

## 利用 SEER 数据库分析族群因素对于黑色素瘤预后的影响

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**【摘要】 目的** 研究族群因素及其与临床因素的交互作用对预后的影响,以明确族群是否是黑色素瘤的关键预后因素。**方法** 基于美国 SEER 数据库,通过 Cox 比例风险模型和两种机器学习方法(随机森林模型和梯度提升树模型)检验族群因素对黑色素瘤预后的重要性。利用 Logistic 回归模型来研究族群和疾病阶段/皮肤溃疡的交互作用对黑色素瘤所导致死亡的影响。**结果** 在 Cox 模型的结果中,非白人相对于白人的死亡风险比体现为临界显著性,且在两种机器学习方法的分析结果中,族群因素的重要性较低。在 Logistic 回归模型中,对于在癌症早期确诊的患者,美国非西班牙裔黑人、亚裔以及西班牙裔由黑色素瘤所致的死亡率显著高于白人,分别为 1.76(95%CI: 1.34~2.31)、1.52(95%CI: 1.16~1.99)和 1.19(95%CI: 1.04~1.35);而对于在癌症晚期确诊的患者,不同族裔由黑色素瘤所致的死亡率相比于白人,差异无统计学意义。**结论** 族群因素不是皮肤黑色素瘤的独立预后因子,有必要加强对非白人黑色素瘤患者的早期筛查和医疗干预。

**【关键词】** 黑色素瘤; 族群; 预后分析; SEER 数据库

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## Effects of race on the survival in melanoma analyzed by the SEER database

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**【Abstract】 Objective** To investigate the impact of race and its interaction with clinical factors on prognosis, and to determine whether racial factor is a key prognostic factor for melanoma. **Methods** We examined the effect of race on survival in melanoma with the Cox proportional hazards (CoxPH) model and two machine learning methods, random forest (RF) model and gradient boosting machine (GBM) model, using the Surveillance, Epidemiology, and End Results (SEER) database. A Logistic regression model was applied to investigate the interaction effects between race and stage/ulceration factors on the melanoma-specific mortality. **Results** Race showed borderline significance in the Cox model and had low variable importance in two machine learning models. In the Logistic regression model, for patients diagnosed at stage I / II, the odds ratios (OR) of melanoma-specific mortality in non-Hispanic blacks, non-Hispanic Asians, and Hispanics were 1.76 (95%CI: 1.34–2.31), 1.52 (95%CI: 1.16–1.99) and 1.19

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(95%CI: 1.04–1.35) relative to whites, while the results were not significant for patients diagnosed at stage III/IV. **Conclusion** Race is not an independent prognostic factor for melanoma. It is necessary to strengthen early screening and medical interventions for melanoma patients of non-white ethnicities.

**【Key words】** melanoma; race; prognosis analysis; SEER database

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There are 75% of deaths from skin malignancies caused by melanomas<sup>[1]</sup>. The incidence of melanoma has been steadily increasing over the last two decades and is expected to continue to increase<sup>[2]</sup>. It is a worldwide burden, not only in the United States, Europe, and Australia, but also in Asian countries<sup>[3]</sup>.

Although the incidence of melanoma in whites is significantly higher than that in other racial groups<sup>[4]</sup>, the survival outcome was found to be worse in nonwhites in most studies<sup>[5-7]</sup>. However, it is still controversial whether race/ethnicity is an important prognostic factor for melanoma. For example, in a retrospective study of patients diagnosed with acral lentiginous melanoma (ALM) between 1987 and 2013 in Northern California, nonwhites demonstrated a lower hazard ratio (HR) of 0.88, as compared with White patients<sup>[8]</sup>. In contrast, Blacks were found to have a slightly higher risk of death (HR=1.1) than White patients diagnosed between 2004 and 2016 in the National Cancer Database<sup>[9]</sup>. Further exploration to explain worse survival outcomes in non-white groups is still lacking.

In this study, we carried out an in-depth investigation of whether race/ethnicity was a key prognostic factor using Cox proportional hazard (CoxPH) analysis and machine learning (ML) methods. As we found that race/ethnicity was not an independent factor in melanoma, we tested the interactions and correlations between races and other factors to explain the survival disadvantage in nonwhites.

## Materials and Methods

**Data source and prefiltering** We retrieved the data of patients with cutaneous melanoma diagnosed between 2004 and 2014 from the SEER database

(SEER-18 Regs Custom registry, Nov 2018) using SEER\*Stat 8.3.6 (<https://seer.cancer.gov/data-software/>). We collected data from 2004, because Collaborative Staging System was introduced in 2004, which is more precise in staging (<https://seer.cancer.gov/tools/collabstaging/>). Patients with the following records were preliminarily excluded: cancer was diagnosed at autopsy; race was classified as “unknown race”; follow-up survival month flag was “0 day of survival” or “unknown”; type of follow-up was “not active”; diagnostic confirmation was “not microscopically confirmed”. We also excluded 49 926 patients who had more than one cancer or who were diagnosed with melanoma after another cancer diagnosis. In total, 149 115 patients with malignant melanoma of the skin were included in this study.

**Variable selection** Race/ethnicity was classified as non-Hispanic white (NHW), non-Hispanic black (NHB), non-Hispanic Asian and Pacific islander (NHAPI), non-Hispanic American Indian/Alaska native (NHAI/AN), and Hispanic. Covariates included demographic and social characteristics (age, sex, diagnosis year, poverty, education, and marital status), clinical factors (stage, tumor thickness, ulceration, histology subtype, tumor site, and metastasis status), treatment data (primary surgery, other surgery, chemotherapy, and radiation), and survival data (survival time in months and survival status). The outcome of the survival analysis was the time in months from diagnosis to death from any cause (overall survival) or death from melanoma (melanoma-specific survival). Stage was defined according to Derived AJCC Stage Group, 6th ed

(2004–2015)<sup>[10]</sup>. The detailed description of all variables in SEER can be found at [https://seer.cancer.gov/manuals/2023/SPCSM\\_2023\\_MainDoc.pdf](https://seer.cancer.gov/manuals/2023/SPCSM_2023_MainDoc.pdf).

**Race importance evaluation and interaction with prognostic factors** Survival analysis and two ML models were used to determine whether race was an independent prognostic factor of melanoma and Logistic model was used to investigate the interaction effects between race and stage/ulceration factors. The Kaplan-Meier (KM) curve was used to describe overall survival and melanoma-specific survival<sup>[11]</sup> and the log-rank method was applied to test differences among racial groups. Since the follow-up consists of annual visits and lasts for a minimum of 5 years, 5-year survival rate was calculated using KM method considering the right-censored data. We used  $\log[-\log(\text{survival})]$  curves to confirm whether covariates satisfied the proportional hazard assumption. Because NHAI/AN ( $n=313$ ) violates the proportional hazards assumption of the Cox model, it was not been included in the Cox model for analysis. An univariable and multivariable CoxPH regression model was fitted (NHW is the reference race) and adjusted for pathological, demographic, surgical, and socioeconomic factors.

Two ML algorithms, random forest (RF) and gradient boosting machine (GBM), were implemented to predict melanoma-specific mortality with the same variables used in the CoxPH model. Since the data were substantially imbalanced with respect to survival outcome, we down-sampled alive patients by randomly selecting one-third of them and up-sampled twice as many dead patients. To obtain consensus feature importance, we sampled and trained the data 50 times with a ratio of 7:3 between the training and testing sets. 5-fold cross validation was used to optimize the hyperparameters through an exhaustive grid search. In each repetition, the model was refitted using the training set with optimal parameters and subsequently used to predict the survival status in the testing set. The average area

under the receiver operating characteristic curve (AUC) and accuracy were calculated for both models.

A multivariable logistic regression model was fitted to evaluate the interaction effect between race/ethnicity and clinical factors (ulceration and stage) on the odds of melanoma-specific mortality (the odds of death). In both the early and later stages, the odds ratios (ORs) of melanoma-specific death (NHWs as the reference race) and 95% CIs were estimated across racial/ethnic groups, after adjusting for demographic and clinical factors.

**Statistical test** Collinearity between categorical variables was assessed using Cramer's V method, and Pearson's test was applied to continuous variables. The Kruskal-Wallis test was applied to examine racial differences in tumor thickness and poverty proportion, and the chi-squared test was used for ulceration and stage. For pairwise comparisons between NHW and non-white groups, the Wilcoxon rank-sum test and proportion test were performed on the tumor thickness/poverty proportion and ulceration/stage proportion, respectively.

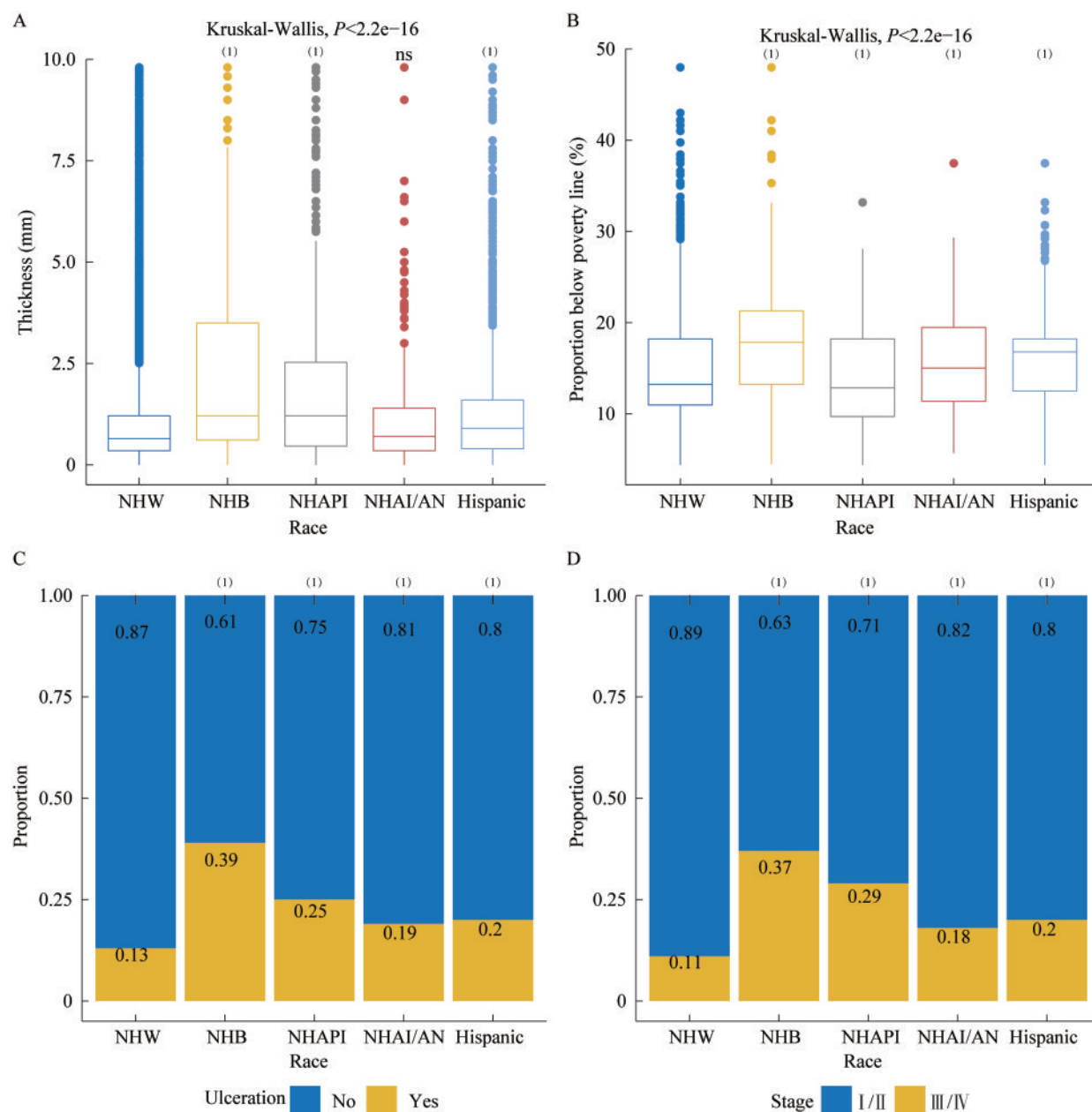
**Data availability statement** The R code and raw data used for this analysis are available at <https://github.com/MinxiBen/Ethnic-Disparity-in-Melanoma>.

## Results

**General condition** For 149 115 patients with malignant melanoma of the skin included in this study, the median follow-up period was 66 months. Comprehensive demographic characteristics of the examined population can be found in Supplementary Tab 1. The sample mostly included NHWs (95.1%), followed by Hispanics (3.5%), NHAPIs (0.7%), NHBs (0.5%), and NHAIs/ANs (0.2%). Histology varied substantially by race ( $P<0.001$ ). Superficial Spreading Melanoma subtype was much more common in NHWs (30.7%). Acral Lentiginous Melanoma was rare in NHWs (0.7%) but had a higher incidence in NHAPIs (12.3%) and NHBs (17.4%). Race showed low correlations with

other variables (Cramer's  $V < 0.1$ ; Supplementary Fig 1). Although the stage was correlated with several factors, it was retained for a more comprehensive adjustment. The discrepancies among races in terms of ulceration, stage, tumor thickness, and poverty proportion factors at diagnosis are shown in Fig 1. NHWs had thinner tumor (mean[*sd*]: 1.19

[1.61]) than other races (Kruskal-Wallis test,  $P < 0.001$ ). The neighborhood poverty proportion was lower in NHWs than other racial groups except NHAPIs (Wilcoxon test,  $P < 0.001$ ). In addition, NHWs had a lower proportion of ulceration (12.9%) and a lower proportion of stage III/IV (11.1%) than other races (chi-squared test,  $P < 0.001$ ).

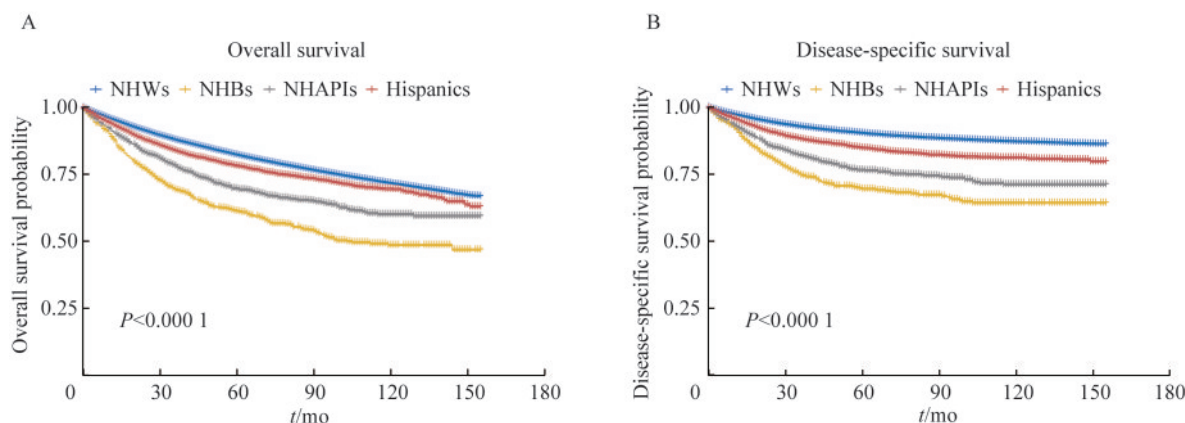


The group difference in tumor thickness (mm) and poverty proportion is tested by the Kruskal-Wallis test. Wilcoxon test is used to assess the difference between NHWs and other racial groups. In ulceration and stage factors, the proportion test is used to examine differences between NHWs and other races. A: Boxplot of tumor thickness; B: Boxplot of poverty proportion; C: Stacked barplot of proportions of ulceration; D: Stacked barplot of proportions of stage III/IV. <sup>(1)</sup> $P < 0.0001$ .

**Fig 1** Discrepancy among races in tumor thickness, poverty proportion, ulceration, and stage factors at diagnosis in SEER

**Survival analysis** In the overall and melanoma-specific KM survival curves stratified by race, NHBs had the worst survival compared to other races, followed by NHAPIs, Hispanics, and NHWs (Fig 2). The 5-year melanoma-specific survival rates for NHWs, NHBs, NHAPIs, and Hispanics were 90.1% (95%CI: 89.9%–90.3%), 69.3% (95%CI: 65.7%–73.0%), 76.2% (95%CI: 73.3%–79.1%) and 84.6% (95%CI: 83.6%–85.7%), respectively. In the unadjusted CoxPH model, mortality HRs in NHBs, NHAPIs, and Hispanics were 3.90 (95%CI: 3.31–4.60), 2.10 (95%CI: 2.03–2.85) and 1.59 (95%CI: 1.45–1.74), respectively, compared with NHWs. However, in the adjusted

model, survival differences by race were attenuated and racial differences remained significant only for Hispanics compared with NHWs (1.15, 95%CI: 1.05–1.26,  $P<0.001$ ) (Tab 1). The HRs for NHAPIs and NHBs exhibited borderline significance (NHAPI: 1.19, 95%CI: 1.00–1.41,  $P=0.05$ ; NHB: 1.21, 95%CI: 1.02–1.43,  $P=0.03$ ) (Tab 1). Clinical factors (e. g., stage, ulceration, and tumor thickness,  $P<0.001$ ), demographic information (e. g., age and diagnosis year,  $P<0.001$ ), and socioeconomic factors, such as education and poverty, were still significant after adjustment (Tab 1).



A: Overall survival curve ( $P<0.0001$ ); B: Melanoma-specific survival curve ( $P<0.0001$ ).

**Fig 2** KM survival curves of patients with melanoma diagnosed between 2004 and 2014 in SEER by race

**Tab 1** Multivariable Cox regression analysis for factors affecting melanoma-specific survival

Factor	HR	95% CI	P
<b>Race</b>			
NHW	Ref		
NHB	1.21	1.02–1.43	<b>0.03</b>
NHAPI	1.19	1–1.41	0.05
Hispanic	1.15	1.05–1.26	<b>&lt;0.001</b>
<b>Sex</b>			
Female	Ref		
Male	1.33	1.27–1.39	<b>&lt;0.001</b>
Age	1.03	1.02–1.03	<b>&lt;0.001</b>
<b>Partner</b>			
Partner	Ref		
No partner	1.26	1.21–1.32	<b>&lt;0.001</b>
Unknown	0.83	0.77–0.89	<b>&lt;0.001</b>

(Continued Tab 1)

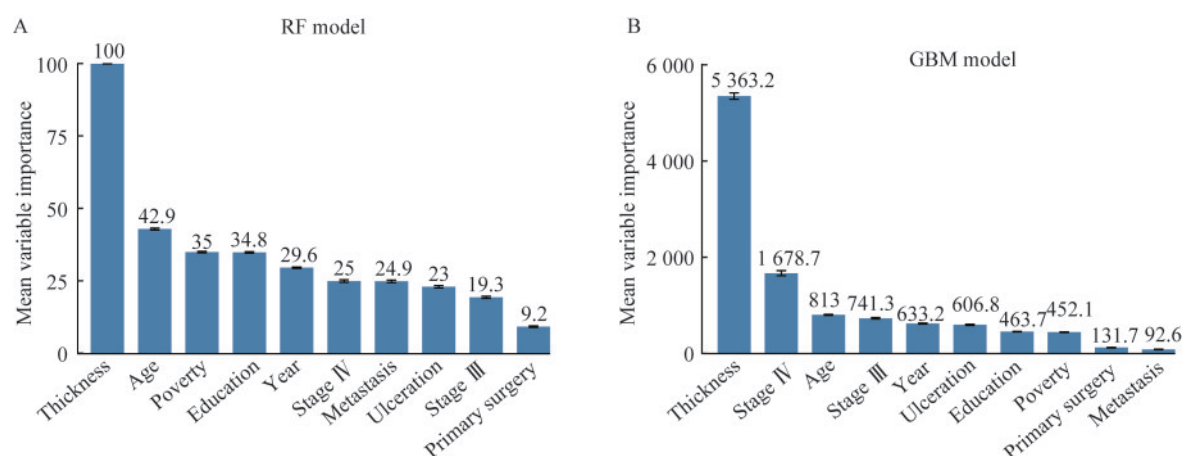
Factor	HR	95% CI	P
<b>Site</b>			
Upper limb and shoulder	Ref		
Lower limb and hip	1.08	1.01–1.15	<b>0.02</b>
Trunk	1.28	1.21–1.35	<b>&lt;0.001</b>
Head and neck	1.44	1.36–1.53	<b>&lt;0.001</b>
Overlapping lesions	1.72	0.89–3.31	0.11
Unknown	1.58	1.39–1.81	<b>&lt;0.001</b>
<b>Histology</b>			
Superficial spreading	Ref		
Lentigo maligna	0.84	0.74–0.96	<b>0.01</b>
Desmoplastic	0.84	0.72–0.97	<b>0.02</b>
Melanoma NOS	1.17	1.11–1.24	<b>&lt;0.001</b>
Amelanotic	1.04	0.83–1.30	0.73
Nodular	1.3	1.22–1.39	<b>&lt;0.001</b>
Acral lentiginous	1.56	1.38–1.77	<b>&lt;0.001</b>

(Continued Tab 1)

Factor	HR	95% CI	P
Poverty	1.01	1.01–1.02	<0.001
Education	1.01	1.00–1.01	0.01
Diagnosis year	0.96	0.95–0.97	<0.001
Stage			
I	Ref		
II	3.45	3.23–3.69	<0.001
III	8.74	8.19–9.32	<0.001
IV	27.33	25.04–29.84	<0.001
Ulceration			
No	Ref		
Yes	1.71	1.63–1.79	<0.001
Thickness	1.11	1.1–1.2	<0.001
Other surgery			
Not performed	Ref		
Performed	0.71	0.65–0.78	<0.001
Unknown	1.32	0.73–2.38	0.36
Primary surgery			
No	Ref		
Yes	0.48	0.44–0.53	<0.001
Radiation			
No	Ref		
Yes	1.72	1.61–1.84	<0.001
Chemotherapy			
No	Ref		
Yes	1.56	1.45–1.67	<0.001

### Machine learning for importance of race factor

Unlike traditional survival analysis, ML techniques are less affected by multicollinearity<sup>[12]</sup> and improve the accuracy of cancer prediction outcomes in clinical research<sup>[13]</sup>. We assessed the accuracy of the ML models before evaluating the importance of race in predicting survival status. The average ROC curves of both models obtained after 50 rounds of training are shown in supplementary Fig 2. The GBM model achieved a mean AUC of 0.915 6 (95%CI: 0.915 2–0.916 0) and an average accuracy of 83.97% (95%CI: 83.91%–84.03%). The RF model outperformed GBM, with an average AUC of 0.967 1 (95%CI: 0.966 8–0.967 4) and an average accuracy of 90.75% (95%CI: 90.70%–90.81%). In both ML models, tumor thickness was the most important factor. The order of the top 10 important variables was similar in the two models, except that education and poverty ranked below stage and ulceration in the GBM model (Fig 3). In contrast, race was a consistently low-ranking variable (not shown in the figure) in both models, suggesting that race/ethnicity may not be a key prognostic factor in melanoma. These results are consistent with those of the CoxPH model, in which clinical and social factors were statistically more significant than race after adjusting for other factors.



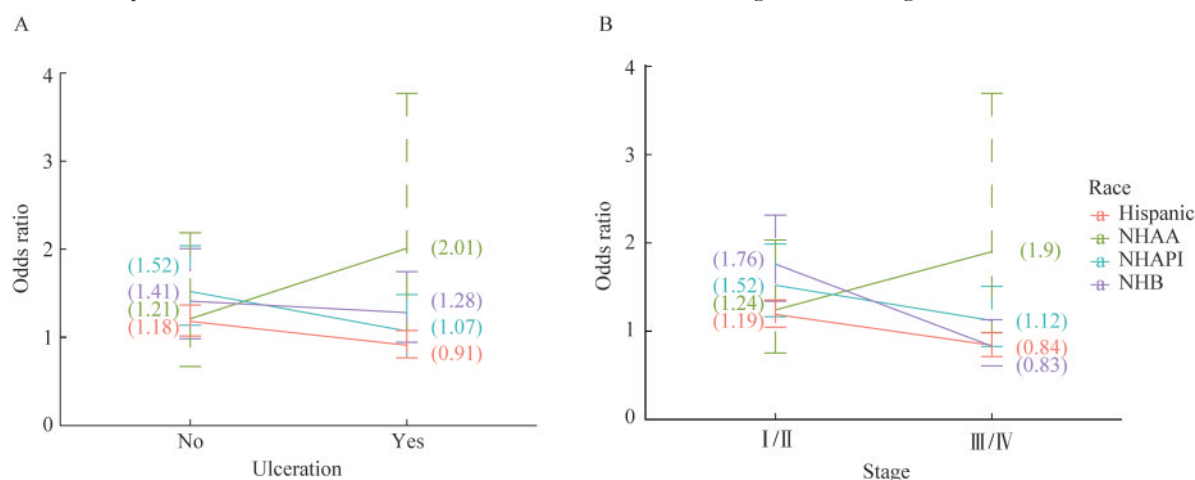
A: Mean variable importance for RF model by calculating mean decrease impurity; B: Mean variable importance for GBM model by calculating the relative influence of variables.

**Fig 3 Mean variable importance of top 10 important variables in the RF and GBM models predicting survival status 50 times**



**Logistic regression model** Since race is not an independent prognostic factor for melanoma, racial disparity may be attributed to the interaction effects between race and other factors. In the Logistic regression model, all races except for NHAIs/ANs reported higher odds of death than NHWs in the early phase (stage I / II without ulceration) of melanoma (Fig 4). In contrast, NHAIs/ANs had higher odds of death than NHWs in advanced stages of cancer. The odds of death were significantly higher in NHAIs, Hispanics, than that in NHWs without

ulcerations. However, when being with ulceration, the odds of death in NHAIs and Hispanics were not significantly different from that in NHWs. In contrast, NHAIs/ANs had significantly higher odds of death than NHWs with ulceration (Fig 4A). NHAIs, Hispanics, NHBs had significantly higher odds of death than NHWs at stage I / II . Nevertheless, at stage III / IV , their odds of death are not significantly different from NHWs'. On the contrary, NHAIs/ANs had higher odds of death than NHWs at stage III / IV (Fig 4B).



A: ORs of death for other racial groups compared with NHWs without and with ulceration; B: ORs of death for other racial groups compared with NHWs at stage I / II and stage III / IV.

**Fig 4 ORs of death for other races compared with NHWs in SEER by Logistic regression analysis**

## Discussion

Previous studies examining the effect of race as a prognostic factor for melanoma spanned a wide time period<sup>[5,7]</sup>. However, the staging systems used in these studies were not as comprehensive or systematic as the Collaborative Stage system introduced in 2004. The SEER dataset utilized in our study benefited from the updated stage system for melanoma staging, which enhanced the objectivity and accuracy of our results. Compared to prior studies, our Cox model incorporated additional confounding factors such as education level, economic status, which increases the reliability of the results. The discrepancies in databases and adjusted factors may result in minor variations in the findings

compared to previous studies. Through our analysis, we determined that race exerts only a marginal effect on disparities in melanoma survival. We also applied ML models with improved predictive performance to further support our conclusions in the Cox model. Racial disparities in survival may be attributed to the interaction between race and other factors.

As stage and ulceration are important prognostic factors in melanoma<sup>[14]</sup>, they were selected to further investigate their interaction with race on melanoma-specific mortality by Logistic model, which was rarely analyzed in previous studies. In Logistic regression analysis, non-white exhibited higher mortality ORs diagnosed at the early stage or in the absence of ulceration as compared to the advanced stage or presence of ulceration, with whites as the reference group. This may be related to the rapid

progression of melanoma from the early stage. On the one hand, this may be caused by divergent melanoma pathogenesis across races. For instance, ALM, as a major subtype in non-white, is associated with a higher propensity to metastasize<sup>[15]</sup>, leading to a poorer prognosis in non-white at the early stage. In SEER, ALM accounts for 17.4% and 12.7% of melanomas in NHBs and NHAPIs, respectively, while only 0.7% of melanomas in NHWs are ALM. Although other cutaneous melanoma subtypes (e.g., SSM) have >18 times more single-nucleotide variants than ALM, somatic structural variants are considerably more frequent in ALM, which implies a potential difference in the pathogenesis of melanoma among different racial groups<sup>[16]</sup>.

On the other hand, certain socioeconomic factors not captured by SEER program may also exert an influence. First, the absence of timely treatment may lead to higher odds of death in non-whites at an early stage. In the National Cancer Database, blacks had more than twice the odds of enduring an extended waiting period from diagnosis to surgery than whites, and a prolonged period between diagnosis and surgery is associated with increased melanoma-specific mortality<sup>[17]</sup>. Second, an unfavorable insurance status may hinder access to timely and high-quality care. With a higher proportion of medicaid and a lower proportion of private insurance<sup>[18]</sup>, non-white groups may experience difficulty in accessing superior preventative and healthcare services. This may, in turn, increase their odds of death for melanoma patients diagnosed at early stage. Additionally, the undocumented immigration status of non-white individuals may lead to diagnostic and therapeutic delays for melanoma, resulting in worse prognosis. Given that non-white groups are more likely to be diagnosed at later stages, they deserve more attention in screening for melanoma and early therapeutic intervention.

There are certain limitations in our study. The socioeconomic factors examined only reflect urban

levels and do not truly represent individual economic and cultural backgrounds. The factors of insurance status and emigration status are not taken into account due to limitations within the database. Genetic prognostic factors and medical care variables may also be important confounding factors, but due to their lack of inclusion in the SEER database, the mechanisms underlying differences in survival between ethnic groups cannot be better analyzed and explained. Additional studies revealing the biological differences between races are required to quantitatively explain the survival disparity among races. Due to the imbalanced representation of data from various ethnic groups in the SEER dataset, there remains a need for additional data pertaining to non-white populations.

**Authors' Contributions** BEN Min-xi Data collection and analysis, visualization, conceptualization, writing, and revision; ZHOU Boyan Conceptualization, writing, and revision; LI Hui Conceptualization, writing, and revision.

**Conflict of Interest Declaration** All authors declare that there are no conflicts of interest.

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