Original Article
Trend and socioeconomic disparities in survival outcome of metastatic melanoma after approval of immune checkpoint inhibitors: a population-based study

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Abstract: Background: The approval of immune checkpoint inhibitors (ICI) for metastatic melanoma in 2011 has changed the treatment landscape of this disease. However, current trend of the population-based survival remains unclear. Methods: 8078 patients with metastatic melanoma diagnosed in the pre-ICI (2005-2010) and post-ICI period (2011-2016) were enrolled from the Surveillance, Epidemiology, and End Results (SEER) program for survival comparison. Propensity score matching (PSM) was performed to reduce selection bias. Cox proportional hazards model was applied for identifying survival-related factors and constructing a prognostic nomogram. The accuracy of the nomogram was determined by concordance index (C-index), calibration curves, and validated by an internal cohort. Results: Patients in the post-ICI period had a significantly longer median overall survival (OS) than those in the pre-ICI period, even after performing PSM between the two periods. We also found socioeconomic disparities in the survival improvement. Significant differences in OS between the two periods were only observed in cases with medical insurance and patients living in urban or low-poverty area, but not uninsured cases and patients from rural or high-poverty area. For patients in the post-ICI period, multivariate analysis demonstrated that socioeconomic and insurance status were independent prognostic factors, which can be combined with other clinical variates into a nomogram for OS prediction with promising C-index of 0.672 and 0.650 in the training- and testing cohort, respectively. Conclusion: An overall trend to favorable survival at the population level and socioeconomic disparities in the survival trend are observed in metastatic melanoma after the ICI approval. The proposed nomogram is available for prognostication in the current melanoma management.

Keywords: Metastatic melanoma, immune checkpoint inhibitors, survival, SEER, nomogram

Introduction

The incidence of melanoma has continuously increased worldwide, particularly in fair-skinned populations [1]. Based on the 2016 data, it was estimated that more than 76,380 new cases of melanoma were diagnosed in the US [2]. Advanced-stage or metastatic melanoma was considered a fatal disease before 2011. Despite the standard of care during this time using dacarbazine chemotherapy and, for selected cases, immunotherapy with high-dose interleukin-2, most patients died within 9 months after diagnosis [3]. In the past decade, the treatment landscape for metastatic melanoma has changed due to the advance in understanding of the genetic basis and anti-cancer immunity [1].

Ipilimumab directed at Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) was the first ICI that received approval by the US Food and Drug Administration (FDA) in 2011 for treating metastatic melanoma according to the breakthrough results of two phase 3 clinical trials [4, 5]. After this, programmed cell death protein 1 (PD-1) inhibitors including nivolumab and pembrolizumab got rapid development and exhibited better efficacies than ipilimumab in subsequent trials [6, 7]. PD-1 inhibitors were thus approved and became the first-line treatment for metastatic melanoma since 2014. Approximately half of melanomas harbor BRAF mutations and
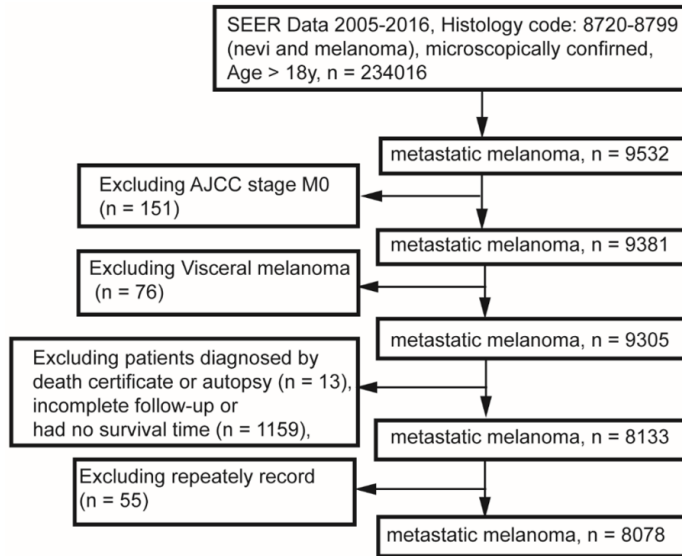
Figure 1. Flow diagram of patient selection.

inhibitors targeting BRAF and downstream MEK signal are alterative choices for these patients [8-10]. However, the development of resistance towards targeted agents is almost inevitable. For target agent-resistant or intolerant cases, ICI remains an essential treatment option [1]. Two recent retrospective studies reported that BRAF-mutant patients receiving first-line treatment with PD-1 inhibitors had favorable OS than those treated with BRAF-targeted therapy [11, 12]. The efficacy of Combining BRAF-targeted and PD-1 immunotherapy for BRAF-mutant melanoma is also promising in clinical trials. These results indicated that the current management of metastatic melanoma has entered the immunotherapy era after the approval of ICI.

Nevertheless, the widespread applications of the novel immunotherapeutic agents were limited by their highly financial burden. It was reported that only about 30% of patients with advanced melanoma diagnosed in 2014 received immunotherapy in the US [13]. Additionally, routine ICI administration in the clinical differs from prospective trials with defined inclusion criteria. The benefit observed in the landmark trial may not equally translate into the survival improvement in an unselected general population. The current trend of survival in metastatic melanoma at the population level need to be elucidated. Therefore, we use data from the SEER program to determine the survival trend

and its association with socioeconomic factors among patients with metastatic melanoma after the ICI approval.

Materials and methods

Patient selection criteria

The SEER program of the National Cancer Institute collects and publishes cancer incidence, treatment and survival data from 18 population-based cancer registries, which covers more than 25% of the US population. Research data use agreement was obtained at the SEER program (https://seer.cancer.gov/data) and data was downloaded by using the SEER*Stat software (Version 8.3.6) and SEER-18 registries dataset (November 2018 submission). Metastatic melanoma patients were identified with the following selection algorithm: International Classification of Diseases for Oncology, Third Edition (ICD-O-3) histology codes of melanoma (8720-8799, nevi and melanomas) and stage IV codes from the Derived AJCC Stage Group 6th Ed (2004-2015), Derived AJCC Stage 7th Ed (2010-2015) or Derived SEER Cmb Stg Grp (2016+). For patients with unknown AJCC stage, distant codes from the SEER historic stage A (1973-2015), Derived SS1977 (2004-2015) and Summary stage 2000 (1988+) was supplemented for identifying metastatic cases. Patients with AJCC stage M0 were excluded to prevent misclassification. We only included patients who had a known age and were more than 18 years old, had microscopically confirmed diagnosis of melanoma and were diagnosed between the year 2005 to 2016. Then, using the definition previously described by Scott et al. [14], melanomas within the visceral organs were excluded and the remaining cases were categorized as cutaneous, mucosal and ocular melanomas according to their primary site of occurrences. We also excluded patients who were diagnosed by death certificate or autopsy, had incomplete follow-up and no survival records. Lastly, for patients with multiple records of diagnosis as metastatic melanoma, we retained the first record. The flow diagram of patient selection is shown in **Figure 1**.

Demographics and clinical data collection

Socioeconomic status was determined using the county poverty rate [15], which is the percentage of persons living below the national poverty threshold with the American Community Survey data from the year 2011 to 2015 (high-poverty: % persons below poverty ≥2000; low-poverty: % persons below poverty < 2000). County-level information on rurality was recognized by the rural-urban continuum code 2013 [16]. Surgery on primary tumor was classified as non-total excision (including no surgery, biopsy and partial excision), total excision and unknown according to the coding manual of the SEER program (available at: seer.cancer.gov/tools/codingmanuals). The primary endpoint was OS defined as the duration from the date of diagnosis to death. Disease-specific survival (DSS) was calculated following the diagnosis to death specifically of melanoma. Other demographics and clinical characteristics including age, sex, race, primary site, histology, brain metastasis and insurance record were also collected (**Table 1**).

Propensity score matching (PSM)

A propensity score study was implemented to reduce selection bias in survival comparison between the pre- and post-ICI periods. Propensity scores were estimated using STATA 15.1 software (StataCorp., College Station, TX) with a logistic regression model based on the both baseline covariates except brain metastasis and insurance record because these two variates contain excessive missing data (**Table 1**). One-to-one matching without replacement was performed with a caliper width of 0.001. The quality of matching was assessed by comparison of each covariate after PSM.

Prognostic nomogram construction

A nomogram was developed using *rms* package in R version 3.6.2 (http://www.r-project.org/) with Cox proportional hazards model integrating all significant independent factors in the training cohort. The performance of nomogram was determined using C-index and calibration curves with 1000 resample bootstraps that compare nomogram-predicted versus actual observed survival probability. An internal testing set was employed for validation. The total point of each patient in the testing cohort

was calculated according to the established nomogram, then treated as a variable for Cox regression analysis and assessed by the c-index and calibration curve [17].

Statistical analysis

The SPSS software version 20 (IBM corp., Santa Monica, CA) was applied for statistical analysis. As the first ICI was approved in 2011, the period year 2005-2010 and 2011-2016 was recognized as the pre- and post-ICI period, respectively, and used for survival comparison by the Kaplan-Meier method with a log-rank test. Categorical variables were compared by the chi-squared or Fisher's exact test. Multivariate analyses were performed using Cox proportional hazards model with the stepwise backward method, adjusted by variables previously associated with survival in univariate analysis at $P < 0.10$ level. All statistical tests were two-sides and $P < 0.05$ was considered statistically significant.

Results

Survival of metastatic melanoma was improving after approval of ICI

A total of 8078 adult patients with metastatic melanoma from the SEER database were found eligible for this study according to our inclusion criteria. Baseline characteristics of patients diagnosed in the pre- and post-ICI periods were compared in **Table 1**. Median OS and DSS of patients in the post-ICI period was 11 months (95% CI 10.4~11.6) and 24 months (95% CI 21.1~26.9), respectively, and significantly longer than patients in the pre-ICI period (median OS: 9 months, 95% CI 8.5~9.5; median DSS: 14 months, 95% CI 12.8~15.2, both log-rank $P < 0.001$, **Figure 2A** and **2B**).

We then grouped the calendar year of diagnosis into four more detailed 3-year periods (2005-2007, 2008-2010, 2011-2013, and 2014-2016). The difference in survival between the period year 2005-2007 and 2008-2010 was not statistically significant. A trend to increased survival was observed in the 2011-2013 period compared with the earlier (log-rank $P=0.045$), and this increasing trend was more pronounced in the 2014-2016 period (log-rank $P < 0.001$; **Figure 2C** and **2D**).

Table 1. Baseline characteristics of patients with metastatic melanoma from the SEER database

Variables	n (%)		p value
	2005-2010 period (n=3542)	2011-2016 period (n=4536)	
Gender			
Female	1197 (33.8)	1435 (31.6)	0.040
Male	2345 (66.2)	3101 (68.4)	
Age (years)			
18-45	401 (11.4)	398 (8.8)	< 0.001
46-65	1459 (41.2)	1782 (39.3)	
>65	1682 (47.4)	2356 (51.9)	
Race/ethnicity			
non-Hispanic Whites	3202 (90.4)	4109 (90.6)	0.778
Other races[†]	340 (9.6)	427 (9.4)	
Primary site			
Cutaneous	3321 (93.7)	4264 (94.0)	0.085
Mucosal	180 (5.1)	199 (4.4)	
Ocular	41 (1.2)	73 (1.6)	
Primary malignancy			
Primary	3319 (93.7)	4143 (91.3)	< 0.001
Secondary	223 (6.3)	393 (8.7)	
Histology			
Malignant melanoma, NOS	2861 (80.8)	3690 (81.3)	0.512
Rare types[‡]	681 (19.2)	846 (18.7)	
Brain metastasis			
No	458 (12.9)	2888 (63.7)	n/a[§]
Yes	212 (6.0)	1418 (31.3)	
Unknown	2872 (81.1)	230 (5.0)	
Primary tumor excision			
Non-total excision	2719 (76.8)	3646 (80.4)	< 0.001
Total excision	747 (21.1)	816 (18.0)	
Unknown	76 (2.1)	74 (1.6)	
Metastatic lesion excision			
No	2376 (67.1)	3123 (68.8)	0.178
Yes	1152 (32.5)	1391 (30.7)	
Unknown	14 (0.4)	22 (0.5)	
Urban-rural distribution			
Urban area	3089 (87.2)	4001 (88.2)	0.176
Rural area	453 (14.8)	535 (11.8)	
Socioeconomic status			
Low-poverty area	3019 (84.7)	3925 (86.5)	0.096
High-poverty area	523 (15.3)	611 (13.5)	
Insurance status			
Insured	2301 (65.0)	4230 (93.2)	n/a[§]
Uninsured	120 (3.4)	152 (3.4)	
Unknown	1121 (31.6)	154 (3.4)	
Follow-up duration, months, median (IQR)	103 (84~122)	29 (15~47)	
Overall deaths	3121 (88.1)	2929 (64.6)	

[†]Include Hispanics, Black, Asian and others. [‡]Include nodular, amelanotic, desmoplastic, epithelioid or spindle cell, blue nevus and other histology types. [§]Comparison would not be executed if unknown data more than 30%.
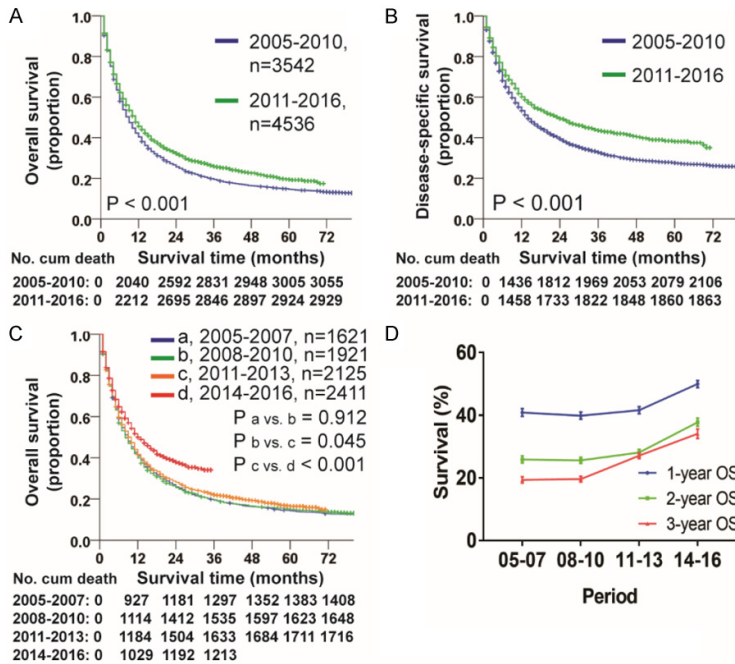
Figure 2. Survival trend in patients with metastatic melanoma in the SEER database. Kaplan-Meier curve comparing overall (A) and disease-specific survival (B) between the 2005-2010 and 2011-2016 periods. (C) Kaplan-Meier curve comparing overall survival among the four 3-year periods (2005-2007, 2008-2010, 2011-2013, and 2014-2016). (D) 1-, 2-, and 3-year relative survival rates from 2005 to 2016.
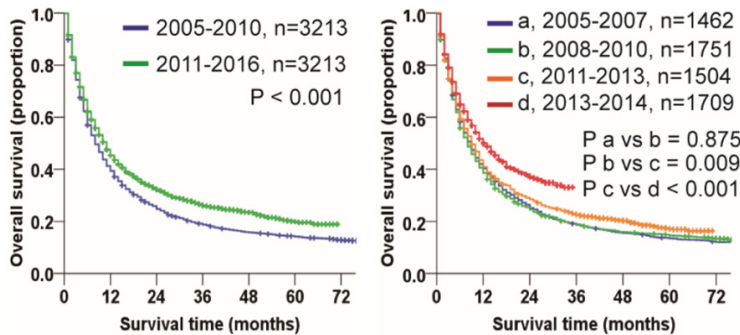

Figure 3. Survival comparison after performing propensity score matching between the period year 2005-2010 and 2011-2016. Kaplan-Meier curve comparing overall survival between the 2005-2010 and 2011-2016 periods (left) and among the four 3-year periods 2005-2007, 2008-2010, 2011-2013, and 2014-2016 (right).

PSM analysis for melanoma survival

PSM was implemented to minimize selection bias between the pre- and post-ICI groups and generate 3213 pairs of patients with balanced covariates (results of covariate comparison were in Table S1). After PSM, a significant improvement in survival was still observed since the ICI approval in 2011 (**Figure 3**).

Stratification analysis for melanoma survival

Stratification analysis were performed to measure the survival trends in different subgroups of the patients. Age-stratified analyses showed significant differences in OS between the two periods for both patients at the age group of 18 to 65 years and those >65 years (**Figure 4A** and **4B**). Then, we found disparities in the survival improvement in patients with different races and histological types. Notably improved OS were only observed in non-Hispanic white along with patients with cutaneous melanoma and primary melanoma (**Figure 4C**, **4E**, **4G**), but not other races/ethnics (Hispanic, black, Asian and others), mucosal melanoma and secondary melanoma (**Figure 4D**, **4F**, **4H**).

Brain metastasis, recorded in the SEER database since the year 2010, is a special stage in advanced melanoma associated with worse outcome [18]. We found that patients with brain metastasis diagnosed in the post-ICI period had a slight and statistically significant advance in OS as compared with those in 2010 (median 6 versus 5 months, log-rank *P* < 0.001, Figure S1).

Socioeconomic disparities in the survival trends

Survival improvement in metastatic melanoma was associated with socioeconomic factors. Patients with medical insurance and cases from urban or low-poverty area diagnosed in the post-ICI period had dramatically increased OS as compared with the pre-ICI period (**Figure 5A**, **5C**, **5E**). Whereas, the differences in survival was not statistically significant for uninsured cases and patients from rural or high-poverty area between the two periods (**Figure 5B**, **5D**, **5F**).
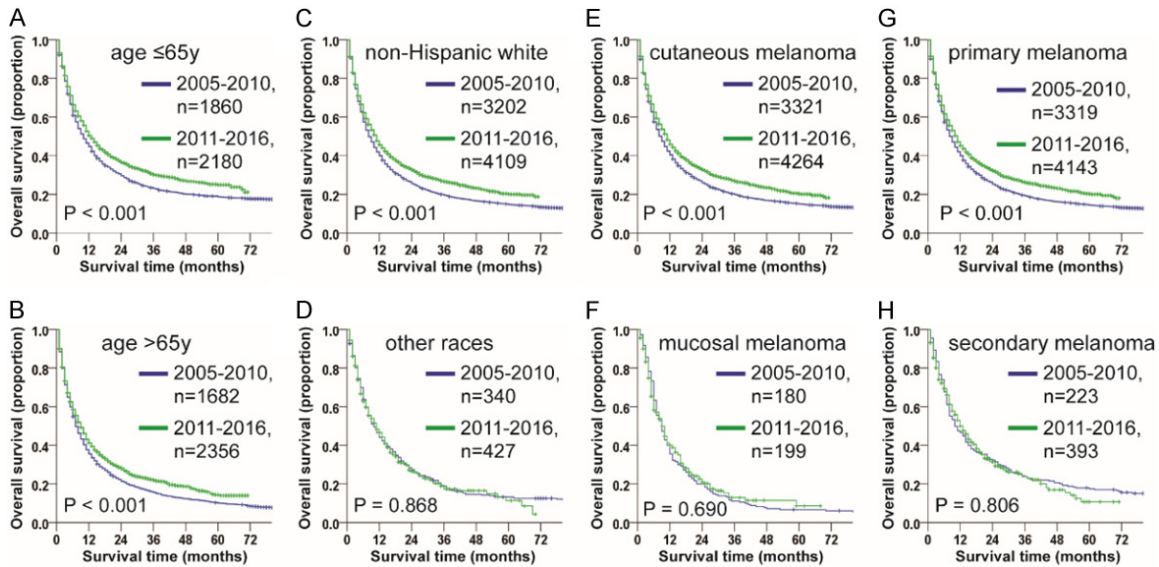
Figure 4. Stratification analyses for the trends of survival in metastatic melanoma. Kaplan-Meier plots comparing overall survival for patients ≤65 or >65 years of age (A, B), non-Hispanic white or other races/ethnics including Hispanic, black, Asian and others (C, D), cutaneous or mucosal melanoma (E and F), and primary or secondary melanoma (G, H).
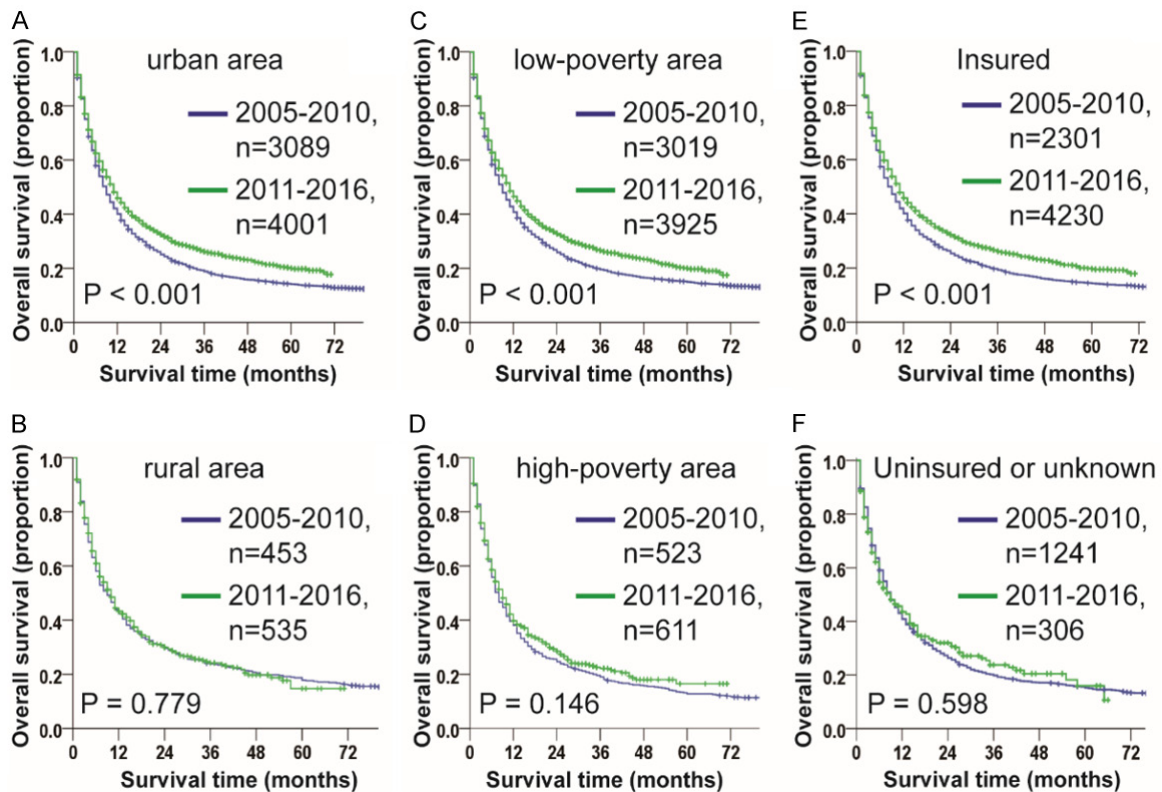

Figure 5. Socioeconomic disparities in the survival improvement of metastatic melanoma. Kaplan-Meier plots comparing overall survival for patients living in urban or rural area (A, B), patients living in low- or high-poverty area (C, D), and patients with medical insurance or cases with no insurance and unknown insurance record (E, F).

Table 2. Multivariate cox regression analysis of overall survival for patients with metastatic melanoma from the SEER database, 2005-2010

Variables	HR	95% CI	p value
Age (years)			
18-45	1		
46-65	1.13	1.00~1.28	0.057
>65	1.42	1.26~1.61	< 0.001
Gender (Female vs. Male)	1.10	1.02~1.18	0.016
Primary tumor (Secondary vs. Primary)	0.81	0.70~0.94	0.004
Histology (rare types vs. malignant melanoma, NOS)	0.90	0.82~1.00	0.044
Brain metastases			
No	1		
Yes	1.95	1.64~2.32	< 0.001
Unknown	1.23	1.11~1.37	< 0.001
Primary tumor excision			
Non-total excision	1		
Total excision	0.61	0.56~0.68	< 0.001
Unknown	0.77	0.60~1.00	0.048
Metastatic lesion excision			
No	1		
Yes	0.55	0.51~0.60	< 0.001
Unknown	0.98	0.56~1.72	0.951

CI: Confidence interval, HR: Hazard ratio.

Identification of survival-related factors and construction of prognostic nomogram

We sought to identify survival-related factors and determine whether these factors were distinct between the pre- and post-ICI periods. When adjusted by all baseline factors (Tables S2 and S3), multivariate analyses found that age, brain metastasis and excision of primary or metastatic lesions were independent prognostic indicators for patients in the both periods (**Tables 2** and **3**). Histological type of classical malignant melanoma and primary tumor were associated with worse OS for patients in the pre-ICI period (**Table 2**), whereas socioeconomic and insurance status independently influenced survival outcomes after the ICI approval (**Table 3**).

Finally, we tried to integrate socioeconomic status and other significantly independent factors into a nomogram to predict patients' OS in the current immunotherapy era. The SEER patients diagnosed in the post-ICI period were randomly divided to a training set (n=3024) for nomogram construction and a testing set (n=1512) for validation in a 2-to-1 ratio. The established prognostic nomogram was shown in **Figure**

6A. The C-index for OS prediction in the training- and testing set was 0.672 (95% CI 0.665~0.679) and 0.650 (95% CI 0.641~0.659), respectively. The calibration plots for the probability of survival at 2 and 3 years displayed an ideal agreement between the prediction by nomogram and actual observation (**Figure 6B-E**).

Discussion

Development of immunotherapies targeting checkpoint receptors including CTLA-1 and PD-1 represents the major advances in the past decade for treating metastatic melanoma. In this epidemiological study using the large SEER data, we observed a corresponding improvement in survival. As compared with the earlier period, patients diagnosed in 2011 to 2013 had an increased survival (median OS 9 months), and the increasing trend in survival was more pronounced in period year 2014-2016 (median OS 13 months). The most likely reason for the survival improvement was the approval and progressive increase in use of novel targeted and immunotherapies for metastatic melanoma since 2011, but not the advances in traditional treatment or supportive care, because in a time interval equal to that in

Table 3. Multivariate cox regression analysis of overall survival for patients with metastatic melanoma from the SEER database, 2011-2016

Variables	HR	95% CI	p value
Socioeconomic status (high-poverty vs. low-poverty area)	1.15	1.04-1.28	0.008
Insurance			
Insured	1		
Uninsured	1.44	1.19~1.75	< 0.001
Unknown	0.90	0.73~1.12	0.348
Age (years)			
18-45	1		
46-65	1.20	1.04~1.39	0.013
>65	1.62	1.40~1.86	< 0.001
Primary site			
Cutaneous	-		
Mucosal	-	-	-
Ocular	-	-	-
Histology (rare types vs. malignant melanoma, NOS)	0.90	0.82-1.00	0.056
Brain metastases			
No	1		
Yes	1.93	1.79~2.09	< 0.001
Unknown	0.98	0.82~1.17	0.807
Primary tumor excision			
Non-total excision	1		
Total excision	0.62	0.55~0.69	< 0.001
Unknown	0.85	0.63~1.16	0.304
Metastatic lesion excision			
No	1		
Yes	0.46	0.42~0.50	< 0.001
Unknown	1.05	0.62~1.79	0.845

CI: Confidence interval, HR: Hazard ratio.

which improved survival was observed, there was no statistically significant difference in survival between the period year 2005-2007 and 2008-2010 (**Figure 2C** and **2D**). In addition, the observed survival in the present study in the post-ICI period is similar to the results of contemporaneous clinical trials assessing the efficacies of ipilimumab, pembrolizumab or BRAF-targeted vemurafenib for advanced melanoma [4, 5, 8, 19], which indirectly support our explanation.

The results of the Checkmate trials showed that nivolumab could not significantly improve survival of patients with metastatic melanoma who had received ipilimumab or BRAF-targeted treatment and progressed [20]. Inversely, for previously untreated patients, nivolumab prolong OS [6]. Consistent conclusions were found in the KEYNOTE trials for pembrolizumab [7,

19]. ICI resistance and side effects are more common in patients who had received numerous treatments and therapeutic efficacy is worse. The above findings can partly explain the result of our stratification analyses that difference in OS between the pre- and post-ICI periods was not significant for patients with secondary melanoma. Improved survival was also not observed in mucosal melanoma at the advanced stage. Mucosal melanoma is a relatively rare but more aggressive subtype of melanoma. In comparison with cutaneous melanoma, mucosal melanoma has distinct mutational landscapes [21] and unfavorable effect on targeted agents and ICI [22, 23]. Brain metastasis occurs in more than 30% of all advanced melanoma and is another crucial challenge in treating malignant melanoma. Most prospective trials excluded such patients with active brain metastases due to their dis-
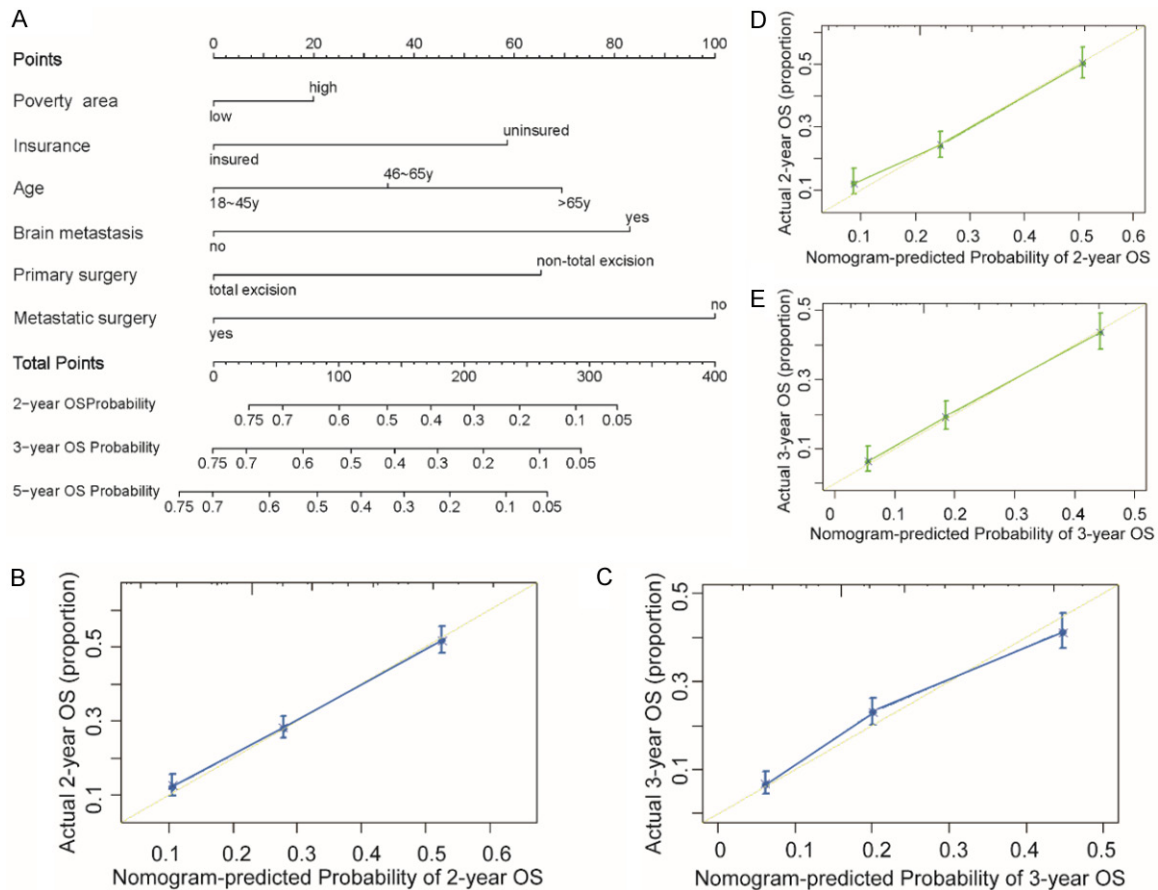
Figure 6. Nomogram and calibration curves for predicting overall survival in metastatic melanoma based on the SEER data, 2011-2016. A. In the nomogram, a Points line is drawn upward to measure the prognostic score of each variable, and the sum of these scores is located on the Total Points axis and then projected on the bottom scale to determine the likelihood of 2-, 3- and 5-year overall survival (OS). B, C. Calibration curves in the training set for prediction of 2- and 3-year OS. D, E. Calibration curves in the testing set for prediction of 2- and 3-year OS.

mal survival [1, 18]. However, emerging evidence from phase 2 trials are now suggesting that novel targeted and immunotherapies may be valuable treatments for melanoma metastatic to the brain [24, 25]. Correspondingly, we observed a slight and statistically significant improvement in survival for the SEER patients with brain metastasis after the ICI approval, indicating the promising efficacies of these new agents for treating melanoma brain metastases.

Although non-white faces higher risks of more advanced stage at diagnosis of melanoma than white population, the expected survival of non-white with metastatic melanoma is equivalent to white [26]. The present SEER study observed a significant improved OS in white population after the approval of ICI. However, the survival of minorities including Hispanic, black and

Asian wasn't increased. Haque et al. [13] has reported that immunotherapy was less likely administered to African American as compared to withes, implying that the racial disparities in survival improvement might be associated with the lack of access to novel therapy in minorities. On the other hand, the efficacies of targeted and immunotherapies for minorities has not been well evaluated due to their limited enrollment into the current trials [27], and the possibility of unfavorable effect on minorities may also result in the difference of prognosis. Additionally, disparities of socioeconomic and insurance status were found in the improvement of the population-based survival after the ICI approval. Multivariate analysis also demonstrated that socioeconomic and insurance status were independent prognostic factors for patients in the post-ICI period. Patients with medical insurance, urban population and those

living in low-poverty area are believed to be more prone to receive advanced therapy and thus get favorable outcomes. The above results addressed that racial and socioeconomic disparities still persist in the delivery of new but high-cost medicine for the care of melanoma and these public health issues deserve more attention and investment.

Excision of primary and metastatic tumor were associated with better outcome for metastatic melanoma in the era without effective systemic treatment [28, 29]. After the approval of ICI, we find that tumor excision remains an independent indicator for increased OS. Surgery still plays an important role in the multidisciplinary management of advanced melanoma. Selected patients with oligometastasis, or responsive/stable disease after systemic treatment should consider surgery [30]. Surgical resection reduces tumor burden and nowadays lower tumor burden indicates greater ICI efficacy and favorable survival [31]. Moreover, the early reports on clinical trials assessing the effects of intensive treatments with pre-operative (neoadjuvant) and adjuvant immunotherapy are encouraging [30].

We integrate survival-related clinical factors and socioeconomic status into a nomogram for prognostication in the current melanoma management. The calibration plots display an ideal agreement between the nomogram-predicted and actual observed survival. The proposed nomogram and further stratification in survival risk might have clinical implication in guiding treatment selection. It is reasonable for high-risk patients to receive intensive therapy, such as targeted and immunotherapy combination regimens, while lower-risk patients should consider less intensive treatment and avoid unnecessary toxicity and cost. We should also pay attention to the advances of new biomarkers, such as circulating cell-free tumor DNA (ctDNA), tumor mutational burden, and PD-L1 expression [32-34], which can be used for survival prediction, response surveillance, and enhance our understanding on the genetic alteration and immune microenvironment of malignant melanoma and help to develop novel treatment strategies.

To the best of our knowledge, this is the latest study measuring the survival trends in meta-static melanoma after the ICI approval. We first report a dramatic improvement in the population-based survival since the year 2014, but further follow-up is needed for estimation of the long-term outcomes. This study is subjected to the inherent limitations of database review. Besides the retrospective nature, SEER database does not provide information about immunotherapy usage. However, a recent study indicated that the proportion of melanoma patients in the US who were treated with immunotherapy has increased from approximately 10% in the year 2011 to more than 30% in 2014, and was continuing to rise [13]. It is reasonable to assume that the overall trend to better survival in the SEER patients is associated with the increasing use of immunotherapy.

Summarily, in this epidemiological study using the large SEER data, an overall trend to favorable survival is observed in metastatic melanoma at the population level after the ICI approval, that provides real-world evidence to support the utilization of ICI for advanced melanoma. In the meanwhile, there are socioeconomic disparities in improving prognosis of this disease. The current treatment for special types of malignant melanoma, including recurrent tumor, mucosal melanoma and brain metastasis, are still unsatisfied and further research are needed. Lastly, we propose a nomogram to effectively predict the clinical outcome of metastatic melanoma in the modern immunotherapy era.

Acknowledgements

Disclosure of conflict of interest

None.

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Table S1. Baseline characteristics of the patients with metastatic melanoma from the SEER database after performing propensity score matching

Variables	n (%)		p value
	2005-2010 period (n=3213)	2011-2016 period (n=3213)	
Gender			
Female	1048 (32.6)	1113 (34.6)	0.086
Male	2165 (67.4)	2100 (65.4)	
Age (years)			
18-45	304 (9.5)	307 (9.6)	0.947
46-65	1344 (41.8)	1331 (41.1)	
>65	1565 (48.7)	1575 (49.0)	
Race/ethnicity			
non-Hispanic white	2954 (91.9)	2944 (91.6)	0.650
Other races[†]	259 (8.1)	269 (8.4)	
Primary site			
Cutaneous	3070 (95.5)	3028 (94.2)	0.045
Mucosal	122 (3.8)	163 (5.1)	
Ocular	21 (0.7)	22 (0.7)	
Primary malignancy			
Primary	3026 (94.2)	3016 (93.9)	0.599
Secondary	187 (5.8)	197 (6.1)	
Histology			
Malignant melanoma, NOS	2630 (81.9)	2651 (82.5)	0.494
Rare types[‡]	583 (18.1)	562 (17.5)	
Primary tumor excision			
Non-total excision	2575 (80.1)	2595 (80.8)	0.709
Total excision	604 (18.8)	580 (18.1)	
Unknown	35 (1.1)	38 (1.2)	
Metastatic lesion excision			
No	2172 (67.1)	2192 (68.8)	0.643[§]
Yes	1038 (32.5)	1016 (30.7)	
Unknown	3 (0.4)	5 (0.5)	
Urban-rural distribution			
Urban area	2864 (89.1)	2861 (89.0)	0.904
Rural area	349 (10.9)	352 (11.0)	
Socioeconomic status			
Low-poverty area	2816 (84.7)	2769 (86.5)	0.082
High-poverty area	397 (15.3)	444 (13.5)	

[†]Include Hispanic, black, Asian and others. [‡]Include nodular, amelanotic, desmoplastic, epithelioid or spindle cell, blue nevus and other histology types. [§]Comparison using Fisher's exact test.
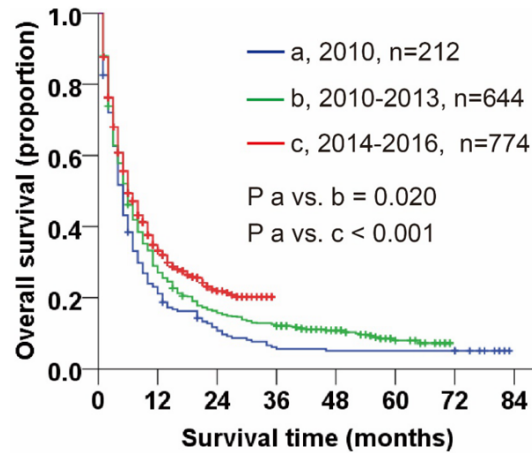
Figure S1. Kaplan-Meier plots of overall survival for melanoma patients with brain metastasis diagnosed in different time period.

Table S2. Univariate cox regression analysis for patients with metastatic melanoma from the SEER database, 2005-2010

Variables	HR	95% CI	P value
Urban-rural distribution (rural vs. urban area)	1.09	0.98-1.21	0.123
Socioeconomic status (high-poverty vs. low-poverty area)	1.07	0.97-1.18	0.177
Insurance			
Insured	1		
Uninsured	1.14	0.93-1.39	0.207
Unknown	0.97	0.90-1.05	0.406
Age (years)			
18-45	1		
46-65	1.19	1.05-1.35	0.006
>65	1.53	1.35-1.73	< 0.001
Race/ethnicity (other races vs. non-Hispanic White)	0.94	0.83-1.06	0.285
Gender (male vs. female)	1.07	1.0-1.16	0.061
Primary site			
Cutaneous	1		
Mucosal	1.13	0.97-1.32	0.114
Ocular	0.82	0.59-1.14	0.242
Primary malignancy (secondary vs. primary)	0.85	0.73-0.98	0.028
Histology (rare types vs. malignant melanoma, NOS)	0.82	0.75-0.89	< 0.001
Brain metastases			
No	1		
Yes	1.96	1.65-2.33	< 0.001
Unknown	1.20	1.08-1.34	0.001
Primary tumor excision			
Non-total excision	1		
Total excision	0.67	0.61-0.73	< 0.001
Unknown	0.74	0.58-0.95	0.019
Metastatic lesion excision			
No	1		
Yes	0.61	0.56-0.66	< 0.001
Unknown	0.99	0.57-1.71	0.972

CI: Confidence interval, HR: Hazard ratio.

Table S3. Univariate cox regression analysis for patients with metastatic melanoma from the SEER database, 2011-2016

Variables	HR	95% CI	P value
Urban-rural distribution (rural vs. urban area)	0.94	0.84-1.05	0.275
Socioeconomic status (poverty vs. non-poverty area)	0.88	0.79-0.98	0.015
Insurance			
Yes	1		
No	1.30	1.07-1.57	0.008
Unknown	0.97	0.79-1.19	0.795
Age (years)			
18-45	1		
46-65	1.15	0.99-1.32	0.062
>65	1.46	1.27-1.68	< 0.001
Race/ethnicity (other races vs. non-Hispanic White)	1.08	0.95-1.22	0.225
Gender (male vs. female)	0.94	0.87-1.01	0.113
Primary site			
Cutaneous	1		
Mucosal	1.23	1.04-1.44	0.015
Ocular	1.15	0.87-1.51	0.321
Primary malignancy (Secondary vs. Primary)	0.98	0.86-1.11	0.721
Histology (rare types vs. malignant melanoma, NOS)	0.78	0.71-0.86	< 0.001
Brain metastases			
No	1		
Yes	1.78	1.64-1.91	< 0.001
Unknown	1.06	0.89-1.25	0.531
Primary tumor excision			
Non-total excision	1		
Total excision	0.62	0.56-0.68	< 0.001
Unknown	0.82	0.62-1.08	0.162
Metastatic lesion excision			
No	1		
Yes	0.53	0.48-0.57	< 0.001
Unknown	0.93	0.58-1.50	0.769

CI: Confidence interval, HR: Hazard ratio.