Factors Associated with Adoption of Immune Checkpoint Inhibitor Treatment for Advanced Melanoma: A SEER-Medicare Cohort Study

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We aimed to explore the differences in immune checkpoint inhibitor (ICI) immunotherapy utilization for advanced melanoma by examining patient and neighborhood characteristics. We performed a retrospective cohort study using a deidentified, random sample of SEER-Medicare beneficiaries aged ≥65 years with stage III or stage IV melanoma (2011–2017). Our primary outcome was initiation of ICI immunotherapy (ipilimumab, pembrolizumab, nivolumab, or atezolizumab) after stage III or stage IV melanoma diagnosis. We analyzed ICI usage with multivariable logistic regression. After analyzing the entire 2011–2017 cohort, we conducted a secondary analysis in which we separately analyzed the 2011–2014 and 2015–2017 cohorts to assess possible differences over time. We included 3531 beneficiaries, with mean follow-up of 2.1 (SD = 2.0) years. Higher likelihood of ICI usage was associated with male sex (OR = 1.21, 95% confidence interval = 1.04–1.42) and higher density of medical oncologists (OR = 1.02, 95% confidence interval = 1.01–1.04). Lower likelihood of ICI usage was associated with older age group and Charlson comorbidity score (score ≥2; OR = 0.72, 95% confidence interval = 0.60–0.86). These associations were diminished in more recent years (no association with sex, medical oncologist density, Charlson comorbidity score, and association with only the oldest age group in years 2015–2017). We found significant sex- and age-related differences in initiation among SEER-Medicare beneficiaries with stage III or stage IV melanoma, which appear to be improving over time.

Keywords: Epidemiology, Health services research, Melanoma

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INTRODUCTION

Cutaneous melanoma is the most fatal skin cancer (Arnold et al, 2014). Immune checkpoint inhibitors (ICIs) have revolutionized advanced melanoma treatment, and they are now part of the standard of care (Coit et al, 2019).

Although the introduction of ICI use has provided significant survival benefits, prior studies have suggested that this disproportionately favors non-Hispanic White patients (Ward-Peterson et al, 2016). Limited evidence exists on how area- and health system–level factors play a role in disparity in access to cancer medication (Gomez et al, 2015). We aimed to explore the association of neighborhood factors and individual patient demographics with the initiation of ICI treatment for Medicare beneficiaries with stage III or stage IV melanoma.

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Abbreviations: CI, confidence interval; ICI, immune checkpoint inhibitor

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RESULTS

We included 3531 beneficiaries with stage III or stage IV melanoma, with a mean follow-up of 2.1 (SD = 2.0) years. Baseline cohort demographics are summarized in Table 1. It shows that patients with later tumor stage, younger age, male sex, and lower Charlson comorbidity score were more likely to have used an ICI. Moreover, patients in areas with metropolitan status, higher median household income, and higher density of medical oncologists were more likely to have used an ICI.

Multivariable logistic regression results are shown in Table 2. Characteristics associated with significantly higher likelihood of ICI usage included later tumor stage (OR = 2.57, 95% confidence interval [CI] = 2.19–3.01), male sex (OR = 1.21, 95% CI = 1.04–1.42), higher density of medical oncologists (OR = 1.02, 95% CI = 1.01–1.04), and later diagnosis year. Characteristics associated with significantly lower likelihood of ICI usage included older age and increased Charlson comorbidity score (score ≥2; OR = 0.72, 95% CI = 0.60–0.86). Patients living in urban neighborhoods may have been less likely to initiate ICI treatment than patients living in metropolitan areas, but this was not statistically significant (OR = 0.77, 95% CI = 0.58–1.01). Neighborhood income tertile was not associated with likelihood of ICI usage.

Our secondary analysis in which we stratified the main logistic regression by year is also shown in Table 2, with the baseline demographics of the 2011–2017, 2011–2014, and 2015–2017 cohorts shown in Table 3 (there were no

Table 1. Baseline Demographics of Melanoma Cohort by ICI Usage

Patient Demographics	All n (Column %)	No ICI n (Row %)	ICI n (Row %)	*P*-Value[1]
Total	3531 (100)	2290 (64.9)	1241 (35.2)	
Tumor stage				<.001
III	2474 (70.1)	1762 (71.2)	712 (28.8)	
IV	1057 (29.9)	528 (50.0)	529 (50.1)	
Age at melanoma diagnosis, y				<.001
65–74	1436 (40.7)	824 (57.4)	612 (42.6)	
75–84	1373 (38.9)	892 (65.0)	481 (35.0)	
≥85	722 (20.5)	574 (79.5)	148 (20.5)	
Sex				<.001
Female	1310 (37.1)	899 (68.6)	411 (31.4)	
Male	2221 (62.9)	1391 (62.6)	830 (37.4)	
Race and ethnicity[2]				.27
Non-Hispanic White	3346 (94.8)	2177 (65.1)	1169 (34.9)	
Other	185 (5.2)	113 (61.1)	72 (38.9)	
Charlson Comorbidity Index				<.001
0	1606 (45.5)	985 (61.3)	621 (38.7)	
1	818 (23.2)	540 (66.0)	278 (34.0)	
≥2	1107 (31.4)	765 (69.1)	342 (30.9)	
Rurality				<.001
Metropolitan	2692 (83.9)	1883 (63.6)	1079 (36.4)	
Urban	389 (11.0)	282 (72.5)	107 (27.5)	
Rural	180 (5.1)	125 (69.4)	55 (30.6)	
Middle income tertile				.003
T1 (26,849–63,877)	1177 (33.3)	807 (68.6)	370 (31.4)	
T2 (63,959–81,842)	1162 (32.9)	743 (63.9)	419 (36.1)	
T3 (82,225–130,890)	1192 (33.8)	740 (62.1)	452 (37.9)	
Number of oncologists/100,000, mean (SD)	4.9 (5.3)	4.7 (4.4)	5.3 (4.8)	.006
Number of ICIs at initiation				—
Dual agent	—	—	92 (7.4)	
Single agent	—	—	1149 (92.6)	
ICI agent				—
Pembrolizumab	—	—	430 (35.7)	
Ipilimumab	—	—	552 (44.5)	
Nivolumab	—	—	350 (28.2)	
Cemiplimab-rwlc	—	—	1 (0.1)	

Abbreviation: ICI, immune checkpoint inhibitor.

[1]Chi-square or *t*-test, as appropriate, between no ICI and ICI groups.

[2]The race and ethnicity variables available in our SEER-Medicare dataset are one for ethnicity (OriginrecodeNHIAHispanicNonHisp, with 2 categories: non-Spanish-Hispanic-Latino, Spanish-Hispanic-Latino) and one for race (RACE_RECODE_WHITE_BLACK_OTHER with 5 categories: White, Black, other [American Indian/Alaska Native, Asian/Pacific Islander], other unspecified, and unknown). CMS stipulates that cell counts <11 cannot be displayed, so patients who were not non-Hispanic White were grouped for this study.

statistically significant differences in demographics between time strata). In more recent years (2015–2017), only patients aged >85 years were significantly less likely to initiate ICI treatment (OR = 0.40, 95% CI = 0.29–0.54). No statistically significant differences in ICI initiation were found for patients aged 75–84 year or for patients with higher Charlson comorbidity scores. In addition, male sex was not associated with significantly higher likelihood of ICI usage in 2015–2017 nor was medical oncologist density.

In a sensitivity analysis excluding 92 patients who had dual-agent ICI treatment at initiation, we found results similar to those of the main analysis (Table 4): significantly higher likelihood of ICI usage with later tumor stage (OR = 2.45, 95% CI = 2.08–2.88), male sex (OR = 1.17, 95% CI = 1.00–1.37), higher density of medical oncologists (OR = 1.02, 95% CI = 1.01–1.04), and later diagnosis year and significantly lower likelihood of ICI usage with older age and increased Charlson comorbidity score (score ≥2; OR = 0.74, 95% CI = 0.61–0.88). Neighborhood income tertile was not associated with likelihood of ICI usage.

In a sensitivity analysis using multivariable Cox regression analyses, later tumor stage (hazard ratio = 3.34, 95% CI = 2.98–3.75), male sex (hazard ratio = 1.20, 95% CI = 1.07–1.36), higher density of medical oncologists (hazard ratio = 1.01, 95% CI = 1.00–1.02), and later diagnosis year were associated with significantly earlier ICI initiation (Table 5). Older age was associated with significantly longer time to ICI initiation. Neighborhood income tertile and rurality were not associated with time to ICI initiation.

Table 2. ICI Usage: Multivariable Logistic Regression

Characteristics	ICI Usage OR (95% CI)	2011–2014: ICI Usage OR (95% CI)	2015–2017: ICI Usage OR (95% CI)
Tumor stage			
III	Ref	Ref	Ref
IV	2.57 (2.19–3.01)	2.05 (1.65–2.55)	3.32 (2.62–4.22)
Age, y			
65–74	Ref	Ref	Ref
75–84	0.79 (0.67–0.93)	0.65 (0.51–0.81)	0.98 (0.77–1.24)
≥85	0.36 (0.29–0.45)	0.32 (0.23–0.45)	0.40 (0.29–0.54)
Sex			
Female	Ref	Ref	Ref
Male	1.21 (1.04–1.42)	1.35 (1.08–1.69)	1.11 (0.89–1.40)
Race and ethnicity[1]			
Other	Ref	Ref	Ref
Non-Hispanic White	0.87 (0.63–1.21)	0.81 (0.52–1.26)	0.98 (0.60–1.59)
Charlson Comorbidity Index			
0	Ref	Ref	Ref
1	0.85 (0.70–1.02)	0.77 (0.59–1.00)	0.95 (0.72–1.25)
≥2	0.72 (0.60–0.86)	0.60 (0.46–0.77)	0.84 (0.65–1.08)
Rurality			
Metropolitan	Ref	Ref	Ref
Urban	0.77 (0.58–1.01)	0.79 (0.54–1.16)	0.76 (0.51–1.12)
Rural	0.94 (0.65–1.37)	0.88 (0.51–1.50)	1.00 (0.59–1.70)
Mid income tertile			
T1 (26,849–63,877)	Ref	Ref	Ref
T2 (63,959–81,842)	1.13 (0.92–1.38)	1.16 (0.88–1.54)	1.13 (0.84–1.51)
T3 (82,225–130,890)	1.14 (0.93–1.40)	0.94 (0.71–1.25)	1.42 (1.06–1.92)
Number of oncologists/100,000	1.02 (1.01–1.04)	1.03 (1.01–1.05)	1.02 (0.99–1.04)
Diagnosis y			
2011	Ref	Ref	N/A
2012	1.41 (1.02–1.93)	1.43 (1.04–1.96)	N/A
2013	2.15 (1.59–2.90)	2.18 (1.61–2.95)	N/A
2014	2.28 (1.68–3.10)	2.30 (1.69–3.13)	N/A
2015	2.87 (2.11–3.89)	N/A	Ref
2016	3.54 (2.64–4.75)	N/A	1.25 (0.95–1.63)
2017	6.38 (4.75–8.57)	N/A	2.22 (1.69–2.92)

Abbreviations: CI, confidence interval; ICI, immune checkpoint inhibitor; N/A, not available; Ref, reference.

[1]The race and ethnicity variables available in our SEER-Medicare dataset are one for ethnicity (OriginrecodeNHIAHispanicNonHisp, with 2 categories: non-Spanish-Hispanic-Latino, Spanish-Hispanic-Latino) and one for race (RACE_RECODE_WHITE_BLACK_OTHER with 5 categories: White, Black, other [American Indian/Alaska Native, Asian/Pacific Islander], other unspecified, and unknown). CMS stipulates that cell counts <11 cannot be displayed, so patients who were not non-Hispanic White were grouped for this study.

DISCUSSION

Our study of 3531 SEER-Medicare beneficiaries with stage III or stage IV melanoma found the individual patient's tumor stage, age, sex, Charlson comorbidity score, and diagnosis year to be associated with ICI initiation. Higher ICI usage associated with higher tumor stage may be confounded owing to the stage 3A patients because this is the most common stage, and ICI usage is not indicated for these patients. In addition, we found decreased and delayed initiation of ICIs for beneficiaries living in neighborhoods with a low density of medical oncologists. ICI usage in patients with melanoma has improved significantly over time, as evidenced by the increasing effect sizes for diagnosis year in both primary and sensitivity analyses.

We observed that male patients were significantly more likely to initiate an ICI and waited less time to start treatment overall, although this association was not present in the most recent years of data. Previous studies have also explored a potential sex difference in response to immunotherapy. A systematic review and meta-analysis of 20 ICI randomized controlled trials found that ICIs were significantly more effective in men than in women (Conforti et al, 2018). However, there are potential limitations to these findings, including women being underrepresented in immunotherapy clinical trials (Carrera et al, 2018). Notably, when only analyzing the more recent time period (2015–2017), male sex was no longer significantly associated with higher likelihood of ICI initiation, indicating that this sex difference has lessened over time.

Older age was associated with lower likelihood of ICI treatment and significantly longer time to ICI initiation, even when adjusting for confounding factors such as tumor stage and Charlson comorbidity score. Our findings align with previous literature that has found a tendency to undertreat

Table 3. Baseline Demographics of Melanoma Cohort by Year Stratification (2011−2014 and 2015−2017 Cohorts)

Patient Demographics	All n (Column %)	2011−2014 Cohort n (Row %)	2015−2017 Cohort n (Row %)	*P*-Value[1]
Total	3531 (100)	1994 (56.5)	1537 (43.5)	—
Tumor stage				.8183
III	2474 (70.1)	1394 (56.3)	1080 (43.7)	
IV	1057 (29.9)	600 (56.8)	457 (43.2)	
Age at melanoma diagnosis, y				.2539
65−74	1436 (40.7)	787 (54.8)	649 (45.2)	
75−84	1373 (38.9)	792 (57.7)	581 (42.3)	
≥85	722 (20.5)	415 (57.5)	307 (42.5)	
Sex				.4302
Female	1310 (37.1)	751 (57.3)	559 (42.7)	
Male	2221 (62.9)	1243 (56.0)	978 (44.0)	
Race and ethnicity[2]				.8159
Non-Hispanic White	3346 (94.8)	1888 (56.4)	1458 (43.6)	
Other	185 (5.2)	106 (57.3)	79 (42.7)	
Charlson Comorbidity Index				.3658
0	1606 (45.5)	917 (57.1)	689 (42.9)	
1	818 (23.2)	471 (57.6)	347 (42.4)	
≥2	1107 (31.4)	606 (54.7)	501 (45.3)	
Rurality				.9135
Metropolitan	2692 (83.9)	1671 (56.4)	1291 (43.6)	
Urban	389 (11.0)	223 (57.3)	166 (42.7)	
Rural	180 (5.1)	100 (55.6)	80 (44.4)	
Middle income tertile				.6668
T1 (26,849−63,877)	1177 (33.3)	675 (57.3)	502 (42.7)	
T2 (63,959−81,842)	1162 (32.9)	645 (55.5)	517 (44.5)	
T3 (82,225−130,890)	1192 (33.8)	674 (56.5)	518 (43.5)	
Number of oncologists/100,000, mean (SD)	4.9 (5.3)	4.9 (5.3)	4.9 (5.3)	.9607

[1]Chi-square or *t*-test, as appropriate, between 2011−2014 cohort and 2015−2017 cohort.

[2]The race and ethnicity variables available in our SEER-Medicare dataset are one for ethnicity (OriginrecodeNHIAHispanicNonHisp, with 2 categories: non-Spanish-Hispanic-Latino, Spanish-Hispanic-Latino) and one for race (RACE_RECODE_WHITE_BLACK_OTHER with 5 categories: White, Black, other [American Indian/Alaska Native, Asian/Pacific Islander], other unspecified, and unknown). CMS stipulates that cell counts <11 cannot be displayed, so patients who were not non-Hispanic White were grouped for this study.

cancer in older patients (Bouchardy et al, 2003). In addition, similar to female patients, older patients are underrepresented in clinical trials (Hutchins et al, 1999; Nipp et al, 2016). However, other factors such as patient preference; adverse event profiles, particularly in the use of dual-agent regimens and drug type, such as CTLA-4 versus PD-1; likelihood to initiate palliative care; and transportation issues may have influenced these results. However, our sensitivity analysis excluding patients who received dual-agent regimens yielded similar results. Patients in the oldest age group (aged ≥85 years) continued to have lower likelihood of ICI initiation in the most recent time period (2015−2017), although patients aged 75−84 years were not less likely to receive ICIs in this time period because they had been previously (2011−2014), which may indicate an improvement in ICI use in older patients. Similarly, Charlson comorbidity score was no longer significantly associated with less likelihood of ICI initiation in the most recent time period (2015−2017). These changes may reflect greater reach of ICIs and greater acceptability of ICIs by oncologists and patients.

Our study has several limitations. We only evaluated patients in the SEER-Medicare database, which could affect the generalizability of our results. Patients without health insurance are known to experience disparities in cancer treatment and outcomes, so future studies including this population are needed. We also are not able to account for certain factors that can drive treatment choices such as patient preference and financial status. The use of claims data relies on the accuracy of diagnostic codes and is not comprehensive of all patient characteristics. To address this, we adjusted for possible known confounders. In addition, our sample size is limited, with few individuals who were not non-Hispanic White. Furthermore, owing to the small number of individuals who did not fall into the non-Hispanic White category, we were only able to categorize race and ethnicity into non-Hispanic White and Other. Owing to this limitation, we were unable to adequately explore the interaction of race and ethnicity with ICI treatment utilization.

We found significant sex- and age-related differences in initiation and time to ICI treatment among SEER-Medicare beneficiaries with stage III or stage IV melanoma. However, these differences appear to have lessened over time. Treatment of patients with advanced melanoma has overall been improving over time, although older patients may still be undertreated. More studies about similar outcomes in older age groups may be needed.

Table 4. ICI Usage: Multivariable Logistic Regression and Sensitivity Analysis, Excluding Patients on Dual-Agent ICI Treatment at Initiation

Characteristics	ICI Usage OR (95% CI)
Tumor stage	
III	Ref
IV	2.45 (2.08–2.88)
Age, y	
65–74	Ref
75–84	0.81 (0.69–0.96)
≥85	0.37 (0.30–0.47)
Sex	
Female	Ref
Male	1.17 (1.00–1.37)
Race and ethnicity[1]	
Other	Ref
Non-Hispanic White	0.92 (0.66–1.28)
Charlson Comorbidity Index	
0	Ref
1	0.83 (0.69–1.01)
≥2	0.74 (0.61–0.88)
Rurality	
Metropolitan	Ref
Urban	0.77 (0.58–1.02)
Rural	0.96 (0.66–1.40)
Middle income tertile	
T1 (26,849–63,877)	Ref
T2 (63,959–81,842)	1.12 (0.91–1.38)
T3 (82,225–130,890)	1.18 (0.96–1.45)
Number of oncologists/100,000	1.02 (1.01–1.04)
Diagnosis y	
2011	Ref
2012	1.36 (0.99–1.86)
2013	2.09 (1.55–2.83)
2014	2.21 (1.62–3.00)
2015	2.70 (1.99–3.67)
2016	3.15 (2.34–4.23)
2017	5.76 (4.27–7.75)

Abbreviations: CI, confidence interval; ICI, immune checkpoint inhibitor; Ref, reference.

[1]The race and ethnicity variables available in our SEER-Medicare dataset are one for ethnicity (OriginrecodeNHIAHispanicNonHisp, with 2 categories: non-Spanish-Hispanic-Latino, Spanish-Hispanic-Latino) and one for race (RACE_RECODE_WHITE_BLACK_OTHER with 5 categories: White, Black, other [American Indian/Alaska Native, Asian/Pacific Islander], other unspecified, and unknown). CMS stipulates that cell counts <11 cannot be displayed, so patients who were not non-Hispanic White were grouped for this study.

Table 5. Time to ICI Initiation: Cox Regression Results

Characteristics	Time to ICI Initiation HR (95% CI)
Tumor stage	
III	Ref
IV	3.34 (2.98–3.75)
Age, y	
65–74	Ref
75–84	0.95 (0.84–1.07)
≥85	0.58 (0.48–0.69)
Gender	
Female	Ref
Male	1.20 (1.07–1.36)
Race and ethnicity[1]	
Non-Hispanic White	Ref
Other	1.01 (0.79–1.29)
Charlson Comorbidity Index	
0	Ref
1	0.94 (0.82–1.08)
≥2	0.90 (0.78–1.03)
Rurality	
Metropolitan	Ref
Urban	0.83 (0.67–1.03)
Rural	1.02 (0.76–1.36)
Middle income tertile	
T1 (26,849–63,877)	Ref
T2 (63,959–81,842)	1.08 (0.93–1.26)
T3 (82,225–130,890)	1.09 (0.93–1.27)
Number of oncologists/100,000	1.01 (1.00–1.02)
Diagnosis year	
2011	Ref
2012	1.27 (0.96–1.67)
2013	1.99 (1.53–2.58)
2014	2.26 (1.74–2.95)
2015	2.87 (2.21–3.73)
2016	4.00 (3.12–5.14)
2017	7.63 (5.97–9.76)

Abbreviations: CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; Ref, reference.

[1]The race and ethnicity variables available in our SEER-Medicare dataset are one for ethnicity (OriginrecodeNHIAHispanicNonHisp, with 2 categories: non-Spanish-Hispanic-Latino, Spanish-Hispanic-Latino) and one for race (RACE_RECODE_WHITE_BLACK_OTHER with 5 categories: White, Black, other [American Indian/Alaska Native, Asian/Pacific Islander], other unspecified, and unknown). CMS stipulates that cell counts <11 cannot be displayed, so patients who were not non-Hispanic White were grouped for this study.

MATERIALS AND METHODS

This retrospective cohort study used the deidentified SEER-Medicare database (2011–2017). We identified beneficiaries aged ≥65 years without Medicare Advantage coverage (fee-for-service only), with continuous enrollment 12 months before and at least 90 days after their cancer diagnosis. We included beneficiaries first diagnosed with stage III or stage IV melanoma. We excluded beneficiaries diagnosed with an additional cancer the year after melanoma diagnosis, who had <90 days follow-up after diagnosis, or whose reporting diagnosis source was an autopsy or death certificate. This study was institutional review board approved (MD Anderson Cancer Center, 2019-0966).

We included all ICIs approved for melanoma as of 2020 (ipilimumab, pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, and cemiplimab). ICI treatment claims were identified using the Healthcare Common Procedure Coding System codes (Table 6). ICI treatment initiation was defined as the service date on the first ICI claim after stage III or stage IV melanoma diagnosis.

We collected patient age, sex, race and ethnicity, Charlson Comorbidity Index, diagnosis year, and tumor stage as patient-level characteristics. Charlson Comorbidity Index (Charlson et al, 1987) was calculated using claims up to 1 year before melanoma diagnosis. We collected median household income of the county of residence, rurality, and density of medical oncologists of the county (per 100,000 people) as neighborhood characteristics. We categorized median household income into tertiles (T1–T3), using data

Table 6. J Codes for Immune Checkpoint Inhibitors for Advanced Melanoma

Generic Name	J Code
ipilimumab	J9228
pembrolizumab	J9271, C9027
nivolumab	C9453, J9299
atezolizumab	C9483, J9022

from the United States Census (United States Census Bureau, 2023). We defined rurality with rural–urban continuum codes, categorizing counties as metropolitan, urban, or rural (U.S. Department of Agriculture, 2020). We extracted density of medical oncologists per county using a prior study (Shih et al, 2021). We compared baseline demographics using chi-square or *t*-tests, as appropriate.

We examined whether patients used any ICIs during the study follow-up using multivariable logistic regression. Covariables included tumor stage, patient age, sex, race and ethnicity, Charlson comorbidity index, rurality, median household income, density of medical oncologists, and year of diagnosis. In a secondary analysis, we carried out the same logistic regression but stratified by year, grouping 2011–2014 and 2015–2017 separately to evaluate whether associations changed over time stratum. We ran a sensitivity analysis excluding patients on dual-agent treatment at initiation because the adverse event profile of dual-agent treatment could confound our analysis. Finally, we ran a Cox regression as a sensitivity analysis, analyzing time from stage III or stage IV melanoma diagnosis to ICI initiation using multivariable Cox proportional hazard models to adjust for potential for differential loss to follow-up.

ETHICS STATEMENT

This study was institutional review board approved (MD Anderson Cancer Center, 2019-0966).

DATA AVAILABILITY STATEMENT

Datasets related to this article can be found at https://healthcaredelivery.cancer.gov/seermedicare/, hosted at the Health Care Delivery Research Program on behalf of the National Cancer Institute.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: CM, CLH, MRW, ML; Data Curation: KL; Formal Analysis: KL; Methodology: CM, CLH, KL, MRW, ML; Project Administration: ML, CLH, MRW; Resources: ML, MRW; Supervision: ML, MRW; Writing - Original Draft Preparation: CM, CLH; Writing - Review and Editing: ML, MRW, CLH, KL

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) OR LARGE LANGUAGE MODELS (LLM)

The author(s) did not use AI/LLM in any part of the research process and/or manuscript preparation.

Disclaimer

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