The Oncologist, 2025, **30**, oyaf086
https://doi.org/10.1093/oncolo/oyaf086
Advance access publication 10 May 2025
Original Article

Poor prognosis of early-stage acral melanoma with a history of trauma: a multicenter analysis of 468 patients

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Abstract

Background: Previous studies have suggested that trauma may be a risk factor for the development and prognosis of acral melanoma (AM).

Methods: This population-based retrospective cohort study included patients with AM and a confirmed history of trauma who received treatment at 5 melanoma treatment centers in China. Factors associated with recurrence and survival were analyzed using univariate and multivariate Cox regression analyses.

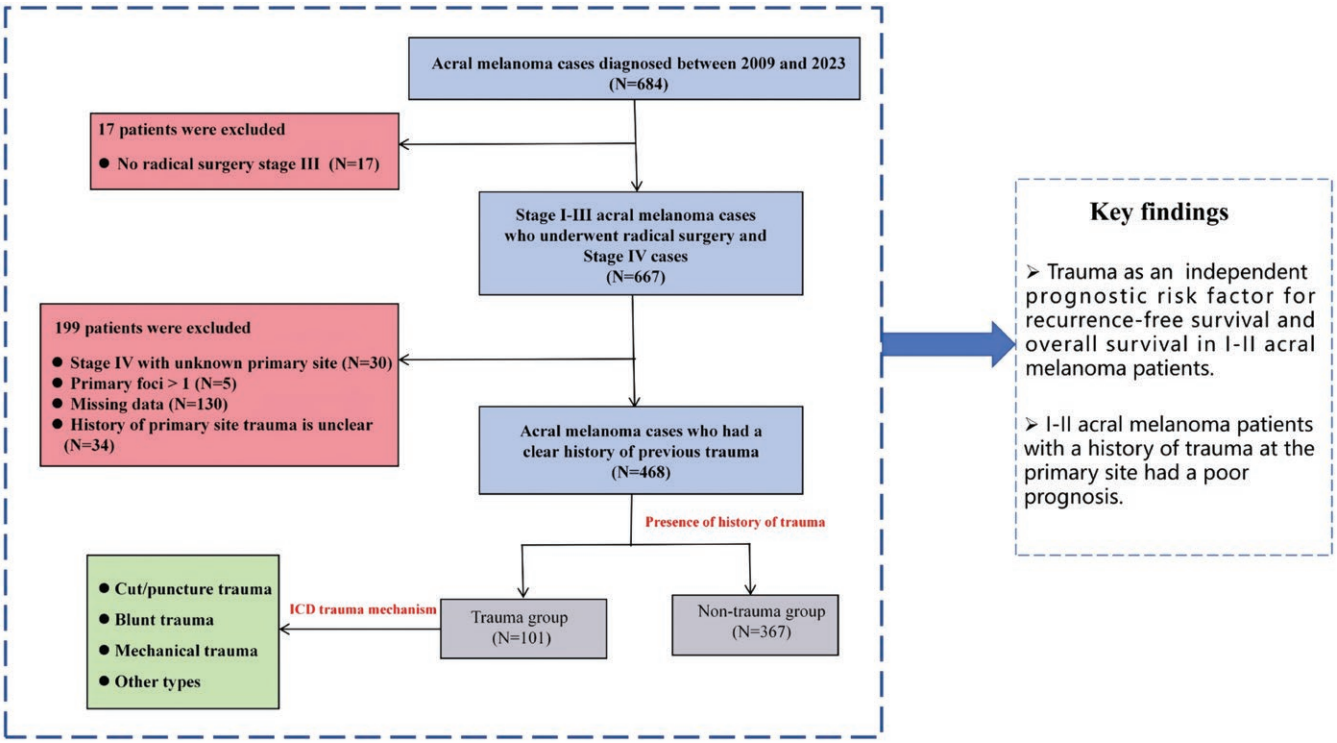
Results: Totally 468 AM cases were included in this study, with 101 patients in the trauma group and 367 in the non-trauma group. The trauma group had more patients with ulceration ($P = .027$), mitotic rate ≥ 1 ($P = .036$), and Clark level IV-V ($P = .009$) than the non-trauma group. Among stage I-II postoperative AM patients, the median recurrence-free survival (RFS) was 33.3 months (95% CI: 18.8-47.8) and 115.6 months (95% CI: 96.3-135.0) in the trauma and non-trauma groups, respectively ($P < .001$). Similarly, the median overall survival (OS) was 64.6 (95% CI: 54.8-74.4) and not reached (95% CI: NR), respectively ($P = .002$). Comparatively, no significant differences were observed in RFS or OS between the trauma and non-trauma groups in patients with stage III and IV AM. Multifactorial analysis showed that trauma was an independent risk factor for RFS and OS only in patients with stage I-II AM patients.

Conclusions: Postoperative stage I-II patients in the trauma group had significantly worse RFS and OS compared to those in the non-trauma group.

Key words: acral melanoma; trauma; recurrence; survival time.

Received: 28 August 2024; Accepted: 1 April 2025.

Graphical Abstract



Implications for Practice

Currently, the prognostic factors affecting acral melanoma (AM) remain unclear. Previous studies have indicated that trauma may be one such factor. Since trauma is an inevitable part of life, it is important to investigate whether it affects AM prognostic outcomes. This study identified trauma as a factor independently predicting recurrence-free survival and overall survival of early-stage AM. A history of trauma at the primary site prior to diagnosis suggests that patients with AM may be related to a worse prognosis, highlighting the need for clinicians to consider this factor in their assessments.

Introduction

Acral melanoma (AM) is a highly malignant subtype of melanoma that predominantly occurs on the hairless skin of the extremities and is associated with a poor prognosis.[1] According to one population-based study involving Hispanic whites, non-Hispanic whites, Asian and Pacific Islanders, and blacks, the annual AM incidence rate is 0.2 per 100 000 people.[2] AM has significantly different racial variation, being more frequent among individuals with darker skin tones. It is the most prevalent melanoma subtype in the Chinese population, accounting for 41.8% of melanoma cases in China.[3] AM shows a poorer prognostic outcome than other melanoma subtypes, with lower overall survival (OS) rates than other malignant melanomas.

The AM etiology remains to be further explored. Since the AM predilection sites are usually sun-shielded areas, ultraviolet exposure is considered less relevant. Trauma, including penetrating injuries and mechanical stress, maybe a predisposing factor for the onset of AM and may also affect survival and prognosis.[4-10] Woo Jin Lee's team reported that trauma-related AM was related to shorter progression-free survival (PFS) and OS.[11] However, the association between trauma and the onset and prognosis of AM remains controversial.[12,13] Given that trauma is an unavoidable part of life, clarifying the association of pre-diagnostic trauma with AM prognosis is of clinical significance. In this study, we aimed to explore the impact of trauma on the recurrence and survival of patients with AM.

Method

Study design

This multicenter retrospective study collected data from patients diagnosed with AM between February 2009 and February 2023 at 5 centers in China. All patients were of Chinese or Asian ethnicity, representing the native Chinese population. Patients were included if they met the following criteria: (1) Patients with a diagnosis of AM based on pathological examination, (2) Patients with a confirmed history of trauma at the primary site, (3) Patients with a single primary lesion, and (4) Patients with a follow-up period more than 12 months. The exclusion criteria were as follows: (1) Patients with stage I-III AM who have not undergone radical resection, (2) Patients with an unclear primary site, (3) Patients with more than one primary lesion, (4) Patients with severe loss of data, and (5) Patients with other malignant tumors. Data analysis was performed in November 2024.

Patient characteristics

The collected data included age, sex, date of diagnosis, clinical stage at diagnosis, specific primary tumor site (left or

right), ulceration status, Breslow thickness (mm), mitotic rate, Clark level, presence of trauma, recurrence-free survival (RFS), OS, and disease stage based on the eighth edition of the American Joint Committee on Cancer Melanoma Staging System (AJCC).[14] Additionally, we recorded the time interval between the traumatic event and the diagnosis of AM.

Patients were divided into trauma and non-trauma groups based on the presence or absence of a history of trauma. Based on histophysiological differences in the anatomical site and tissue of origin, AM was further classified into 2 subtypes: palmar AM and subungual AM. According to the International Classification of Diseases (ICD) trauma mechanism, trauma events were classified into cut/puncture trauma, blunt trauma, mechanical trauma, and other types that could not be classified by the above mechanism.[15]

Statistical analysis

SPSS statistical package version 27.0 was used for data analysis. OS refers to the duration between pathological diagnosis and all-cause mortality. RFS represented the duration between diagnosis and the initial occurrence of local recurrence, regional metastasis, and distant metastasis. For patients without recurrence, RFS was censored at the time of death, the last recurrence-free follow-up, or the end of the study period, whichever occurred first. Categorical variables between the trauma and non-trauma groups were compared using the chi-square test. The Kaplan–Meier method was used to generate the survival curve, and the log-rank test was used to analyze whether the difference was significant. The Cox regression model was used to evaluate the relationship between clinical/pathological variables and OS/RFS, with hazard ratios (HR) and 95% confidence intervals (CI) reported. The variables with a P value < .05 in the univariate regression analysis were included in the multivariate Cox regression analysis, and the Enter method was used for variable selection. $P < .05$ was considered statistically significant.

Results

Patient characteristics of the overall population

Totally 468 patients with AM were included in this study. The median follow-up period was 75.5 months (95% CI: 71.1-79.9). The median age of the overall cohort was 60.0 years. **Table 1** presents the demographic and clinicopathological characteristics of the overall population and the 2 patient groups. There were 220 females (47.0%) and 248 males (53.0%). Most AM patients (54.9%) had the disease on the right side of the body. Besides, AM more frequently occurred in the palmar region than subungual region (82.7% vs 17.3%). According to the eighth edition of the AJCC staging system, there were 86 cases (18.4%) were classified as stage I, 177 cases (37.8%) as stage II, 147 cases (31.4%) as stage III, and 58 cases (12.4%) as stage IV. Regarding Breslow thickness, 69 cases (14.7%) had a thickness ≤1 mm, 115 cases (24.6%) had a thickness of 1.01-2 mm, 107 cases (22.9%) had a thickness of 2.01-4.0 mm, and 177 cases (37.8%) had a thickness >4 mm. In addition, 373 cases (79.7%) had a mitotic rate ≥1, and 321 cases (68.6%) were classified as having Clark level IV-V.

Trauma group and non-trauma group characteristics

Of the 468 cases involved in this study, 101 (21.6%) had a history of trauma, while 367 (78.4%) denied any such history (Table 1). The duration between trauma onset and AM diagnosis was 1-36 months, with an average duration of 15.0 months. Meanwhile, male-to-female ratios were 1.5:1 and 1.03:1 in trauma and non-trauma groups. The peak AM incidence was observed in individuals aged 60-69 years in 2 groups.

In terms of disease staging, the proportion of patients classified as stage I was less than 10% in the trauma group, compared to over 20% in the non-trauma group. The proportions of stage II-IV were similar between the 2 groups. However, the proportion of patients with ulceration (67.3% vs 55.0%, $P = .027$), mitotic rate ≥1 (87.1% vs 77.7%, $P = .036$), and Clark level IV-V (79.2% vs 65.7%, $P = .009$) were higher in the trauma group. There were no statistically significant differences observed between the trauma and non-trauma groups regarding gender, age, laterality of the primary tumor site at diagnosis (including overall, palmar comparison, and subungual comparisons), tumor stage, or Breslow thickness.

In the trauma group, the top 3 lesions of AM were the foot plantar region (54.5%), hallux toe (17.8%), and the thumb (9.9%; **Table S1**). The primary tumor site was often tightly associated with the previous trauma location. Similarly, the top 3 lesions of AM of the non-trauma group were the foot plantar region (52.0%), the thumb (14.2%), and the hallux toe (13.9%).

Moreover, characteristics in palmar and subungual trauma groups were compared with the non-trauma group (**Table S2**). For palmar region in the trauma group, more patients had Clark level IV-V compared with the non-trauma group (79.5% vs 66.0%, $P = .022$). There were more subungual ulcers in the trauma group than non-trauma group (82.6% vs 55.2%, $P = .021$). No statistically significant differences were observed in the remaining data.

Furthermore, we examined the distribution of different types of trauma (**Table S3**). Among the 101 patients in the trauma group, cutting or puncture injuries were the most common (41.6%), with an approximately equal distribution between the right and left sides of the body.

Analysis of risk factors for RFS and OS in patients with AM

Among 410 patients eligible for stage I–III radical surgery, the median RFS were 24.4 months (95% CI: 15.8-33.0) and 48.6 months (95% CI: 32.4-64.9) in trauma and non-trauma groups, respectively ($P < .001$; **Figure 1A**). For stage I-II patients, their median RFS were 33.3 months (95% CI: 18.8-47.8) and 115.6 months (95% CI: 96.3-135.0) in the trauma and non-trauma groups ($P < .001$; **Figure 1B**). Nevertheless, among patients with stage III disease after radical resection, no significant differences in median RFS were found between the 2 groups ($P > .05$; **Figure 1C**).

Across the entire cohort, the median OS of trauma and non-trauma groups were 49.5 months (95% CI: 36.0-62.9) and 88.7 months (95% CI: 76.4-101.0), respectively ($P < .001$; **Figure 2A**). For stage I-II patients, their median OS was 64.6 months (95% CI: 54.8-74.4) in the trauma group, while it was not reached (NR; 95% CI, NR) for the non-trauma group ($P = .002$; **Figure 2B**). However, median OS was not significantly different in both groups of stage III-IV patients ($P > .05$; **Figure 2C**, **Figure S1**).

Multivariate Cox proportional hazards regression analysis indicated that, trauma (HR 1.76; 95% CI: 1.17-2.65; $P = .007$), ulceration (HR 1.70; 95% CI: 1.13-2.57; $P = .011$), and Breslow thickness ($P = .004$) were independent risk factors for RFS in

Table 1. Characteristics of the study patients in acral melanoma.

Factors	Patients, No. (%)[a]			*P* value[b]
	Overall (*n* = 468)	Trauma group (*n* = 101)	Non-trauma group (*n* = 367)	
Sex				
Female	220(47.0)	40(39.6)	180(49.0)	.092
Male	248(53.0)	61(60.4)	187(51.0)	
Age, y				
<40	20(4.3)	1(1.0)	19(5.2)	.287
40-49	66(14.1)	15(14.9)	51(13.9)	
50-59	140(29.9)	34(33.7)	106(28.9)	
60-69	146(31.2)	34(33.7)	112(30.5)	
≥70	96(20.5)	17(16.8)	79(21.5)	
Location (left/right)	211(45.1)/257(54.9)	46(45.5)/55(54.5)	165(45.0)/202(55.0)	.917
Palmar	177(45.7)/210(54.3)	38(48.7)/40(51.3)	139(45.0)/170(55.0)	.554
Hand	28(51.9)/26(48.1)	3(60.0)/2(40.0)	25(51.0)/24(49.0)	1.000
Foot	149(44.7)/184(55.3)	35(47.9)/38(52.1)	114(43.8)/146(56.2)	.534
Subungual	34(42.0)/47(58.0)	8(34.8)/15(65.2)	26(44.8)/32(55.2)	.409
Finger	19(39.6)/29(60.4)	4(30.8)/9(69.2)	15(42.9)/20(57.1)	.447
Toe	15(45.5)/18(54.5)	4(40.0)/6(60.0)	11(47.8)/12(52.2)	.722
Stage				
I	86(18.4)	10(9.9)	76(20.7)	.071
II	177(37.8)	43(42.6)	134(36.5)	
III	147(31.4)	32 (31.7)	115(31.3)	
IV	58(12.4)	16(15.8)	42(11.4)	
Ulceration				
Yes	270(56.7)	68(67.3)	202(55.0)	.027
No	198(43.3)	33(32.7)	165(45.0)	
Breslow thickness(mm)				
≤1	69(14.7)	9(8.9)	60(16.3)	.106
>1-2	115(24.6)	22(21.8)	93(25.3)	
>2-4	107(22.9)	30(29.7)	77(21.0)	
>4	177(37.8)	40(39.6)	137(37.3)	
Mitotic-rate/mm^2				
<1	95(20.3)	13(12.9)	82(22.3)	.036
≥ 1	373(79.7)	88(87.1)	285(77.7)	
Clark level				
I–III	147(31.4)	21(20.8)	126(34.3)	.009
IV–V	321(68.6)	80(79.2)	241(65.7)	

[a]Data are given as numbers (percentage). The sum of percentages may not equal 100 because of rounding.
[b]By Pearson χ^2 test.

stage I-II patients (Table 2). Likewise, trauma (HR 1.78; 95% CI: 1.09-2.91; *P* = .022), ulceration (HR 1.71; 95% CI: 1.05-2.78; *P* = .032), Breslow thickness (*P* = .037), and mitotic rate (HR 2.01; 95% CI: 1.06-3.83; *P* = .033) were identified as independent risk factors for OS in stage I-II patients (Table 3). Surprisingly, trauma was not an independent risk factor for RFS and OS in patients with stage III and stage IV AM (Tables S4–S6).

Discussion

Previous studies have suggested that trauma may be a risk factor for the prognosis of AM, with the melanoma-related death risk being approximately 5 times higher in traumatic patients compared with those without trauma.[11,16,17] This study represents the most large-scale retrospective study so far examining a pre-diagnostic history of trauma on AM survival and recurrence.

Our results indicated that the prevalence of men and women were different in 2 groups, and the male proportion was higher in the trauma group. This conformed to previous results in China, which have reported a significantly increased post-traumatic AM incidence in men.[18] One possible explanation for this gender difference could be societal roles, particularly in China, where the labor force

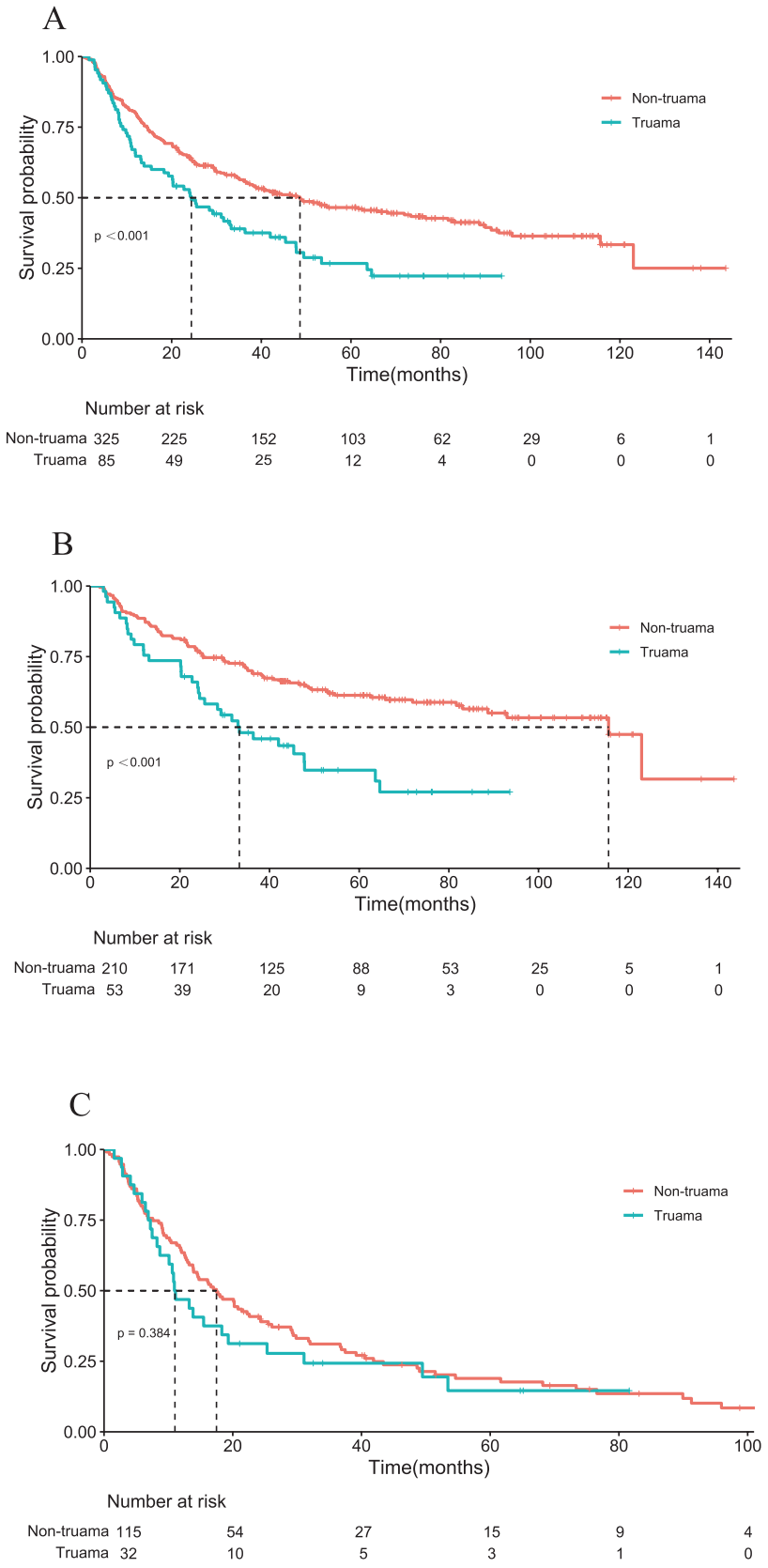


Figure 1. Kaplan-Meier Recurrence-free survival across different groups.

in manufacturing and agriculture is predominantly male. Previous studies have also found that trauma-related AM was more common among individuals with lower education levels. More than 80.9% of affected patients had less than a high school education, and most of these patients were farmers or fishermen.[10,19]

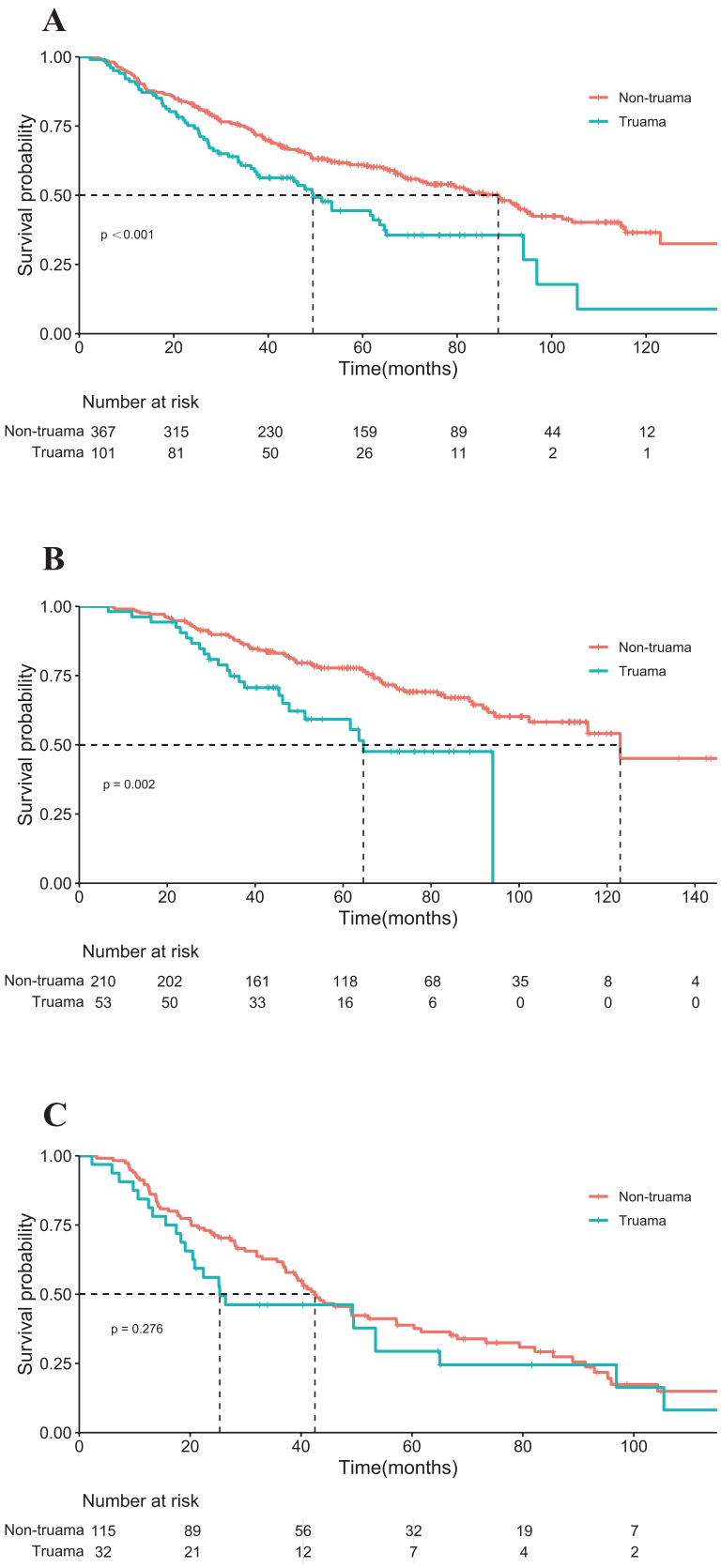


Figure 2. Kaplan-Meier Overall survival across different groups.

In the trauma group, AM predominantly occurred in the palmar region, with the plantar surface of the foot as the most commonly affected site. This finding may be owing to the previously reported association between plantar pressure and an increased risk of AM.[4,8,9,18,20-22] Our study also found that the site of AM in the trauma group was more commonly

Table 2. Univariate and multivariate analysis of risk factors associated with RFS in Stage I-II.

	Univariate		Multivariate	
	HR (95%CI) [a]	*P* value[b]	HR (95%CI) [a]	*P* value[b]
Sex				
Female	1	.031	1	.171
Male	1.491(1.038-2.141)		1.295(0.894-1.874)	
Age, y				
<40	1	.168		
40-49	1.817(0.678-4.870)			
50-59	0.944(0.364-2.453)			
60-69	1.229(0.482-3.136)			
≥70	1.564(0.610-4.011)			
Ulceration				
NO	1	<.001	1	.011
YES	2.350(1.589-3.477)		1.703(1.129-2.568)	
Breslow thickness(mm)				
≤1	1	<.001		.004
>1-2	2.201(1.047-4.627)		1.645(0.766-3.530)	
≥2-4	3.405(1.688-6.947)		2.173(1.018-4.636)	
>4	4.846(2.464-9.532)		3.141(1.524-6.474)	
Mitotic rate(/mm²)				
<1	1	.004	1	.237
≥1	2.040(1.253-3.320)		1.365(0.815-2.285)	
Clark level				
I-III	1	.069		
IV-V	1.413(0.973-2.050)			
Traumatic stimulation				
NO	1	<.001	1	.007
YES	2.122(1.420-3.170)		1.759(1.168-2.647)	

[a]Abbreviations: HR, hazard ratio.
[b]By Cox regression model.

located on the right side of the body. Among subungual melanomas, fingernails were more common than toenails. This may be related to the fact that the right hand is the dominant hand, thus showing a greater chance of external injury. Interestingly, Myoung Eun Choi et al. found a higher incidence of trauma-related AM in toenails, potentially due to the small sample size, which could have led to outcome bias.[11] In conclusion, we speculate that trauma may increase the risk of AM, consistent with the results of previous studies.[10,23,24]

Although the tumor stage was not obviously different in both groups, some variations were observed. The trauma group showed a higher proportion of stage IV cases relative to the non-trauma group. Furthermore, significant differences were observed in the proportion of patients with ulcers, a high mitosis rate, and Clark grade IV-V between the trauma and non-trauma groups. Our findings were consistent with those of a Colombian study, which showed that post-traumatic AM was associated with higher ulcer rates.[22] A South Korean study, also conducted in East Asia, found that the pathological stage of trauma-related nail melanoma was worse than that of non-trauma-related nail melanoma.[11] These findings suggest an association between trauma and later tumor stage, as well as adverse pathological features.

We found that trauma was an independent risk factor for both RFS and OS in AM patients with postoperative stage I-II. Additionally, in stage I-II cases, the trauma group had shortened RFS and OS in comparison with the non-trauma group, similar to the findings from other studies.[11,16] Specifically, trauma did not independently predict the prognostic outcome of stage III-IV cases. These findings suggested an association between trauma and AM. Trauma may not only contribute to the pathogenesis of AM but may also play an important role in the progression of stage I-II AM. In patients with stage III-IV AM, our study suggested that adverse pathological factors seem to play a more prominent role in disease progression than trauma. Interestingly, in stage IV patients, the trauma group had longer OS in comparison with the non-trauma group. It is probably because our sample size of stage IV patients was small and some patients in the trauma group might not have experienced clinical outcomes.

The poor prognosis outcome observed in traumatic patients may be associated with trauma-mediated inflammation. Existing research regarding the association of trauma with tumor development suggests the role of physical trauma in inducing local inflammation and tissue injury. Inflammation and wound healing can change tumor microenvironment, and create conditions beneficial for cell metastatic and distant metastasis, thus promoting tumor progression.[25-29]

Table 3. Univariate and multivariate analysis of risk factors associated with OS in Stage I-II.

	Univariate		Multivariate	
	HR (95%CI)[a]	*P* value[b]	HR (95%CI)[a]	*P* value[b]
Sex				
Female	1	.063		
Male	1.494 (0.979-2.281)			
Age, y				
<40	1	.368		
40-49	0.833 (0.289-2.401)			
50-59	0.664 (0.248-1.779)			
60-69	0.888 (0.341-2.316)			
≥70	1.224 (0.469-3.192)			
Ulceration				
NO	1	<.001	1	.032
YES	2.300 (1.445-3.661)		1.706 (1.048-2.776)	
Breslow thickness(mm)				
≤1	1	<.001	1	.037
>1-2	1.752 (0.707-4.341)		1.147 (0.444-2.961)	
≥2-4	3.783 (1.639-8.730)		2.204 (0.894-5.433)	
>4	4.313 (1.930-9.637)		2.517 (1.028-6.165)	
Mitotic rate(/mm^2)				
<1	1	.001	1	.033
≥1	2.715 (1.468-5.021)		2.014 (1.059-3.830)	
Clark level				
I-III	1	.010	1	.953
IV-V	1.796 (1.151-2.803)		1.015 (0.623-1.652)	
Traumatic stimulation				
NO	1	.002	1	.022
YES	2.140 (1.314-3.483)		1.777 (1.085-2.911)	

[a]Abbreviations: HR, hazard ratio.
[b]By Cox regression model.

Neutrophils are the first responders to tissue injury.[30,31] The wide range of cytokines released by neutrophils under different conditions enables them to promote tumor growth in a direct or indirect manner.[32] In cutaneous melanoma, tumor-associated neutrophils(TANs) have been shown to promote vascular proliferation and suppress anti-tumor immune responses by T lymphocytes.[33] As demonstrated in a Chinese study, traumatic AM patients had an immunosuppressed state, with an increased invasive margin M2 macrophage proportion in comparison with non-traumatized AM patients.[19] The number of M2 macrophages has been correlated with poor prognosis in melanoma patients.[34] Therefore, trauma probably contributes to AM development by altering the tumor microenvironment, thereby influencing the disease process. At the same time, we analyzed the types of trauma in AM cases who had trauma. The incidence of cut/puncture injuries was the highest, suggesting that patients at risk for AM should prevent these potential risk factors during their daily lives.

However, this study still had the following limitations. At first, as a retrospective multicenter study, recall bias may be present. In addition, all 468 patients were Chinese. Therefore, the applicability of the results to other ethnic groups needs to be confirmed through studies involving different populations. Prospective large-scale and population-based studies are warranted for further elucidating the association of trauma with AM and exploring the underlying biological mechanisms.

Conclusions

Our retrospective study demonstrated that AM patients with a history of trauma had poorer pathohistological features and later clinicopathological staging. The association between trauma and recurrence and survival outcomes in AM varied by clinical stage. Trauma was identified as an independent risk factor for RFS and OS in stage I-II AM, significantly affecting both RFS and OS in these patients. Further studies are necessary to elucidate the underlying mechanisms between trauma and the AM disease process.

Acknowledgments

None.

Author Contributions

Conception/design: Di Wu, Yi Teng, Shijie Lan, Zhen Guo, Yongqi Li. Provision of study material or patients: Di Wu, Yi Teng, Jin Wu, Xin Cai, Weizhen Zhang, Kui Jiang, Hongfeng

Zhou, Zhen Guo, Jiwei Liu, Yan Wang, Fang Liu, Shijie Lan, Hongxue Meng, Xiang Ji, Mei Xiang, Yongqi Li. Collection and/or assembly of data: Di Wu, Yi Teng, Jin Wu, Xin Cai, Weizhen Zhang, Kui Jiang, Hongfeng Zhou, Zhen Guo, Jiwei Liu, Yan Wang, Fang Liu, Shijie Lan, Hongxue Meng, Xiang Ji, Mei Xiang, Yongqi Li. Data analysis and interpretation: Yi Teng. Manuscript writing: Yi Teng, Di Wu, Shijie Lan, Zhen Guo, Yongqi Li. Final approval of manuscript: All authors.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare that there is no conflict of interest. *Declaration of interest:* The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data that support the findings of this study are available from the corresponding author, Di Wu, upon reasonable request.

Institutional Review Board Statement

The study was approved by the Ethics Committee of the First Hospital of Jilin University (AFIRB-032-06), and individual consent was not required for this retrospective analysis. All study procedures were performed in accordance with the Declaration of Helsinki (revised 2013) and Good Clinical Practice Guidelines.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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