



# Skin melanoma survival is not superior in females in the new stage IIID of the 8th edition of the staging system: an analysis of data from the Surveillance, Epidemiology, and End Results (SEER) database

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**Background:** In the 8th edition of the melanoma staging system, stage III was divided into stages IIIA–IIID. Previous studies have found that the long-term survival rate of females is much higher than that of males. This study was designed to explore whether this sex-specific advantage still exists in the new staging subgroups.

**Methods:** We obtained data from individuals diagnosed with skin melanoma between 2004 and 2015 from the Surveillance, Epidemiology, and End Results (SEER) database. A total of 8,726 patients with stage III disease were enrolled in the study (5,370 males and 3,356 females). Among these patients, 505 had stage IIID disease (370 males and 135 females).

**Results:** In the 7th edition of the staging system, there were significant sex-specific differences in overall survival (OS) and melanoma-specific survival (MSS) in each subgroup of stage III. In stages IIIA–IIIC in the 8th edition, there were also significant differences between males and females ( $P < 0.001$ ), but in stage IIID patients, there were no significant differences in either OS ( $P = 0.312$ ) or MSS ( $P = 0.288$ ). Cox analysis confirmed that stage IIID does not affect prognosis in males. Further research found no difference between males and females with stage IIID disease in any age subgroup.

**Conclusions:** We compared sex-specific survival differences in patients with stage III disease according to the 8th edition of the staging system. Females with stage IIIA–IIIC disease have better survival rates than males. However, among patients with stage IIID disease, there is no significant difference in survival between males and females.

**Keywords:** Melanoma; skin melanoma; Surveillance, Epidemiology, and End Results (SEER); TNM staging system; sex-specific

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## Introduction

Melanoma is the deadliest skin tumor. In developed countries, the incidence of skin melanoma is 9.3 per 100,000 people (1), and it accounts for 80% of deaths caused by skin tumors. Skin melanoma accounts for 1–2% of all cancer-related deaths. In recent years, skin melanoma has increased in incidence, with higher long-term survival rates (2,3).

The etiology of skin melanoma is not yet clear. Several factors, such as genetics and environmental exposure (e.g., ultraviolet (UV) rays, smoking, drug use, and drinking), probably affect the incidence of skin melanoma. Females have a clear advantage over males in terms of melanoma-specific survival (MSS). Several studies have verified the advantages of female sex in many countries and different populations; these advantages have included a low melanoma incidence and high long-term survival rates. Furthermore, these advantages of female sex have increased gradually in recent years and have been verified in all pathological stages of melanoma (4-7). However, there is no clear theoretical foundation that could account for this phenomenon.

The 8th edition of the American Joint Committee on Cancer (AJCC) staging system for skin melanoma was published in 2017. The staging system for melanoma was adjusted by reducing the importance of the mitotic rate in the T category and adjusting the N category to include more details (8,9). Stage III was divided into 4 subgroups, with a new IIID subgroup, and the IIIA, IIIB and IIIC subgroups were adjusted (*Figure 1*). In past studies, the long-term survival rate in females was verified to be higher than that in males (10). However, no studies have investigated sex-specific survival based on the 8th edition of the staging system, especially in patients with stage III disease. Therefore, we selected skin melanoma patients from the Surveillance, Epidemiology, and End Results (SEER) database in the United States. The aim of our study was to evaluate sex-specific survival in patients with stage III disease based on the 8th edition of the staging system. The guidelines in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement were followed in this study (available at <http://dx.doi.org/10.21037/atm-20-3332>).

## Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards

of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments revised in 2013 or comparable ethical standards.

Patients were selected from the SEER database. The current SEER database is a population-based cancer registry sponsored by the National Cancer Institute of the United States. We selected individuals diagnosed with skin melanoma between 2004 and 2015. Based on the 7th and 8th editions of the melanoma staging system, patients diagnosed with pathological T0-T4b, N1a-N3c and M0 disease were enrolled. Other enrollment criteria included skin melanoma as the first malignant tumor, active follow-up, and positive histology. Patients were excluded if diagnosed during autopsy or if the cause of death was unknown.

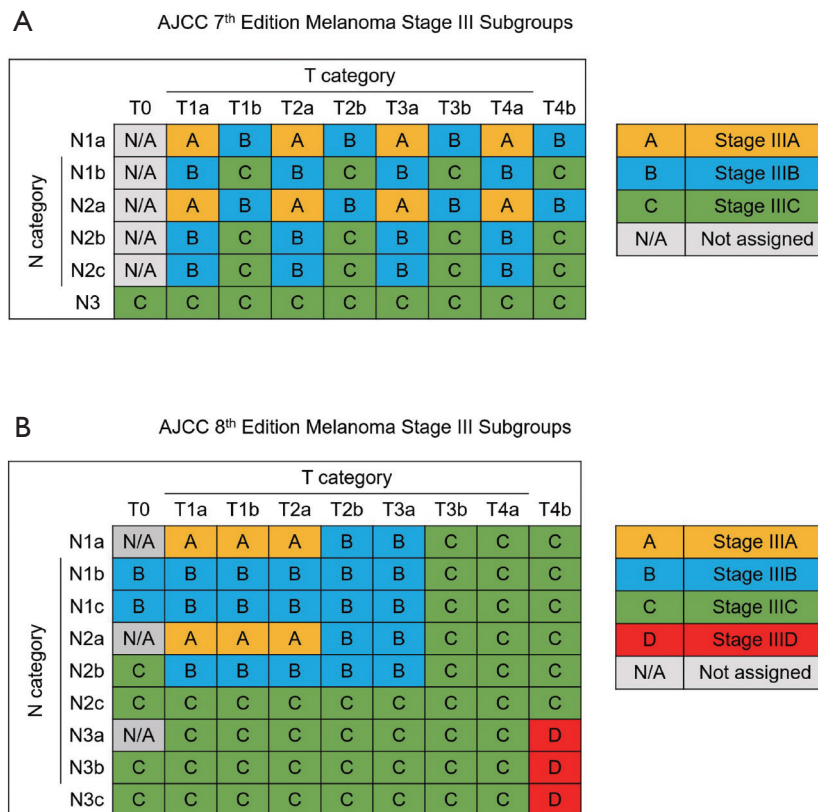
Baseline data, including patient information (age, sex), and melanoma characteristics (location, subtype, Clark class, Breslow thickness, mitotic rate, and ulceration) were obtained from the SEER database. In this study, overall survival (OS) and melanoma-specific survival (MSS), which were collected from the SEER database through December 31, 2015, were used to evaluate the outcomes. OS and MSS were defined as the intervals from diagnosis until death from any cause or death as a result of melanoma, respectively.

## Statistical analysis

We used one-way ANOVA with a multiple comparison post hoc test and a chi-square test to analyze all continuous and categorical variables with normal distributions. The Kruskal-Wallis test was used to analyze data with nonnormal distributions after adjusting for multiple comparisons. Kaplan-Meier survival curves were estimated and compared with the log-rank test. Cox regression analysis was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Risk factors with a P value <0.1 in the univariate analysis and with substantial clinical value were selected for the multivariate analysis. A two-sided P value <0.05 was considered statistically significant. SPSS 24.0 (SPSS, Chicago, IL, USA) and GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA) were used for the analyses.

## Results

A total of 8,726 stage III patients (5,370 males and



**Figure 1** AJCC stage III subgroups based on T and N categories (A) 7th edition (9). (B) 8th edition (8). N/A, not assigned. AJCC, American Joint Committee on Cancer.

3,356 females) were enrolled in this study. According to the 8th edition of the staging system, 505 patients were classified as having stage IIID disease (370 males and 135 females). Baseline data are shown in *Table 1*. Among all stage III patients, the males were older (57.0±15.7 vs. 53.9±18.0 years, P<0.001) and had a worse Breslow thickness (316.3±241.2 vs. 290.5±231.5 mm, P<0.001). The trunk (42.2%) was the most frequent location of skin melanoma in males, while the lower limb and hip (38.3%) were most frequent in women. There were more Caucasians among the males with stage III (96.9% vs. 96.1%, P=0.045) and stage IIID (94.6% vs. 89.7%, P=0.049) disease (*Table S1*). The rate of ulceration was higher in males than in females (45.3% vs. 39.4%, P<0.001), and males had a lower mitotic rate (P=0.021). There was no difference between males and females with regard to the subtype of melanoma and Clark class.

Among the patients with stage IIID disease, there was no significant difference in age, and the average patient age was slightly older in women than in men (59.1±15.5

vs. 61.2±18.1 years, P=0.121). The Breslow thickness also showed the same trend (727.9±205.2 vs. 699.3±208.6 mm, P=0.234), and the baseline data were basically consistent among those with stage III disease.

In terms of differences in sex-specific survival, the Kaplan-Meier survival curves showed significant differences in both OS and MSS between male and female patients with stage IIIA, IIIB, and IIIC disease based on the 7th edition of the staging system (*Figures 2,3*). The only nonsignificant difference in OS was among patients with stage IIIC disease (P=0.050, borderline significant). After classifying patients based on the 8th edition of the staging system, there were significant differences in both OS and MSS between males and females with stage IIIA, IIIB, and IIIC disease (P<0.001). However, among patients with stage IIID disease, neither OS (P=0.288) nor MSS (P=0.312) differed between males and females (*Figures 4,5*). There were more Caucasians among males with stage III and IIID disease. To determine whether there was a sex-specific survival advantage among white patients and nonwhite patients, we estimated the

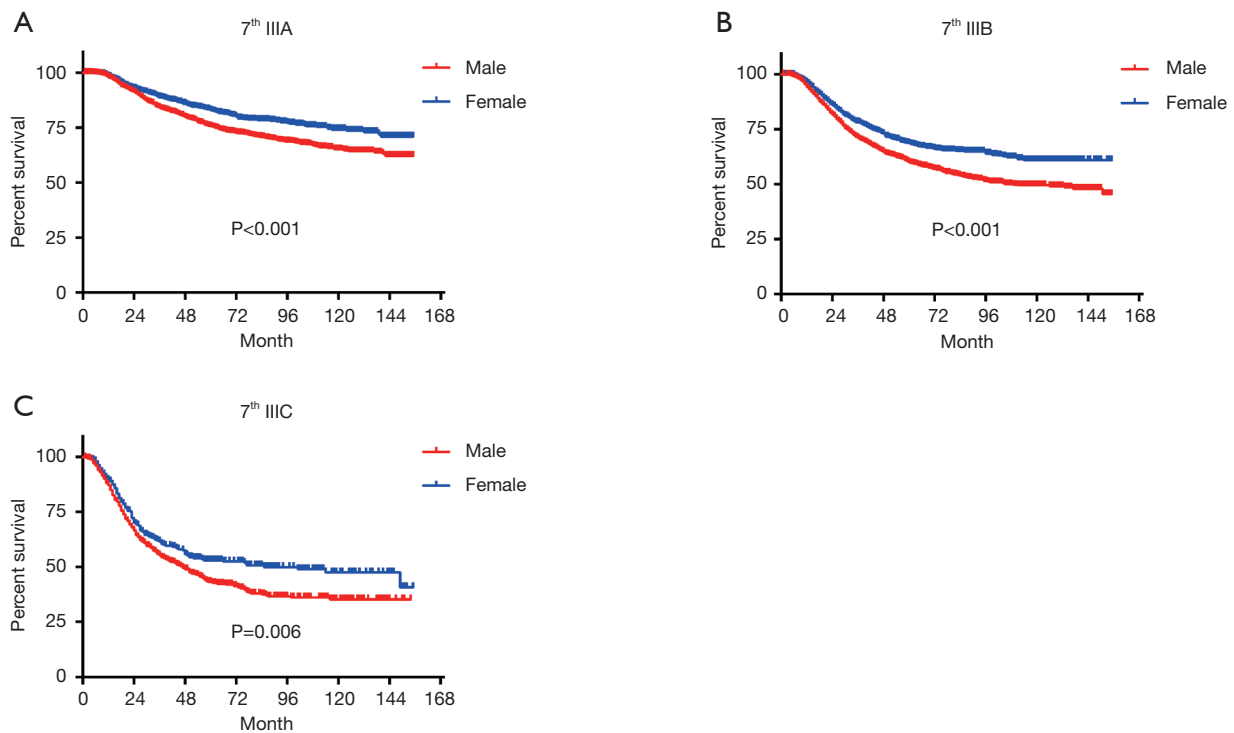
Table 1 Baseline data of patients

	All stage III patients (n=8,726)			Stage IIID patients (n=505)		
	Male (n=5,370)	Female (n=3,356)	P value	Male (n=370)	Female (n=135)	P value
Age, years (%)	57.0±15.7	53.9±18.0	<0.001	59.1±15.5	61.2±18.1	0.121
<35	487 (9.1)	523 (15.6)	<0.001	30 (8.1)	11 (8.1)	0.090
35–54	1,705 (31.8)	1,186 (35.3)		100 (27.0)	35 (25.9)	
55–74	2,490 (46.4)	1,164 (34.7)		176 (47.6)	48 (35.6)	
≥75	688 (12.8)	483 (14.4)		64 (17.3)	41 (30.4)	
Location (%)						
Head and neck	1,022 (19.0)	322 (9.6)	<0.001	75 (20.3)	13 (9.6)	<0.001
Trunk	2,265 (42.2)	958 (28.6)		144 (38.9)	32 (23.7)	
Upper limb and shoulder	1,122 (20.9)	787 (23.5)		48 (13.0)	19 (14.1)	
Lower limb and hip	951 (17.7)	1,284 (38.3)		101 (27.3)	71 (52.6)	
Others	10 (0.2)	5 (0.1)		2 (0.5)	0 (0)	
Subtype of melanoma (%)						
Superficial spreading	1,373 (25.6)	884 (26.3)	0.357	56 (15.1)	16 (11.9)	0.571
Nodular	1,379 (25.7)	774 (23.1)		150 (40.5)	65 (48.1)	
Lentigo maligna melanoma	47 (0.9)	27 (0.8)		1 (0.3)	0 (0)	
Acral lentiginous	153 (2.8)	134 (4.0)		19 (5.1)	12 (8.9)	
Others	281 (5.2)	135 (4.0)		23 (6.2)	5 (3.7)	
Melanoma not specified	2,137 (39.8)	1,402 (41.8)		121 (32.7)	37 (27.4)	
Clark classification (%)						
II	102 (1.9)	90 (2.7)	0.103	1 (0.3)	0 (0)	0.857
III	565 (10.5)	352 (10.5)		8 (2.2)	3 (2.2)	
IV	3,300 (61.5)	2,082 (62.0)		144 (38.9)	49 (36.3)	
V	690 (12.8)	409 (12.2)		160 (43.2)	70 (51.9)	
Unknown	713 (13.3)	423 (12.6)		57 (15.4)	13 (9.6)	
Breslow thickness (mean ± SD) (%)	316.3±241.2	290.5±231.5	<0.001	727.9±205.2	699.3±208.6	0.234
<1.0 mm	664 (12.4)	483 (14.4)	<0.001	0 (0)	0 (0)	0.457
1.1–2.0 mm	1,539 (28.7)	1,120 (33.4)		0 (0)	0 (0)	
2.1–4.0 mm	1,800 (33.5)	1,030 (30.7)		0 (0)	0 (0)	
>4 mm	1,359 (25.3)	715 (21.3)		369 (99.7)	134 (99.3)	
Unknown	8 (0.1)	8 (0.2)		1 (0.3)	1 (0.7)	
Mitotic rate (%)						
<1	253 (4.7)	160 (4.8)	0.021	8 (2.2)	1 (0.7)	0.066
1	427 (8.0)	323 (9.6)		10 (2.7)	2 (1.5)	
≥2	2,322 (43.2)	1,462 (43.6)		183 (49.5)	59 (43.7)	
Unknown	2,368 (44.1)	1,411 (42.0)		169 (45.7)	73 (54.1)	

Table 1 (continued)

Table 1 (continued)

	All stage III patients (n=8,726)			Stage IIID patients (n=505)		
	Male (n=5,370)	Female (n=3,356)	P value	Male (n=370)	Female (n=135)	P value
Ulceration (%)						
Yes	2,434 (45.3)	1,321 (39.4)	<0.001	369 (99.7)	135 (100.0)	0.546
No	2,921 (54.4)	2,026 (60.4)		0 (0)	0 (0)	
Unknown	15 (0.3)	9 (0.3)		1 (0.3)	0 (0)	



**Figure 2** Long-term OS based on the 7th edition of the TNM staging system. (A) Stage IIIA; (B) stage IIIB; (C) stage IIIC. OS, overall survival.

Kaplan-Meier survival curves for patients with stage III and IIID disease. There was a significant difference in OS between males and females among white patients ( $P<0.001$ ) and among nonwhite patients ( $P=0.002$ ) with stage III disease. In contrast, no significant difference was observed in OS between males and females among white patients ( $P=0.323$ ) and among nonwhite patients ( $P=0.840$ ) with stage IIID disease (Figure S1).

Further Cox analysis suggested that among all stage III patients, after adjusting for age, tumor location, Breslow thickness, mitotic rate, and ulceration, males with stage III disease had a significantly increased risk of mortality (HR

=1.431, 95% CI: 1.311–1.562,  $P<0.001$ ) (Table 2). There were no significant difference in the factors used to adjust the analysis between males and females with stage IIID disease (HR =1.133, 95% CI: 0.847–1.517,  $P=0.400$ ) (Table 3).

There was a significant difference in age between males and females with stage III disease but not among those with stage IIID disease. To verify whether age is related to survival, we further divided the patients into the following groups based on age: <55, 55–74 and  $\geq 74$  years. Cox analysis was performed in all groups. The results suggest that the risk of mortality in males is significantly higher than that in females in all age groups ( $P<0.001$ ). In patients with stage

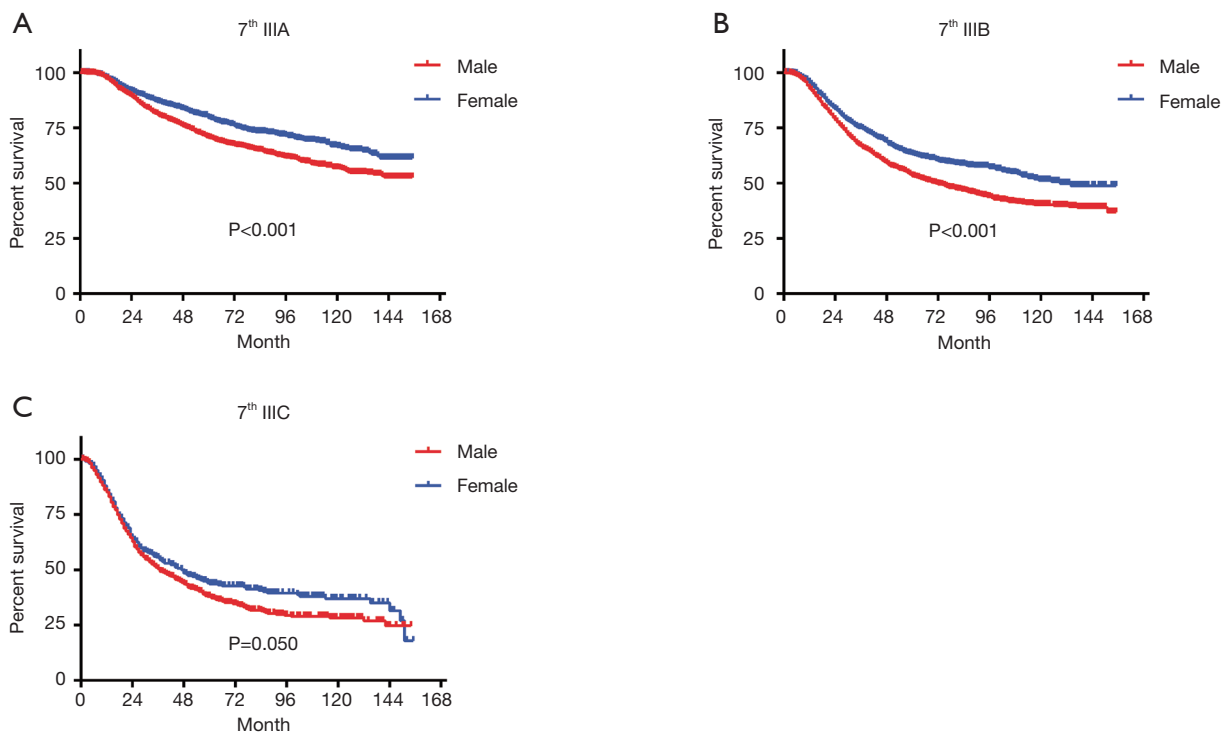


Figure 3 Long-term MSS based on the 7th edition of the TNM staging system. (A) Stage IIIA; (B) stage IIIB; (C) stage IIIC.

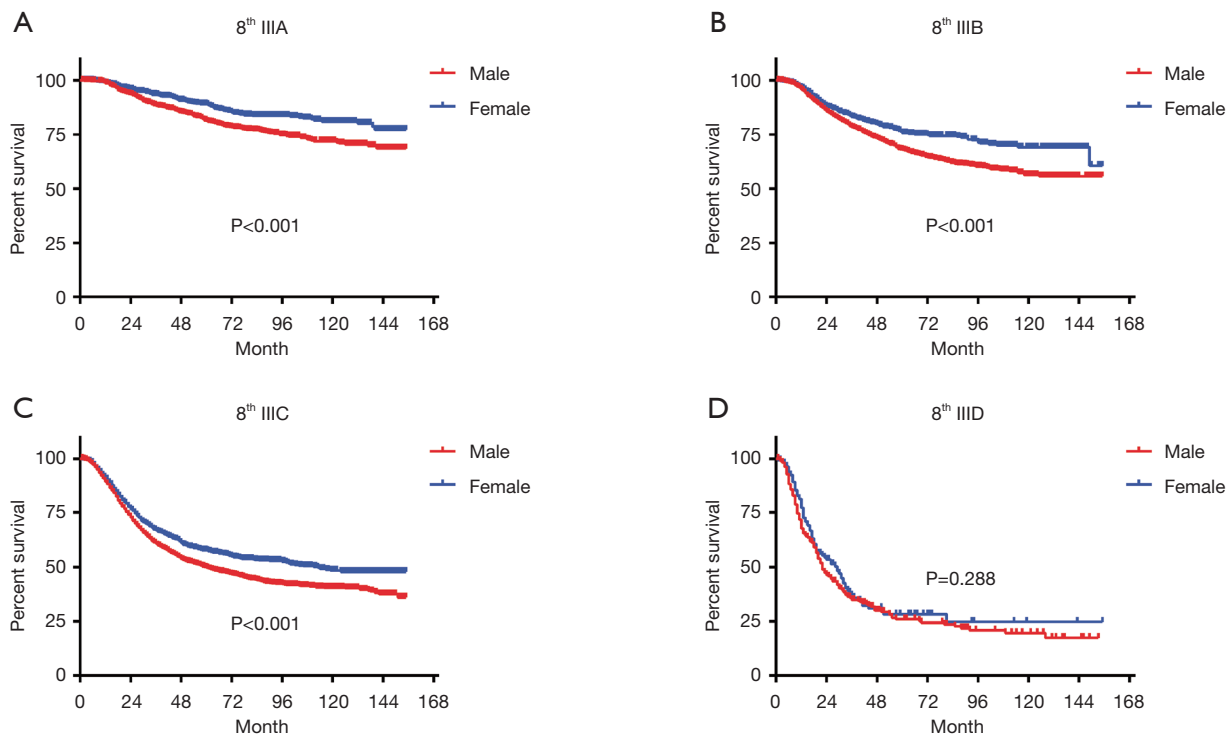
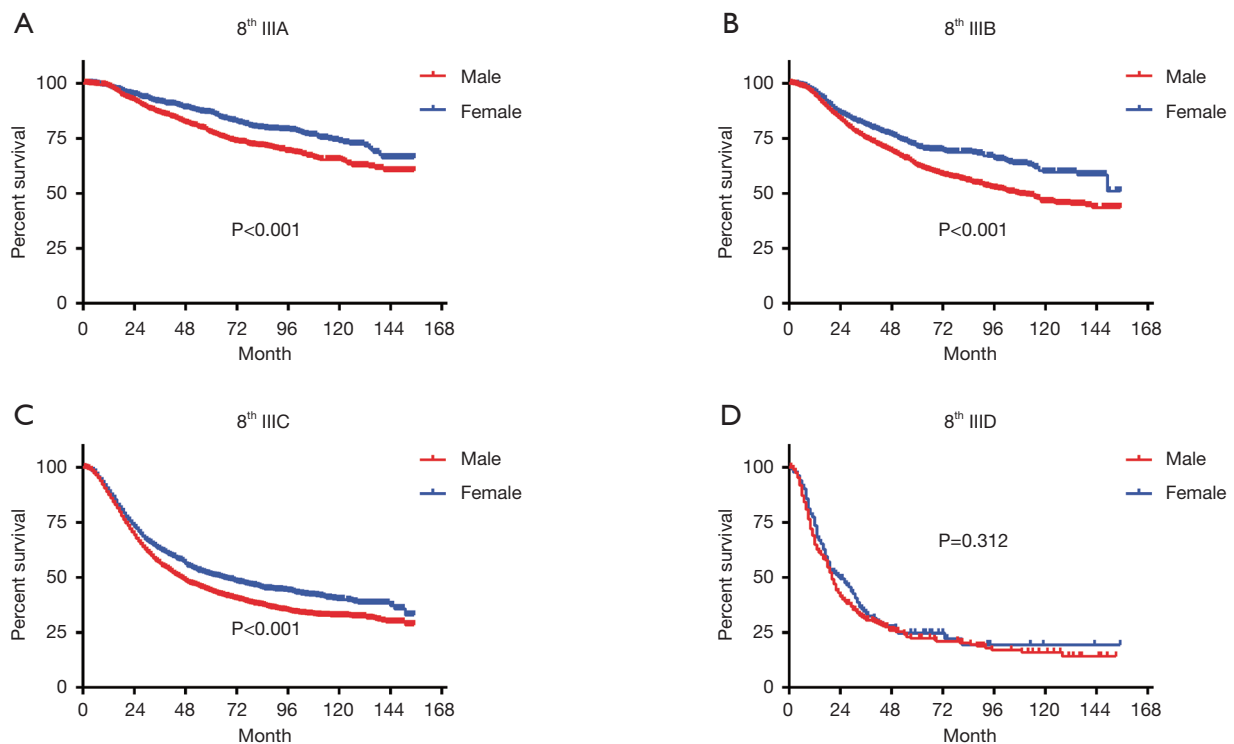


Figure 4 Long-term OS based on the 8th edition of the TNM staging system. (A) Stage IIIA; (B) stage IIIB; (C) stage IIIC; (D) stage IIID. OS, overall survival.



**Figure 5** Long-term MSS based on the 8th edition of the TNM staging system. (A) Stage IIIA; (B) stage IIIB; (C) stage IIIC; (D) stage IIID. MSS, melanoma-specific survival.

**Table 2** Cox analysis of the sex-specific risk of mortality among all stage III patients

	P value	HR	95% CI
Male vs. female	<0.001	1.431	1.311–1.562

HR, hazard ratio; CI, confidence interval. Models adjusted by age, location, Breslow thickness, mitotic rate, ulceration.

**Table 3** Cox analysis of the sex-specific risk of mortality among all stage IIID patients

	P value	HR	95% CI
Male vs. female	0.400	1.133	0.847–1.517

Models adjusted by age, location, Breslow thickness, mitotic rate.

IIID disease, there was no significant sex-specific difference in survival in any age group (*Table 4*).

## Discussion

In the new 8th edition of the staging system, the staging of most tumors has been adjusted. For example, in esophageal

adenocarcinoma, stage I has been redistributed. However, it was found that survival did not differ between patients with the new stages IA and IB (11). Skin melanoma staging was adjusted mainly in stage III, with the addition of another subgroup to further differentiate among patients with regard to survival. The application of the 8th edition of the staging system led to a the 5-year tumor-specific survival rate ranging from 93% (stage IIIA) to 32% (stage IIID), showing better discrimination than the 7th edition of the staging system, which ranged from only 78% (stage IIIA) to 40% (stage IIIC) (12).

Although the difference in survival between subgroups is very obvious in the 8th edition of the staging system, we observed a very interesting phenomenon. Among stage IIID patients, the survival advantage of female sex does not exist, which may be due to the combination of T4b + N3 in stage IIID disease (i.e., more lymph node metastasis and relatively advanced tumors). Hence, stage IIID patients experience a lower survival rate, which may affect the advantage of women (13). In patients with stages IIIA–IIIC disease, the tumor prognosis is better, making a sex-specific advantage more feasible. Therefore, males and females may have



**Table 4** Cox analysis of the sex-specific risk of mortality among patients in different age groups

Age, years	All stage III patients			Stage IIID patients		
	P value	HR	95% CI	P value	HR	95% CI
<55	<0.001	1.397	1.177–1.659	0.916	1.028	0.618–1.709
55–74	<0.001	1.566	1.275–1.924	0.440	1.175	0.780–1.771
≥74	<0.001	1.500	1.245–1.807	0.748	1.113	0.578–2.114

Models adjusted by location, Breslow thickness, and mitotic rate.

significantly different survival rates.

The higher female survival rates may be related to multiple factors. In this study, among patients with stage III disease, male patients were generally older; no such difference in age was observed in stage IIID patients. To verify whether the difference in survival was driven by age, we performed a Cox analysis of different age groups and found that the trend remained the same in each age group as in the entire group. The location of the disease may be one of the reasons for this observation. Some studies have found that the most common location of malignant melanoma in women is the lower limb, while that in men is the trunk. The surgical margins and external stresses differ in various parts of the body, which may lead to differences in prognosis (14–17). Our baseline data also confirm this distribution difference. Among all stage III patients, male patients had worse Breslow thickness and a higher ulceration rate, but no significant differences were observed in these factors between males and females with stage IIID disease. These factors were included as predictors of survival in melanoma patients according to the current 8th edition of the AJCC staging system. However, after adjusting for multiple factors, Cox analysis showed that there was still a significant difference in age between males and females among all patients with stage III disease but not among the subgroup of patients with stage IIID disease. On the other hand, some studies have suggested that women are more likely to apply sunscreen in their daily lives, thereby reducing their UV exposure, which is considered the most important environmental factor leading to skin melanoma and affecting prognosis (4,14,18). In addition, studies on stage I melanoma have found that only in the >60-year-old group is female sex associated with a higher survival rate (10). Moreover, pregnant women have better survival rates, possibly due to sex hormone secretion. However, there is no clear evidence to support this conjecture (19).

Genetics is also a potential factor affecting the survival advantage in females. Some studies have analyzed The

Cancer Genome Atlas (TCGA) database and found that the missense mutation burden in males was significantly higher than that in females [median in males 298 *vs.* females 211.5; male to female ratio (M: F) =1.85, 95% CI: 1.44 to 2.39] (19). The link between the burden of missense mutations and the immune response may partially explain the survival advantages in females. Studies have found that inherited MC1R mutations at specific sites are associated with prolonged survival in females, whereas in males, these mutations do not affect survival (20). However, there are still few studies on the roles of genetics in sex-based differences, and there is no comprehensive theoretical basis.

In our study, a large number of samples were analyzed, and this real-world study provides information that more closely reflect the real situation than information obtained from RCTs, which use carefully selected patients populations. This study was performed to evaluate the sex-specific survival advantage, so we used Cox analysis and adjusted for multiple factors to ensure the reliability of the results.

There are also some limitations of our research. Although the overall sample size was very large, the number of patients with stage IIID disease was small, which may have affected the results. Although it is difficult to collect sufficient patient samples for some stages of disease, further large-scale controlled studies can still be expected to confirm this result.

## Conclusions

In summary, we analyzed patients with stage III disease based on the 8th edition of the staging system. Among patients with stages IIIA–IIIC disease, female patients had a significantly higher survival rate than males. However, this sex-specific benefit did not exist among patients with stage IIID disease. This research can provide a theoretical basis for future clinical trials on diagnosis and prognosis.



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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-3332>

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*Ethics Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments revised in 2013 or comparable ethical standards.

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