Racial Disparities In Metastatic Non-Small Cell Lung Cancer In The Post-Immunotherapy Era

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Racial Disparities in Metastatic Non-Small Cell Lung Cancer in the Post-Immunotherapy Era

By: Victoria McClare

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Secondary Thesis Advisor: Dr. Leah M. Ferrucci, PhD, MPH

A Thesis Submitted in
Candidacy for the Degree of Master of Public Health

Yale School of Public Health
Chronic Disease Epidemiology Department
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Abstract

**Importance:** The approval of immune checkpoint inhibitors (ICI) has improved survival among those with metastatic non-small cell lung cancer (mNSCLC). However, it is unclear to what extent existing racial and ethnic disparities in survival outcomes for those with mNSCLC are widening under the new ICI treatment era.

**Objective:** Examine changes in racial and ethnic disparities in mNSCLC survival rates before and after the U.S. Food and Drug Administration (FDA) approval of ICI in the United States.

**Design, Setting, and Participants:** This study is a population-based retrospective cohort of patients with NSCLC from the Surveillance, Epidemiology, and End Results (SEER) database (2000-2020), which consists of 17 registries in the United States. The pre-ICI time period for the study was 2010-2014, and the post-ICI time period was 2016-2020.

**Main Outcomes and Measures:** Median cause-specific survival and 2-year difference-in-difference survival analysis was calculated using accelerated failure time models. We evaluated the association between race and ethnic categories and time periods with an interaction term. Race and ethnic categories included non-Hispanic White (NHW), non-Hispanic Black (NHB), non-Hispanic Asians/Pacific Islander (NHAPI), and both Hispanic and non-Hispanic American Indians/Alaska Natives (HNHAI).

**Results:** The study sample included 24,445 patients. The 2-year survival rate increased from the Pre-ICI to Post-ICI period among NHW (Pre-ICI = 13.8% and Post-ICI = 23.0%), NHB (Pre-ICI = 13.1% and Post-ICI = 21.2%), HNHAI (Pre-ICI = 14.6% and Post-ICI = 24.7%), with NHAPI having the highest survival in both periods (Pre-ICI = 24.4% and Post-ICI = 35.1%). Survival disparities were not significantly different from pre-ICI to post-ICI.
Conclusion: We did not observe any evidence of ICI widening the racial and ethnic disparity gap among those with mNSCLC from pre-ICI to post-ICI.
Acknowledgments

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Introduction

Metastatic non-small cell lung cancer (mNSCLC) has poor survival outcomes, with a 5-year survival rate of approximately 5% prior to the introduction of immunotherapy (Ganti et al., 2021). However, survival rates have been improving with the advent of new treatments, including Food and Drug Administration’s (FDA) approval of targeted oral agents in 2003 and immune checkpoint inhibitors (ICI) in 2015 (Cohen et al., 2003; Burotto et al., 2015; Kazandjian et al., 2016; Saxena et al., 2020). A recent study found the median survival increased from 11.5 months in 2011 to 16 months in 2019 among individuals 55 years and younger, four years after the first approval of ICI (Voruganti et al., 2023). Furthermore, prior to ICI, there was also a decrease in mortality rates attributed to targeted therapy, in which the 5-year survival rate increased from 3.2% in 2010 to 5.8% in 2016 (Bar et al., 2021; Ganti et al., 2021; Howlader et al., 2020).

ICI is a type of immunotherapy used to treat cancer by utilizing the individual's immune system to attack cancerous cells and can be given as monotherapy or concurrently with chemotherapy (Saxena et al., 2020). Clinical trials have shown higher survival rates among individuals with NSCLC who utilized ICI compared to chemotherapy drugs such as docetaxel (Borghaei et al., 2021; Brahmer et al., 2015). The FDA approved ICI for patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy on March 4, 2015, and expanded it for those with nonsquamous disease on October 9, 2015 (Kazandjian et al., 2016) (Center for Drug Evaluation and Research, 2015).
However, despite seeing improvement in survival for NSCLC prior to ICI, there is a significant disparity in survival among Black and White patients. In one study, the five-year survival among White patients with NSCLC was 16.3% compared to 10.5% among Black patients from 1996 to 2007 (Tannenbaum et al., 2014). Many factors may contribute to the poorer survival rate among Black patients. Black patients are more likely to be diagnosed with advanced-stage cancer than White patients for NSCLC (Du et al., 2011). Furthermore, Black patients with NSCLC are more likely to have a delay in treatment and experience non-guideline-concordant care from healthcare professionals compared to white patients (Rekulapelli et al., 2022). Among NSCLC patients identifying as Hispanic, a higher survival rate was observed compared to Non-Hispanic White patients. For instance, the 5-year survival rate for Hispanic patients diagnosed between 2010 and 2015 was 8%, while for White patients, it was 4.1% (Kumar et al., 2022). Among NSCLC patients who identify as Asian, their survival rates are among the highest compared to other racial groups, including White patients (Howlader et al., 2020). Asian patients exhibit a higher prevalence of EGFR mutation-positive NSCLC tumors, increasing the likelihood of gaining clinical benefit from EGFR-targeted therapy (Primm et al., 2022).

When investigating racial disparities within cancer survival, it is crucial to contextualize the systematic and structural racial inequalities that can contribute to the disparities in cancer survival to prevent misleading conceptions that could give rise to biological explanations (Chowkwanyun & Reed, 2020; Tong et al., 2022). For example, Black patients may face implicit bias from healthcare professionals, resulting in inadequate treatment or care that does not follow the standard guidelines (Chapman et al., 2013; Tong et al., 2022). Furthermore, hospitals that predominantly serve Black patients are often more likely to receive lower
payments for patient care, which can affect the services and staffing provided, resulting in poor quality of care (Himmelstein et al., 2023). Moreover, these hospitals may be less likely to stay up to date with new technologies and healthcare recommendations (Nelson, 2020).

Given these disparities and inequities in the healthcare field, the emergence of novel therapies, such as ICI, can further worsen existing disparities (Figueroa, 2017; Osarogiagbon et al., 2021). The widening of racial disparities can be attributed to unequal access to new emerging treatments, particularly among historically marginalized populations who are more susceptible to discrimination and hold less societal influence (Link & Phelan, 1995; Osarogiagbon et al., 2021).

A study among 21,098 patients with NSCLC found that Black patients had lower odds (adjusted odds ratio = 0.60, 95% confidence interval = 0.44 to 0.80) of receiving immunotherapy compared to white patients (Chang et al., 2023). Moreover, Black patients were more likely to have delays in immunotherapy treatment compared to White patients, with an average nine-day delay among those with advanced-stage NSCLC (Deng et al., 2020). Lack of access, delays in treatment, and other related factors could affect survival of individuals with NSCLC.

Currently, to our knowledge no research has evaluated how the introduction of ICI has impacted racial disparities in mNSCLC survival in the United States. This study examines changes in racial disparities in mNSCLC survival before and after the FDA’s approval of immune checkpoint inhibitors. This study is important because research has shown that when provided with access to immunotherapy, Black patients had similar survival outcomes compared to White patients when both groups received immunotherapy (Chang et al., 2023; Olateju et al., 2022).
Methods

Study Design and Data Source

We conducted a retrospective cohort study of patients with mNSCLC diagnosed between 2010-2012 and 2016-2018 in the United States, each with a 2-year follow-up. Our primary objective was to compare the survival outcomes of patients with mNSCLC in the periods before and after the initial FDA approval of ICIs in 2015 to examine changes in racial and ethnic disparities. Data was obtained from the November 2022 submission of the Surveillance, Epidemiology, and End Results (SEER) database (2000-2020). The analysis was restricted to 17 registries that cover approximately 26.5% of the United States population and included the geographic areas of San Francisco-Oakland, Connecticut, Hawaii, Iowa, New Mexico, Seattle, Utah (Puget Sound), Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey, and Greater Georgia (Surveillance, Epidemiology, and End Results, 2020).

Cohort Selection and Construction of Variables

Patients included in the study cohort were 18 years of age or older diagnosed with mNSCLC between 2010-2012 or 2016-2018. Patients were excluded if they had multiple primary cancers, race was unknown/other, unknown year of diagnosis, diagnosis at autopsy or death, and benign tumors. Based on the exclusion criteria, 39,536 patients were excluded from the study. The sample was divided into two time periods: before ICI (2010-2014) and after ICI (2016-2020). Race and ethnicity were categorized as Hispanics and non-Hispanic American Indians/Alaska Natives (HNHAI), non-Hispanic Asian or Pacific Islander Patients (NHAPI), non-Hispanic Black (NHB), and non-Hispanic White patients (NHW). Hispanics and non-Hispanic American
Indians/Alaska Natives (HNHAI) were grouped because they had a small sample size, resulting in inadequate power to test for significance in each group separately. In this current study, race and ethnicity were considered a social construct. While SEER, relies on race and ethnicity abstracted from medical records; it is important to note that the collection of race and ethnicity from healthcare and clinical facilities is not standardized (Centers for Disease Control and Prevention, 2023).

Statistical Analysis
The primary endpoint was 2-year mNSCLC survival among each racial and ethnic group, defined by the survival time from diagnosis until death. Individuals in the study were censored if they had another cause of death not related to mNSCLC or were still alive at the end of the 2-year follow-up. The primary exposure was the patient's race and ethnicity; with NHW patients, as the largest race and ethnic group, serving as the comparison group. Bivariate analyses examined the associations between racial and ethnic groups and the additional study variables (e.g., sex, marital status at diagnosis, median household income, geographic region, histology, and age at diagnosis). ANOVA was performed to compare continuous variables, and Chi-Square was performed to compare categorical variables by racial and ethnic groups. The Kaplan-Meier survival curve was used to plot the survival rates for each racial and ethnic group, stratified by time period. The survival curves across the different time periods were compared using log-rank tests.

The proportional hazards assumption was not met for the covariates of age and histology. Therefore, we used a difference-in-difference model accelerated failure time model (AFT),
which does not need to meet the proportional hazards assumption (KC et al., 2023). The parameter estimates from AFT models were exponentiated to get the time ratio (TR) to interpret the effect (KC et al., 2023). A TR greater than 1 indicates that the covariate is associated with a longer survival time, and a TR less than 1 indicates that the covariate is associated with a shorter survival time (KC et al., 2023). An unadjusted AFT model was created to examine the effects of race and ethnicity on mNSCLC survival for each of the time periods. Our adjusted AFT model included race (categorical), sex (binary), marital status at diagnosis (categorical), median household income (categorical), geographic region (binary), histology (binary), and age at diagnosis (continuous) for each of the time periods. To evaluate the association between race and ethnicity with mNSCLC survival by time period, an interaction term between time period and race/ethnicity was added to the model. The p-value of the interaction term was used to determine if racial disparities have increased after the approval of ICI.

All P values were 2-sided, and P<0.05 was considered statistically significant. SAS (version 9.4) and R (version 4.2.1) statistical software were used for all analyses and data visualizations.

Results:

Study cohort characteristics

A total of 24,445 patients with mNSCLC were included in the study, with the majority of the cohort being composed of NHW patients (70.6%) (Table 1). NHW patients were diagnosed at an older age (69.0) compared to NHB (64.7), NHAPI (68.2), and HNHAI (66.9) patients. Furthermore, the difference in marriages rates was quite substantial in which NHW patients and NHAPI were more likely to be married at diagnosis (53.1% and 64.9%, respectively) compared to NHB patients (31.5%) and HNHAI patients (47.5%). Most racial and ethnic groups were more
likely to live in an urban area. NHW and NHB patients were more likely to have a household income of $50,000 to $74,999 compared to NHAPI and HNHAI patients, with a household income of $>=75,000. The majority of NHW, NHB, NHAPI, and HNHAI patients were more likely to have had non-squamous NSCLC.

Improvement of survival following introduction of ICI therapy

NHAPI patients had a higher survival compared to other racial and ethnic groups in both time periods (Figure 1 and Figure 2). Furthermore, survival improved for all racial and ethnic groups after the post-approval of ICI. The 2-year survival rate (24 months) for mNSCLC increased from 13.8% (95% CI: 13.06-14.52) to 23.0% (95% CI: 22.07-23.98) for NHW patients. Among NHB patients, it increased from 13.1% (95% CI: 11.33-15.23) to 21.2% (95% CI: 18.88-23.69). Among NHAPI patients, it improved from 24.4% (95% CI: 22.21-26.77) to 35.1% (95% CI: 32.90-37.60). Lastly, among HNHAI patients, the survival rate increased from 14.6% (95% CI: 12.19-17.46) to 24.7% (95% CI: 21.83-28.01). All improvements over time were statistically significant (log-rank p = <.0001).

Limited evidence of increasing racial disparity

In the unadjusted model (Table 2), NHB patients in the Post-ICI period had a significantly shorter survival time compared to NHW patients (TR: 0.91; 95% CI: 0.83-0.99); however, this did not persist in the multivariable adjusted model (Table 3). In the adjusted model, there was no statistically significant difference in survival time among NHB patients versus NHW patients for both the Pre-ICI (TR: 0.97; 95% CI: 0.90-1.05) and Post-ICI (TR: 0.91; 95% CI: 0.83-1.00) (Table 3). Furthermore, there was no significant difference in survival time among HNHAI patients versus NHW patients in Pre-ICI (TR: 1.05; 95% CI: 0.95-1.16) and Post-ICI (TR: 1.00;
95% CI:0.89-1.12). However, there was a significant difference in survival among NHAPI patients compared to NHW patients in both the Pre-ICI (TR: 1.35; 95% CI: 1.24-1.45) and Post-ICI (TR: 1.34; 95% CI: 1.23-1.47). NHAPI patients had a 35% longer survival time for pre-ICI and a 34% longer survival time for post-ICI compared to NHW patients. Based on the P-value for interaction, survival disparities by race and ethnicity did not worsen after the approval of ICI as there was no statistically significant difference between the Pre-ICI and Post-ICI for any race or ethnic group.

Discussion:

To our knowledge, this is the first study to investigate whether the FDA approval of ICI exacerbated racial disparities in mNSCLC survival. In unadjusted analysis, a slightly inferior survival was associated with NHB patients, however, this difference was not significant in adjusted analyses. In adjusted analyses that accounted for age at diagnosis, sex, geographic region, histology, household income, and marital status, we found that there was no statistically significant difference in survival time among the different racial and ethnic groups in both time periods but did observe significant better survival time among NHAPI patients compared to NHW. We did not observe evidence of significant interaction by race/ethnicity and time period, which suggests that ICI has not widened the gap between racial and ethnic survival disparities. However, our TR results show there may be a downward trend from Pre-ICI to Post-ICI for NHB and HNHA– but nothing significant.

Our study found similar results to previous studies’ findings indicating that mNSCLC survival rates for Black patients do not significantly differ from those for White patients, and similarly, survival rates for Hispanics are comparable to those for non-Hispanics (Aldrich, 2013;
Tannenbaum, 2014). These findings suggest that tumor characteristics or treatment may be the primary factors influencing survival rates (Tannenbaum, 2014). This outcome is surprising given the issue of non-concordant-guideline care, delay in treatment, and lower odds of receiving immunotherapy (Chang et al., 2023; Deng et al., 2020; Rekulapelli et al., 2022). However, our results show that survival rates for Asian patients significantly differ from White patients which is seen similarly in the literature due to higher EGFR mutation prevalence among Asian patients (Howlader et al., 2020).

One major limitation of the study is that the SEER dataset lacks information on treatment types, specifically ICI. This makes it challenging to disentangle the disparity that may persist because of ICIs versus targeted therapy. However, to overcome this issue, we used a difference-in-difference approach for the analysis, in which specific treatment information is unnecessary. There has been an increased trend in patients receiving ICI, especially during the year 2018, in which 38.8% received ICI compared to 7.7% who received tyrosine kinase inhibitors and 29.3% who received another form of treatment (Voruganti et al., 2023). Therefore, we can argue that the study design can identify any potential increase in disparities due to ICI. The database also lacks information on insurance status and comorbidities, which can impact the survival of those with mNSCLC. As a result, unobserved factors that may correlate with our outcome and exposure of interest could result in omitted variable bias. Previous studies have shown that these variables can affect patients' ability to get treatment and their survival (Maguire et al., 2019; Iachina et al., 2015). Another limitation is combining Hispanic and non-Hispanic American Indians/Alaska Natives into one group due to limited statistical power. Lastly, the survival is measured in months and not in days. Therefore, there is a lack of precision in follow-up.
Conclusion

Our study did not observe evidence of worsening racial disparities in mNSCLC survival in patients diagnosed between 2010-2012 and 2016-2018. From a population health perspective, the findings of this study are reassuring that racial disparities in mNSCLC survival have not been worsening overtime even with the advent of more advanced treatment options. However, it is important to note that this finding does not negate the presence of disparities in other aspects of cancer care for mNSCLC. It is important to address the multifactorial reasons behind health disparities to improve health outcomes for all populations. Future studies should include a larger sample size of patients who identified as Hispanic and non-Hispanic American Indians/Alaska Natives and additional years of data to increase statistical power. Furthermore, future studies should include specific information on the patient's treatment and follow-up length counted in days. Future research is also warranted to ensure that disparities do not emerge in more modern cohorts.
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https://doi.org/10.1097/ppo.0000000000000058


https://doi.org/10.1001/jamaoncol.2022.6901
## Table 1. Description of the Sample by Race/Ethnicity*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-Hispanic White (n = 17,251)</th>
<th>Non-Hispanic Black (n = 2,465)</th>
<th>Non-Hispanic Asians and Pacific Islanders (n = 3,160)</th>
<th>Hispanic and non-Hispanic American Indian/Alaska Native (n = 1,569)</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis (years), mean ± SD</td>
<td>69.0 ± 11.0</td>
<td>64.7 ± 10.82</td>
<td>68.2 ± 12.4</td>
<td>66.9 ± 12.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>9,224 (53.5)</td>
<td>1,380 (56.0)</td>
<td>1,755 (55.5)</td>
<td>846 (53.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Year of Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-ICI</td>
<td>9,200 (53.3)</td>
<td>1,263 (51.2)</td>
<td>1,475 (46.7)</td>
<td>771 (49.1)</td>
<td></td>
</tr>
<tr>
<td>Post-ICI</td>
<td>8,051 (46.7)</td>
<td>1,202 (48.8)</td>
<td>1,685 (53.3)</td>
<td>798 (50.9)</td>
<td></td>
</tr>
<tr>
<td>Married at diagnosis, n (%)</td>
<td>8,803 (53.1)</td>
<td>728 (31.5)</td>
<td>1,948 (64.9)</td>
<td>697 (47.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urban, n (%)</td>
<td>13,888 (80.5)</td>
<td>2,432 (98.7)</td>
<td>2,979 (94.3)</td>
<td>1,345 (85.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Household Income, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$35,000-49,999</td>
<td>764 (4.4)</td>
<td>95 (3.9)</td>
<td>10 (0.3)</td>
<td>230 (14.7)</td>
<td></td>
</tr>
<tr>
<td>$50,000-74,999</td>
<td>8,709 (50.5)</td>
<td>1,264 (51.3)</td>
<td>420 (13.3)</td>
<td>611 (39.0)</td>
<td></td>
</tr>
<tr>
<td>$≥75,000</td>
<td>7,775 (45.1)</td>
<td>1,106 (44.9)</td>
<td>2,730 (86.4)</td>
<td>726 (46.3)</td>
<td></td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Squamous</td>
<td>3,700 (21.5)</td>
<td>470 (19.1)</td>
<td>484 (15.3)</td>
<td>317 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Non-squamous</td>
<td>13,551 (78.6)</td>
<td>1,995 (80.9)</td>
<td>2,676 (84.7)</td>
<td>1,252 (79.8)</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers may not sum to totals due to missing data, and column percentages may not sum to 100% due to rounding.

† P-value for analysis of variance (ANOVA) (continuous variable) or χ² test (categorical variable).
Figure 1. Survival by Race and Ethnicity (Pre-Period)
Figure 2. Survival by Race and Ethnicity (Post-Period)
Table 2. Unadjusted Survival Time Ratio by race/ethnicity and ICI time period

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-ICI (TR)</th>
<th>Post-ICI (TR)</th>
<th>P-value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>1.00</td>
<td>1.00</td>
<td>---</td>
</tr>
<tr>
<td>NHB</td>
<td>0.99 (0.92-1.07)</td>
<td>0.91 (0.83-0.99)</td>
<td>0.1673</td>
</tr>
<tr>
<td>NHAPI</td>
<td>1.41 (1.21-1.52)</td>
<td>1.55 (1.43-1.69)</td>
<td>0.2177</td>
</tr>
<tr>
<td>HNHAI</td>
<td>1.07 (0.97-1.18)</td>
<td>1.06 (0.95-1.19)</td>
<td>0.8579</td>
</tr>
</tbody>
</table>
Table 3. Adjusted Survival Time Ratio by race/ethnicity and ICI time period

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-ICI TR (95%CI) *</th>
<th>Post-ICI TR (95% CI) *</th>
<th>P-value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>1.00</td>
<td>1.00</td>
<td>---</td>
</tr>
<tr>
<td>NHB</td>
<td>0.97 (0.90-1.05)</td>
<td>0.91 (0.83-1.00)</td>
<td>0.5598</td>
</tr>
<tr>
<td>NHAPI</td>
<td>1.35 (1.24-1.45)</td>
<td>1.34 (1.23-1.47)</td>
<td>0.7256</td>
</tr>
<tr>
<td>HNHAI</td>
<td>1.05 (0.95-1.16)</td>
<td>1.00 (0.89-1.12)</td>
<td>0.7803</td>
</tr>
</tbody>
</table>

*Adjusted for age at diagnosis, sex, geographic region, histology, household income, and marital status at diagnosis