

Prognostic value of ulceration varies across Breslow thicknesses and clinical stages in acral melanoma: a retrospective study*

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Summary

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Conflicts of interest

J.G. serves as a consultant or is on advisory boards for MSD, Roche, Pfizer, Bayer, Novartis, Sincere Pharmaceutical Group, Shanghai Junshi Biosciences and OriGene. All of the remaining authors declare they have no conflicts of interest.

Data availability

The research data are not shared.

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Background Ulceration is regarded as an adverse prognostic factor and is used together with tumour thickness to subcategorize patients with cutaneous melanoma. However, the prognostic impact of ulceration in acral melanoma (AM) is controversial. **Objectives** To assess the prognostic impact of ulceration in AM and the variability across different Breslow thicknesses and clinical stages.

Methods A multicentre retrospective study of patients diagnosed with AM between January 2000 and December 2017. Differences in melanoma-specific survival (MSS) between patients with and without ulceration were assessed using the multivariable Cox proportional hazards model and log-rank test.

Results Among 1053 enrolled patients, 62.6% had ulceration. After a median follow-up of 61 months, patients with ulceration had a lower median MSS than those without: 66.1 months, 95% confidence interval (CI) 60.0–86.0 vs. not reached; hazard ratio 1.41, 95% CI 1.09–1.82; $P = 0.012$. Among patients with thin (≤ 1 mm) melanoma, the survival curves of patients with vs. without ulceration clearly separated over time ($P < 0.001$). No association between ulceration and MSS was observed for melanomas of thickness > 1 mm (subgroups of T2, T3 and T4; all P -values > 0.05) or patients with stage III disease (hazard ratio 1.09, 95% CI 0.71–1.68, $P = 0.39$).

Conclusions Ulceration is an independent negative prognostic factor for patients with AM, but the impact varies across Breslow thicknesses and clinical stages. Ulceration has a significant effect on prognosis for patients with thin (≤ 1 mm) melanoma, but there was no association between ulceration and survival in intermediate/thick AM or stage III AM.

What is already known about this topic?

- Ulceration status is used together with Breslow tumour thickness to subcategorize patients into different stages according to the America Joint Committee on Cancer melanoma staging system.
- As one distinctive subtype of cutaneous melanoma, acral melanoma (AM) is characterized by poor survival outcomes due to delayed diagnosis and a high prevalence of negative prognostic and genetic features.
- The prognostic impact of ulceration in AM is still controversial.

What does this study add?

- This was the first large-scale study to assess the prognostic and staging values of ulceration in patients with AM.
- Ulceration has a significant effect on prognosis for patients with thin (≤ 1 mm) melanoma, but no association between ulceration and survival was found in intermediate/thick or stage III AM.
- These findings should be considered when using ulceration-based staging systems.

Cutaneous melanoma is a life-threatening condition associated with poor survival and increasing incidence.¹ Apart from important prognostic factors such as Breslow thickness and clinical stage, ulceration is also regarded as a key parameter affecting patient survival.^{2,3} The America Joint Committee on Cancer (AJCC) melanoma staging system, first introduced several decades ago, provides the most commonly used framework for risk stratification and clinical treatment of melanoma.^{1,2,4} In the AJCC staging system, from the sixth to the current eighth edition, ulceration status (with vs. without ulceration) is used together with measured tumour thickness to subcategorize patients into thickness (T) stages T1a–T4b.⁵ Patients with a given tumour thickness would be upstaged from stage IB to IIA, IIA to IIB, IIB to IIC, and IIIA to IIIB to IIIC based on the presence of ulceration. In addition, the prognostic impact of ulceration in cutaneous melanoma has been confirmed by numerous published reports.^{1,5–7}

Acral melanoma (AM) is one distinctive subtype of cutaneous melanoma occurring on the soles, palms and nailbed.^{8,9} Although AM represents a minority of all cases of melanoma in white patients (< 5%), it is the most common melanoma subtype in Asia and Africa.^{10–12} AM is characterized by aggressive progression, with poor survival outcomes due to delayed diagnosis as well as a high prevalence of negative prognostic and genetic features.^{12,13} Several studies have reported an association between ulceration and higher mortality risk in patients with AM compared with patients without ulceration.^{14–17} However, other studies have reported no association between ulceration and prognosis in AM.^{8,18,19} Furthermore, the impact of ulceration across patients with AM of different Breslow thicknesses and clinical stages remains unclear.

In this study, we assessed the overall prognostic impact of ulceration in a population of patients with stage I–III AM, and explored the impact of ulceration on survival across different Breslow thickness categories [≤ 1 mm (T1), > 1 –2 mm (T2), > 2 –4 mm (T3) and > 4 mm (T4), based on the AJCC melanoma staging system] and clinical stages.

Patients and methods**Study design and patients**

This was a multicentre, retrospective study incorporating data from the medical records of patients with AM treated at six large

tertiary hospitals in China. Eligibility criteria for enrolment were (i) diagnosis of AM without distant metastases (stage I, II or III; based on the AJCC staging system eighth edition); (ii) initial date of diagnosis from 1 January 2000 to 31 December 2017; and (iii) documented ulceration status (present vs. absent). Patients with an initial diagnosis date of January 2018 or later were excluded due to inadequate follow-up time. Data extracted from medical records included initial date of diagnosis, age at diagnosis (years), sex (male vs. female), Breslow tumour thickness (mm), primary site (sole vs. palm vs. nailbed), ulceration (present vs. absent), clinical stage at diagnosis, treatment regimens received, and date of death or date last known alive. The study received ethical approval from the institutional review board at Peking University Cancer Hospital (number 2021YJZ49), and a waiver of consent was granted.

Statistical analysis

The Kaplan–Meier method was used to plot the survival curves and estimate the 5- and 10-year survival rates within each stratum. Melanoma-specific survival (MSS) was defined as the time from the initial diagnosis to the date of melanoma-specific death, and differences in MSS between groups were compared by log-rank test. Hazard ratios (HRs) for MSS were estimated using a multivariable Cox proportional hazard model controlling for age, sex, primary site and indicator variable of immunotherapy or targeted treatment. Meanwhile, Breslow thickness was also adjusted for when we assessed the prognostic impact of ulceration in the overall and stage III populations. The proportional hazards assumption was tested using the Schoenfeld residual method and a graphical approach.

Analyses of the association between prognosis and ulceration were conducted separately in patients with stage I/II and stage III melanoma. Furthermore, as this study covered a long time period during which significant changes in treatments have occurred, we generated a dichotomous indicator variable of immunotherapy or targeted treatment (taking the value 1 if the patient had received immunotherapy or targeted therapy, and 0 otherwise) as one covariate to control for this potential confounding effect in the Cox regression model.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Patient characteristics

In total 1053 patients were enrolled in this study, of whom 62.6% had ulceration. The median age of all patients was 55.7 years and the distributions were similar for patients with and without ulceration ($P = 0.11$) (Table 1). Compared with patients without ulceration, those with ulceration had a higher proportion of men (56.4% vs. 47.5%, $P = 0.005$), a higher mean Breslow thickness (4.8 vs. 3.0 mm) and a higher proportion of patients with Breslow thickness > 2 mm (73% vs. 46%, $P < 0.001$). Among all patients in the analysis, the majority (69.9%) had a primary tumour site on the soles, and the distribution of primary sites was similar between patients with and without ulceration ($P = 0.42$). With regard to sentinel lymph node biopsy (SLNB), the percentages of patients undergoing SLNB were similar for those with and without ulceration (35.1% vs. 37.3%, $P = 0.68$).

We also summarized the characteristics of patients subdivided by stage I/II and III AM (Table 2). In total, 791 and 262 patients were initially diagnosed with stage I/II and III AM, respectively. The patient demographics and characteristics among patients with and without ulceration in the stage I/II and III subgroups were generally similar to those observed in the overall population. However, among patients with ulceration, a higher proportion of those with stage I/II melanoma

were aged ≥ 65 years, were female, had a Breslow thickness ≤ 4 mm and had a non-sole primary site compared with patients with stage III AM.

Ulceration and survival

At a median follow-up of 61 months, the median MSS for all patients included in this analysis was 93.1 months [95% confidence interval (CI) 80.1–111.0], with 1-, 5- and 10-year survival rates of 96.4% (95% CI 95.1–97.4), 61.6% (95% CI 58.1–64.9) and 42.8% (95% CI 37.0–48.5), respectively. Patients with ulceration had a lower median MSS than those without (HR 1.41, 95% CI 1.09–1.82; stage-stratified log-rank $P = 0.012$) (Figure 1). The 1-year MSS rates were similar for patients with (95.3%, 95% CI 93.4–96.7) and without (98.2%, 95% CI 96.2–99.1) ulceration. However, the MSS rates at 5 and 10 years were lower for patients with ulceration (54.7% and 34.4%, respectively) than for those without (72.9% and 57.7%, respectively).

Influence of ulceration on prognosis in stage I/II acral melanoma by different Breslow thicknesses

In the setting of nonmetastatic disease, the ulceration rate monotonically increased with incremental thickness (T1: 33.3%, T2: 50.3%, T3: 69.3%, T4: 77.1%; Table 3). Among patients with thin (≤ 1 mm) melanoma, the survival curves of

Table 1 Clinical characteristics of patients with acral melanoma with stage I–III disease

Characteristics	Ulceration	No ulceration	Total	P-value ^a
N (%)	659 (62.6)	394 (37.4)	1053	
Age, years				
Mean (SD)	56.8 (12.9)	54.0 (13.2)	55.7 (13.1)	
Median (IQR)	57.0 (48.0–66.0)	54.0 (46.0–64.0)	56.0 (48.0–65.0)	
< 65	477 (72.4)	303 (76.9)	780 (74.1)	0.11
≥ 65	182 (27.6)	91 (23.1)	273 (25.9)	
Sex				
Male	372 (56.4)	187 (47.5)	559 (53.1)	0.005
Female	287 (43.6)	207 (52.5)	494 (46.9)	
Breslow thickness (mm)				
Mean (SD)	4.8 (3.5)	3.0 (2.9)	4.1 (3.4)	
Median (IQR)	4.0 (2.2–6.0)	2.0 (1.0–4.0)	3.0 (2.0–5.0)	
≤ 1 (T1)	49 (7.4)	100 (25.4)	149 (14.2)	< 0.001
> 1 –2 (T2)	93 (14.1)	92 (23.4)	185 (17.6)	
> 2 –4 (T3)	190 (28.8)	89 (22.6)	279 (26.5)	
> 4 (T4)	290 (44.0)	89 (22.6)	379 (36.0)	
Not assessed	37 (5.6)	24 (6.1)	61 (5.8)	
Primary site				
Sole	457 (69.3)	279 (70.8)	736 (69.9)	0.42
Palm	47 (7.1)	34 (8.6)	81 (7.7)	
Nailbed	155 (23.5)	81 (20.6)	236 (22.4)	
Sentinel lymph node biopsy				
Yes	231 (35.1)	147 (37.3)	378 (35.9)	0.68
No	423 (64.2)	243 (61.7)	666 (63.2)	
Missing	5 (0.8)	4 (1.0)	9 (0.9)	

The data are presented as n (%) unless stated otherwise. IQR, interquartile range. ^aP-values calculated by χ^2 -tests.

Table 2 Clinical characteristics of patients with acral melanoma with stage I/II and stage III disease

Characteristics	Stage I/II			Stage III		
	Ulceration	No ulceration	P-value ^a	Ulceration	No ulceration	P-value ^a
N	489	302		170	92	
Age (years)						
Mean (SD)	57.6 (12.8)	54.0 (13.7)		54.5 (13.2)	53.8 (11.6)	
Median (IQR)	58.0 (50.0–66.0)	54.0 (45.0–65.0)		54.0 (46.0–64.0)	54.5 (46.5–62.0)	
< 65	346 (70.8)	226 (74.8)	0.91	131 (77.1)	77 (84)	0.93
≥ 65	143 (29.2)	76 (25.2)		39 (22.9)	15 (16)	
Sex						
Male	266 (54.4)	144 (47.7)	0.039	106 (62.4)	43 (47)	0.011
Female	223 (45.6)	158 (52.3)		64 (37.6)	49 (53)	
Breslow thickness (mm)						
Mean (SD)	4.6 (3.5)	2.8 (2.9)		5.6 (3.5)	4.3 (2.9)	
Median (IQR)	4.0 (2.0–5.5)	2.0 (1.0–3.5)		5.0 (3.0–7.0)	3.9 (2.0–6.0)	
≤ 1 (T1)	45 (9.2)	90 (29.8)	< 0.001	4 (2.4)	10 (11)	0.003
> 1–2 (T2)	83 (17.0)	82 (27.2)		10 (5.9)	10 (11)	
> 2–4 (T3)	156 (31.9)	69 (22.8)		34 (20.0)	20 (22)	
> 4 (T4)	205 (41.9)	61 (20.2)		85 (50.0)	28 (30)	
Not assessed	0	0		37 (21.8)	24 (26)	
Primary site						
Sole	333 (68.1)	203 (67.2)	0.66	124 (72.9)	76 (83)	0.15
Palm	38 (7.8)	29 (9.6)		9 (5.3)	5 (5)	
Nailbed	118 (24.1)	70 (23.2)		37 (21.8)	11 (12)	
Sentinel lymph node biopsy						
Yes	176 (36.0)	113 (37.4)	0.84	55 (32.4)	34 (37)	0.45
No	308 (63.0)	185 (61.3)		115 (67.6)	58 (63)	
Missing	5 (1.0)	4 (1.3)		0	0	

The data are presented as n (%) unless stated otherwise. IQR, interquartile range. ^aP-values calculated by χ^2 -tests.

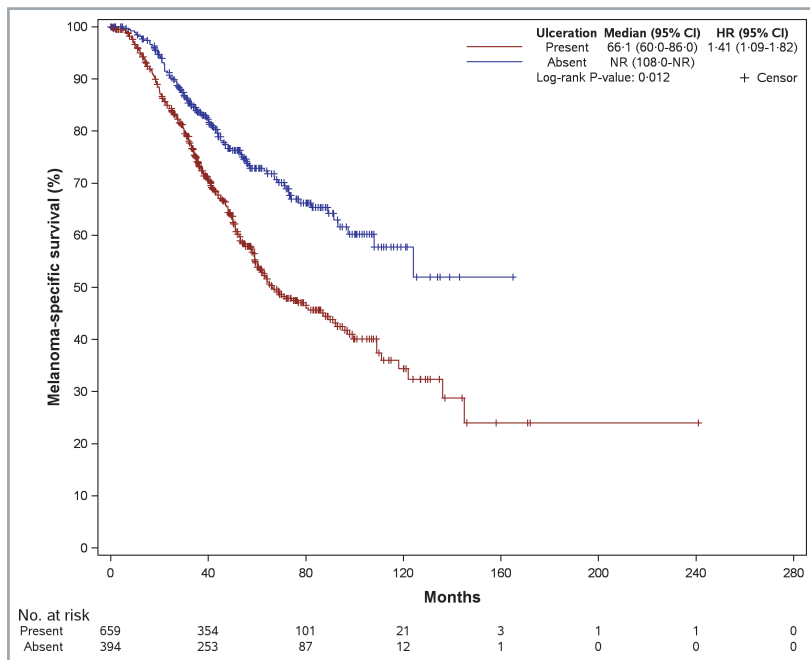


Figure 1 Kaplan–Meier curve of melanoma-specific survival for patients with vs. without ulceration. CI, confidence interval; HR, hazard ratio; NR, not reached. The P-value was calculated by stage-stratified log-rank test. The HR was calculated by Cox regression adjusting for age, sex, primary site, an indicator variable of immunotherapy or targeted treatment (yes vs. no) and Breslow thickness.

patients with and without ulceration clearly separated over time (HR 7.87, 95% CI 2.46–25.1; $P < 0.001$), and the median MSS was 97.1 months vs. not reached, respectively (Figure 2a). In addition, the 10-year survival among the ulcerated group was 49.1% (95% CI 26.9–68.0), which was significantly lower than in the nonulcerated group (89.7%, 95% CI 69.5–96.8) (Table 3). As for patients with Breslow thickness > 1 mm (i.e. T2a vs. T2b, T3a vs. T3b and T4a vs. T4b), although patients without ulceration tended to have longer MSS than those with ulceration (all HRs for presence vs. absence of ulceration > 1), no statistically significant differences were observed (Figure 2b–d, all P -values > 0.05).

We further compared survival for subgroups of patients across a range of melanoma thicknesses and ulceration statuses (Figure 3a). Subgroups of T1 with ulceration, T2b, T3a, T3b and T4a had similar survival trends. Thickness of T1 with absence of ulceration indicated the best survival, and T4b showed the worst survival, with an HR of 0.07 (95% CI 0.03–0.20). Patients with stage T2a melanoma had longer survival than patients with T1 melanoma with ulceration (median MSS: not reached vs. 97.1 months).

Following the AJCC eighth edition staging manual for melanoma, melanoma with a thickness of ≤ 1 mm is subcategorized into T1a: < 0.8 mm without ulceration; and T1b: < 0.8 mm with ulceration, or ≥ 0.8 mm regardless of ulceration status (hereafter referred to as method 1). To further explore the impact of ulceration in thin melanoma (< 1 mm), we proposed a simplified subcategory definition based on ulceration alone regardless of thickness: T1_a, without ulceration; or T1_b, with

ulceration (hereafter referred to as method 2). The results (Figure 3b) showed that the separation of MSS for T1_a vs. T1_b was larger than for T1a vs. T1b (the log-rank P -values of method 2 and method 1 were < 0.001 and 0.026, respectively). We also defined a new subgroup, T1_ge0.8a, as melanoma with thickness 0.8–1 mm and absence of ulceration. The survival curves for patients with T1a vs. T1_a vs. T1_ge0.8a were similar. In addition, the mortality risk associated with T1_b melanoma seemed higher than that of T1b, with a median MSS of 97.1 vs. not reached, respectively (Figure 3b).

In the eighth edition of the AJCC staging manual, non-metastatic melanoma is substaged into IA, IB, IIA, IIB and IIC based on Breslow thickness and ulceration. Comparisons of survival across all these substages are shown in Figure 3(c). Stage IA and IB melanomas were associated with significantly longer survival than stage IIC melanoma, with HRs of 0 (as no melanoma-specific death event occurred) and 0.29, respectively. The survival curves for patients with stage IIA and IIB melanoma overlapped with each other and were comparable. Five-year MSS rates for patients with stage IIA and IIB AM were similar (69.0% and 63.2%, Table 3), and the 10-year MSS rate for patients with stage IIB disease was numerically higher than for stage IIA (47.5% vs. 32.3%).

Ulceration and prognosis in stage III acral melanoma

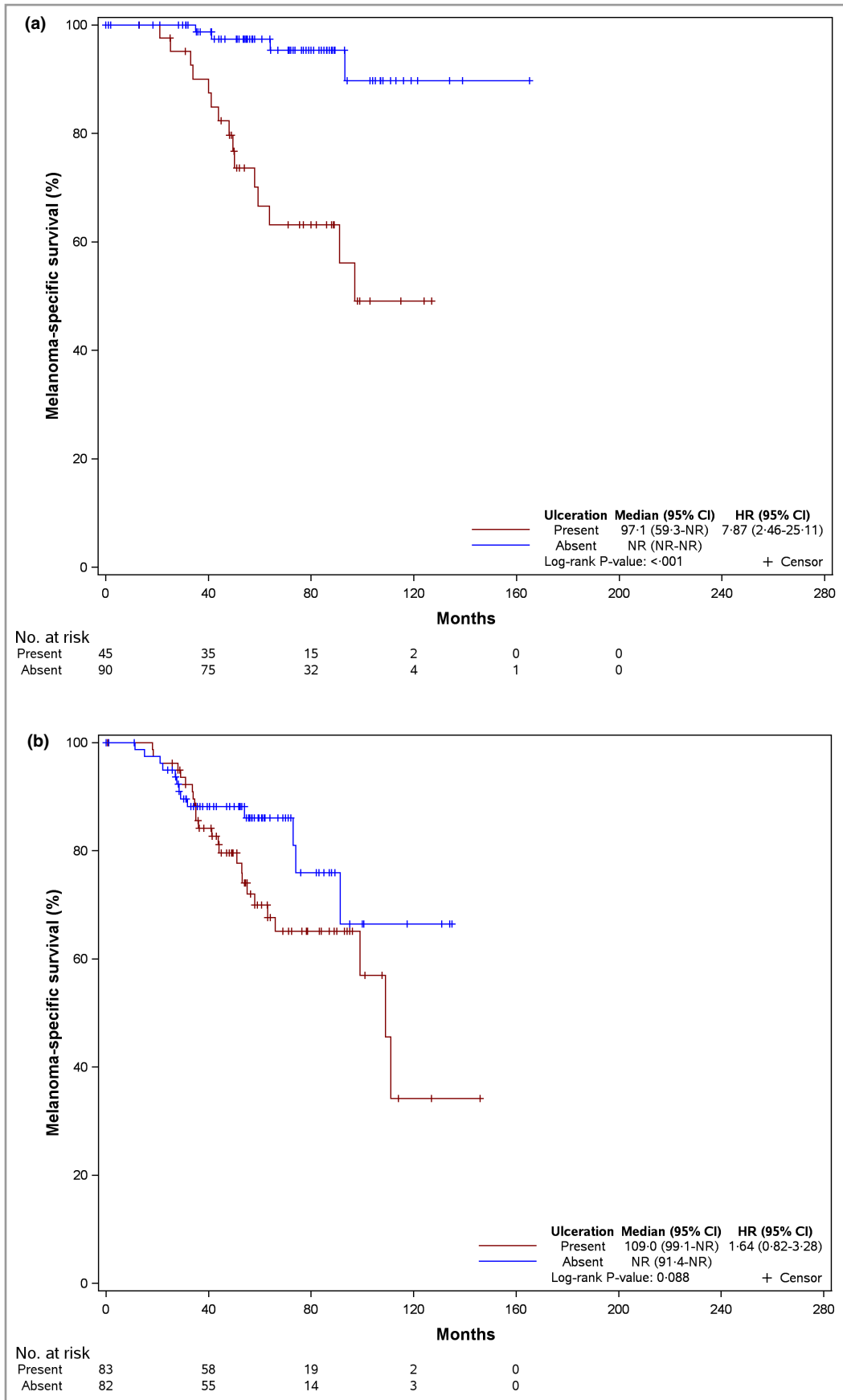
The prevalence of ulceration among patients with stage III AM was 64.9%. The 5- and 10-year survival rates for patients without ulceration were 43.3% and 36.5%, respectively,

Table 3 Five- and 10-year melanoma-specific survival rates for patients with vs. without ulceration

Category	Ulceration rate, %	5-year rate, % (95% CI)		10-year rate, % (95% CI)	
		Ulceration	No ulceration	Ulceration	No ulceration
Breslow thickness (mm) ^a					
≤ 1 (T1)	33.3	66.6 (48.3–79.7)	97.4 (89.9–99.3)	49.1 (26.9–68.0)	89.7 (69.5–96.8)
> 1 –2 (T2)	50.3	70.0 (57.0–79.7)	86.1 (75.4–92.4)	34.2 (10.7–59.7)	66.5 (40.2–83.3)
> 2 –4 (T3)	69.3	61.4 (50.9–70.3)	67.3 (51.8–78.8)	46.9 (32.5–60.0)	33.0 (8.3–61.1)
> 4 (T4)	77.1	54.9 (46.5–62.6)	66.5 (50.6–78.4)	31.7 (20.4–43.7)	48.5 (29.0–65.5)
Stage at diagnosis					
Stage I ^b					
IA	–	94.3 (83.2–98.1)		85.6 (64.6–94.6)	
IB	–	78.9 (68.7–86.1)		59.7 (41.1–74.2)	
Stage II ^b					
IIA	–	69.0 (59.4–76.7)		32.3 (13.5–52.7)	
IIB	–	63.2 (54.7–70.5)		47.5 (36.1–58.0)	
IIC	–	54.9 (46.5–62.6)		31.7 (20.4–43.7)	
Stage III	64.9	38.4 (30.1–46.5)	43.3 (31.7–54.4)	24.8 (15.9–34.7)	36.5 (24.7–48.3)

CI, confidence interval. ^aOnly for patients with nonmetastatic disease. ^bAs subcategorization of stages I and II is based on ulceration and thickness (criteria of the America Joint Committee on Cancer eighth edition melanoma staging system), the survival rates were provided regardless of ulceration status.

Figure 2 Kaplan–Meier curves of melanoma-specific survival for nonmetastatic disease with vs. without ulceration. (a) Tumour thickness ≤ 1 mm, T1; (b) tumour thickness > 1 –2 mm, T2; (c) tumour thickness > 2 –4 mm, T3; (d) tumour thickness > 4 mm, T4. CI, confidence interval; HR, hazard ratio; NR, not reached. The HR was calculated by Cox regression adjusting for age, sex, primary site, and an indicator variable of immunotherapy or targeted treatment (yes vs. no).



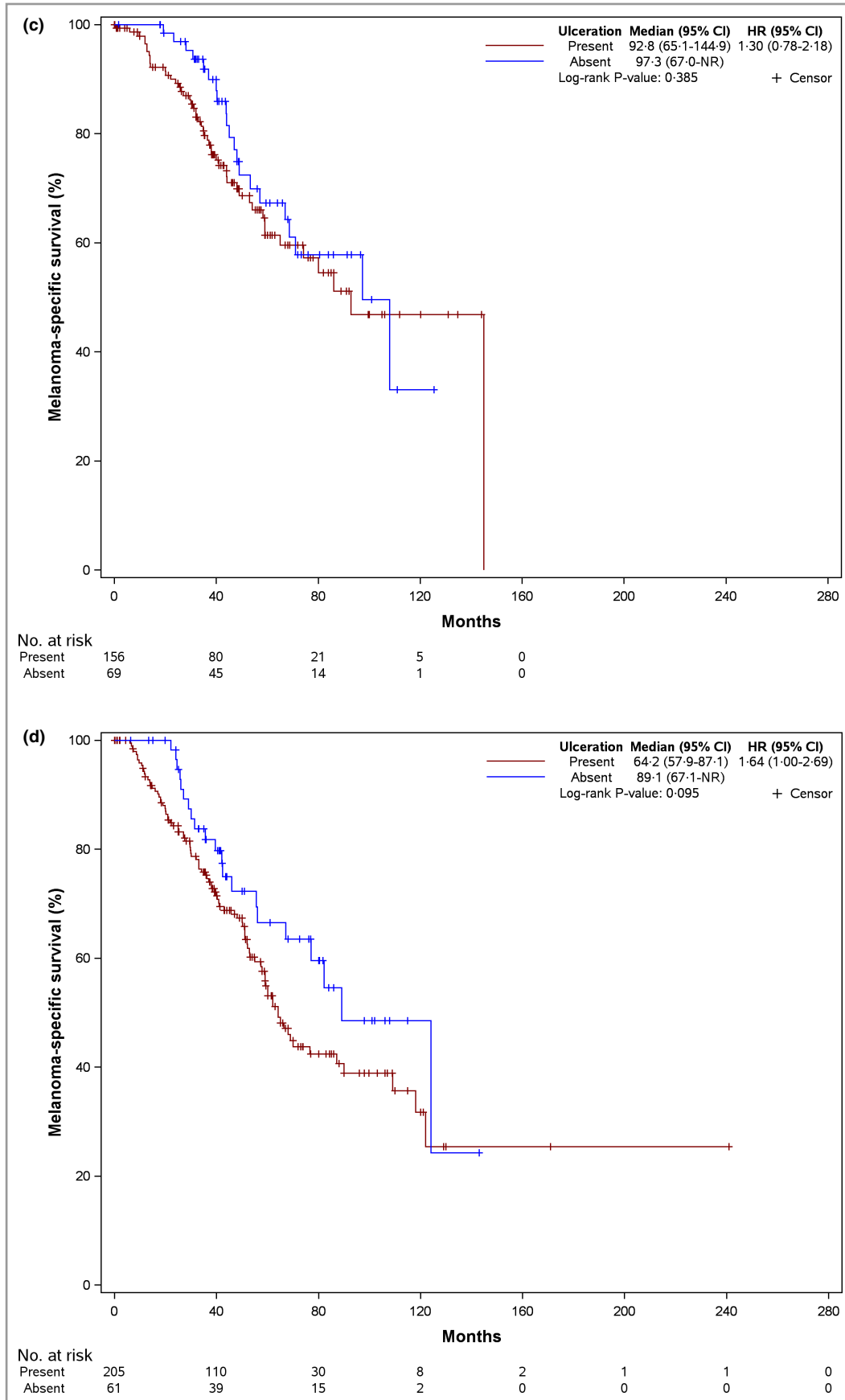


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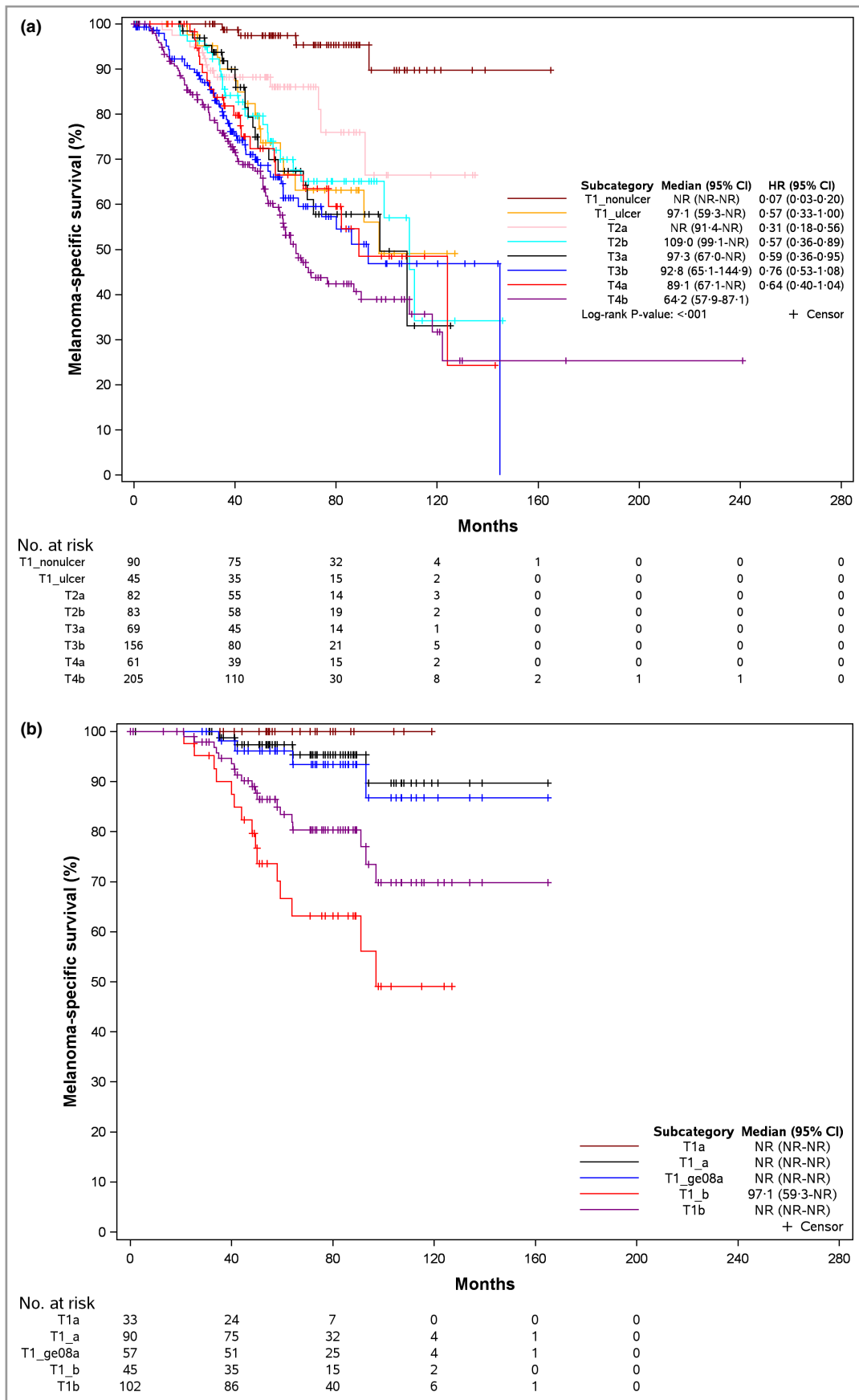


Figure 3 Kaplan–Meier curves of melanoma-specific survival across different subgroups. (a) Subgroups of T1 with or without ulceration, T2a/b, T3a/b, T4a/b. (b) Subgroups of T1a/b, T1_a/b and T1_ge08a. (c) Subgroups of IA, IB, IIA, IIB and IIC. As no melanoma-specific death event occurred for the IA population, the associated hazard ratio (HR) was 0 and the 95% confidence interval (CI) was not robust in the Cox regression model. NR, not reached; T1_a, T1 without ulceration; T1_b, T1 with ulceration; T1_ge08a, melanoma with a thickness of 0.8–1 mm and absence of ulceration. The HR was calculated by Cox regression adjusting for age, sex, primary site, and an indicator variable of immunotherapy or targeted treatment (yes vs. no).

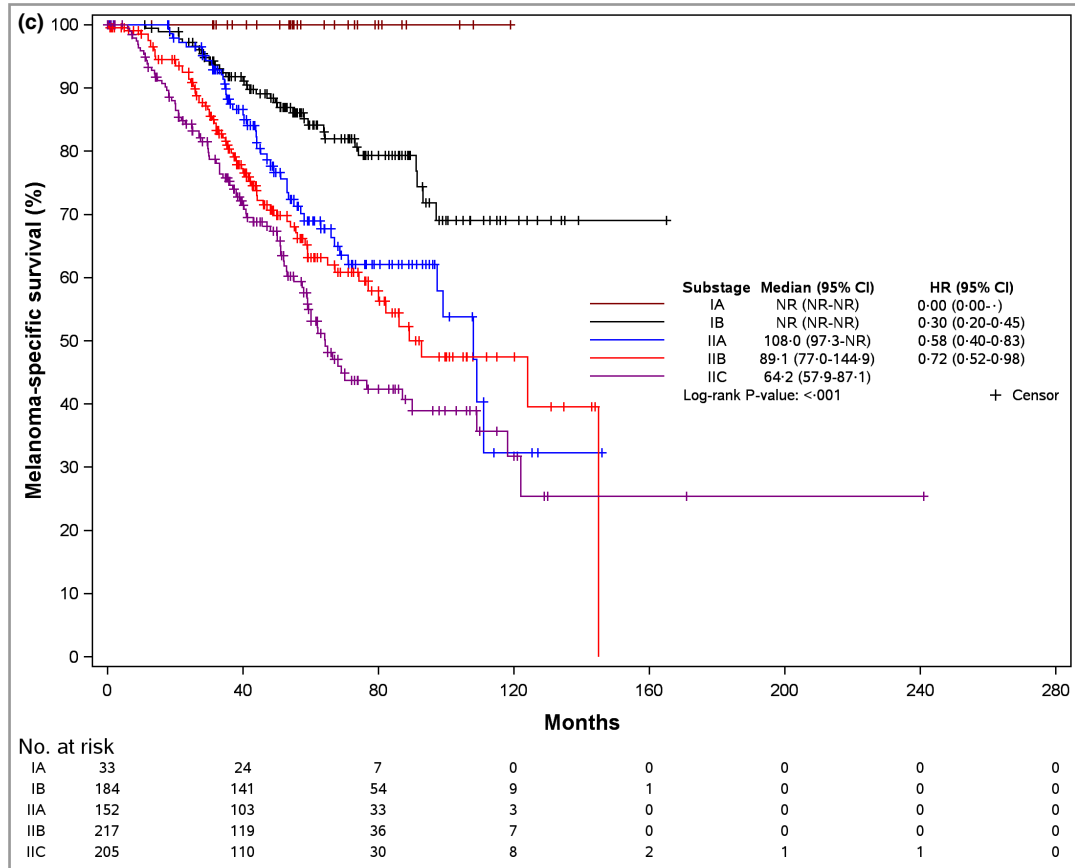


Figure 3 Continued.

which were higher than in patients with ulcerated melanoma (38.4% and 24.8%, respectively; Table 3). However, there was no association between ulceration and MSS, with an HR of 1.09 (95% CI 0.71–1.68; Figure 4). The median MSS times were 46.0 and 48.0 months for patients with and without ulceration, respectively.

Discussion

Ulceration is regarded as an important prognostic factor for patients with cutaneous melanoma.^{1,5,6} It is one of the sub-staging determinants associated with survival for stage I–III melanoma in the sixth to eighth editions of the AJCC melanoma staging system; however, it is less well established as a prognostic factor for AM.^{1,5} In this regard, our study verified the prognostic value of ulceration for AM. We found that, overall, patients with AM and ulceration had worse survival and increased mortality risk than those without ulceration,

which is in line with multiple previous reports on AM.^{14–16,20} However, our results also show that the prognostic value of ulceration is higher for patients with thin AM (< 1 mm) and lower for patients with thicker tumours.

Our study found that ulceration prevalence monotonically increased with incremental AM thickness, which is consistent with the overall trend reported for cutaneous melanoma. Eigentler *et al.*²¹ examined the prevalence of ulceration in non-metastatic cutaneous melanoma and found increasing prevalence as thickness increased from T1 to T4, with prevalences of 2.5%, 15.9%, 38.7% and 55.2%, respectively. A similar result was reported in two further studies.^{2,7} For cutaneous melanoma in the nonmetastatic setting, the current AJCC melanoma staging manual states that tumours with ulceration have worse predicted survival within the same T category, and the presence of an ulcerated primary tumour is associated with an MSS similar to that of a nonulcerated tumour in the next highest thickness category.² These statements were not fully

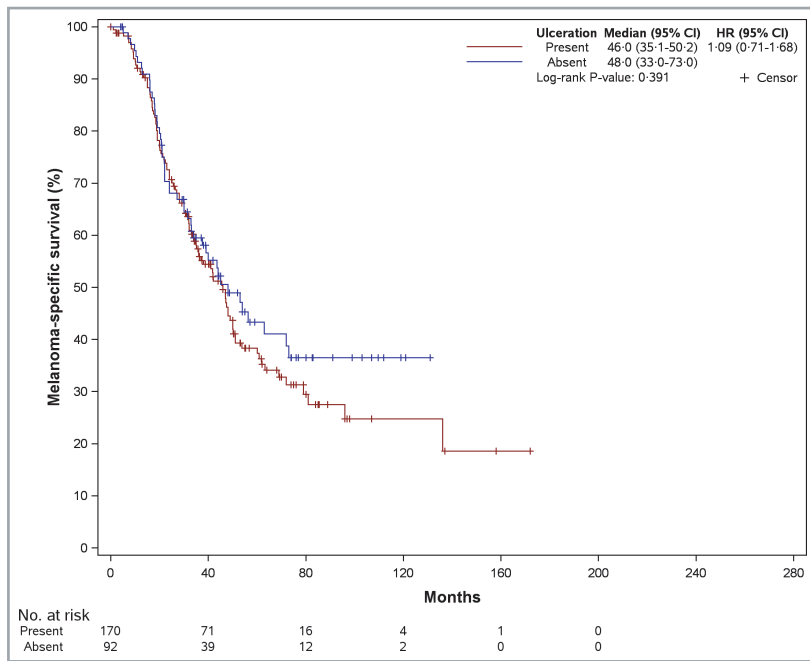


Figure 4 Kaplan–Meier curve of melanoma-specific survival for stage III disease with vs. without ulceration. CI, confidence interval; HR, hazard ratio. The HR was calculated by Cox regression adjusting for age, sex, primary site, an indicator variable of immunotherapy or targeted treatment (yes vs. no) and Breslow thickness.

confirmed for the population with AM included in our study, as ulceration was associated with worse survival only for thin (≤ 1 mm) melanoma. While patients with AM without ulceration tended to have longer survival, no statistically significant difference was found when the tumour thickness was > 1 mm. This finding is supported by a previous study,²¹ which found no survival difference associated with ulceration for T1 and T4 cutaneous melanoma. Our study did find that the prognosis for AM of subcategory T2a was better than for T1 with ulceration. In addition, the Kaplan–Meier curves for the subcategories of T2b, T3a, T3b and T4a were basically comparable, and similar survival curves were observed for patients with stage IIa and IIb AM, which are composed of T2b/T3a and T3b/T4a, respectively.

In a further exploration of the prognostic impact of ulceration in thin melanoma, we found that a T1 subcategorization scheme based only on ulceration had a higher separation power than combining 0.8-mm thickness and ulceration (method 2 vs. method 1). Furthermore, the survival of patients in subgroup T1_ge0.8a (0.8–1.0-mm thickness and absence of ulceration) was closer to that in patients categorized as T1a than in T1b. These findings suggest that, for AM, using only ulceration to subdivide T1 may be a better choice to stratify mortality risk. These surprising results are contrary to the generally accepted cutaneous melanoma substaging criteria and suggest that ulceration may be a stronger prognostic factor than thickness in thin AM.

Ulceration is regarded as an important factor for subgrouping melanoma of stage III.^{1,6,7} However, in our study we did not find an association between ulceration and MSS in patients

with stage III AM. This finding contrasts with the AJCC staging system and with multiple prior investigations in cutaneous melanoma that support the prognostic value of ulceration. Our findings partially align with two previous reports^{21,22} that could not establish the prognostic value of ulceration in a melanoma population with positive lymph nodes.

Our results show that the prognostic value of ulceration varies by tumour thickness and disease stage, and therefore the staging system described in the current AJCC eighth edition manual may lose the ‘linearity of severity’ in patients with AM. Namely, a more advanced stage does not necessarily represent worse survival, which is a viewpoint recently expressed by others.^{23,24} Based on our findings in AM, it is recommended that ulceration be given less weight for prognosis and could even be removed from the subcategory criteria for stages II and III. These results also raise important considerations for designing and interpreting clinical trials, particularly current investigations of adjuvant immunotherapy or targeted therapy in stage II melanoma.²⁵ For example, KEYNOTE-716 evaluated adjuvant pembrolizumab vs. placebo in patients with high-risk stage II (IIB and IIC) melanoma.²⁶ Based on our findings, patients with stage IIA AM should also be included in trials conducted in patients with stage II melanoma as they have comparable survival to patients with stage IIB disease.

In conclusion, the prevalence of ulceration monotonically increases with incremental thickness of AM. Ulceration was identified as an independent adverse prognostic factor, but the impact varied across different tumour thicknesses and clinical stages. The presence of ulceration was only

associated with lower MSS in patients with a tumour thickness ≤ 1 mm and, for stage III AM, ulceration was not associated with survival. Our results suggest that, for AM, the AJCC staging system and risk stratification may be simplified by removing ulceration-based upstaging. The proposal requires further validation in a larger-scale population of patients with AM.

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