meier curves for (a, b) MSS, (c, d) MSS in patients with metastasis and (e, f) PFS. (a, c, e) Comparison of nevus-associated melanomas (NAM) versus de-novo melanomas (DNM) and (b, d, f) acquired and congenital NAM (aNAM and cNAM) versus DNM.

TABLE 5 MSS and PFS analysis for nevus-associated (NAM) versus de-novo (DNM) melanomas.

Survival analysis	Variables	Log rank	Cox's regression analysis							
				99% CI for HR				99% CI for aHR		
			HR	Lower	Upper	#p vaue	aHR	Lower	Upper	#p value
MSS	Nevus-association status (DNM vs. NAM)	0.042	1.36	0.92	2.02	0.043	1.09	0.62	1.91	0.700
	DNM		ref.				ref.			
	aNAM	0.019	0.49	0.22	1.12	0.026	0.39	0.13	1.20	0.030
	cNAM	<0.001	1.87	1.24	2.82	<0.001	1.80	0.97	3.33	0.014
	cNAM		ref.				ref.			
	aNAM	<0.001	0.26	0.11	0.60	<0.001	0.22	0.07	0.72	0.001
MSS in patients with metastasis	Nevus-association status (DNM vs. NAM)	0.005	1.60	1.03	2.47	0.006	1.54	0.82	2.89	0.080
	DNM		ref.				ref.			
	aNAM	0.398	0.80	0.33	1.90	0.499	0.59	0.17	2.00	0.263
	cNAM	<0.001	1.92	1.22	3.03	<0.001	2.52	1.24	5.09	<0.001
	cNAM		ref.				ref.			
	aNAM	0.014	0.41	0.17	1.00	0.010	0.23	0.06	0.89	0.005
PFS	Nevus-association status (DNM vs. NAM)	0.628	1.05	0.78	1.43	0.655	0.80	0.52	1.24	0.187
	DNM		ref.				ref.			
	aNAM	0.008	0.58	0.33	1.03	0.015	0.54	0.25	1.15	0.036
	cNAM	0.018	1.31	0.95	1.82	0.032	0.98	0.59	1.63	0.923
	cNAM		ref.				ref.			
	aNAM	<0.001	0.44	0.24	0.81	<0.001	0.55	0.23	1.31	0.076

Note: Log rank test and Cox regression analysis are reported; hzard ratios (HR) are adjusted for Breslow's thickness and age (aHR).
Abbreviation: aNAM and cNAM, acquired and congenital nevus-associated melanoma; CI, confidence interval.
#$p < 0.01$.

AUTHOR CONTRIBUTION

V.P., R.P., G.A., E.M., M.M., A.K., M.L. contributed to study concept and design, interpretation of data and writing of the report. R.P. and A.K. performed statistical analysis. T.R., V.P., S.P., G.C., G.B. and E.V.D.B. contributed to study search and title/abstract screening. M.M. and R.P. performed full-text examination and data extraction. All authors approved the final version of the report.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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