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Factors associated with immune checkpoint inhibitor use among older adults with late-stage melanoma

A population-based study

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Abstract

Improvement in overall survival by immune checkpoint inhibitors (ICI) treatment in clinical trials encourages their use for late-stage melanoma. However, in the real-world, heterogeneity of population, such as older patients with multimorbidity, may lead to a slower diffusion of ICIs. The objective of this study was to examine the association of multimorbidity and other factors to ICI use among older patients with late-stage melanoma using real world data.

A retrospective cohort study design with a 12-month baseline and follow-up period was adopted with data from the linked Surveillance, Epidemiology, and End Results cancer registry/Medicare database. Older patients (>65 years) with late-stage (stage III/IV) melanoma diagnosed between 2012 and 2015 were categorized as with or without multimorbidity (presence of 2 or more chronic conditions) and ICI use was identified in the post-index period. Chi-square tests and logistic regression were used to evaluate factors associated with ICI use.

In the study cohort, 85% had multimorbidity, 18% received any treatment (chemotherapy, radiation, and/or ICI), and 6% received ICI. Only 5.5% of older patients with multimorbidity and 6% without multimorbidity received ICIs. Younger age, presence of social support, lower economic status, residence in northeastern regions, and recent year of diagnosis were significantly associated with ICI use; however, multimorbidity, sex, and race were not associated with ICI use.

In the real-world clinical practice, only 1 in 18 older adults with late stage melanoma received ICI, suggesting slow pace of diffusion of innovation. However, multimorbidity was not a barrier to ICI use.

Abbreviations: AOR = adjusted odds ratio, CI = Confidence interval, ICD = International Classification of Diseases, ICI = immune checkpoint inhibitors, NCCN = National Cancer Comprehensive Network, OR = Odds ratio, RCT = randomized clinical trials, SEER = surveillance, epidemiology, and end results, US = United States.

Keywords: Geriatrics, Immune Checkpoint Inhibitors, Melanoma, Metastatic cancer, Multimorbidity, Older patients

1. Introduction

Newer therapies, namely immune checkpoint inhibitors (ICIs) with a unique mechanism of action and unknown side effect profile,[1] have significantly increased the survival prognosis for adults with late-state melanoma.[2–4] The first ICI was approved in 2011 by the United States (US) Food and Drug Administration and has since been recommended as the first-line treatment for late-stage melanoma by the National Cancer Comprehensive Network (NCCN) guidelines.[3,5] These recommendations were based on the evidence presented in randomized clinical trials (RCTs), which have strict inclusion and exclusion criteria.[2,6,7] These stringent criteria, while beneficial to ensure patient safety,

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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do not capture the heterogeneity of various patient subpopulations.

This lack of information on heterogeneity of treatment effects may be a reason that despite being around for nearly a decade, the uptake of ICI in the real-world setting is dismal.[8] One of the patient subpopulations where evidence on use of ICI is lacking is the older populations. Although utility of ICI in older patients with late-stage melanoma is debated, data from studies have shown that these therapies are well tolerated in older patients.[9–11] Older patients are also known to have multiple chronic conditions (also known as multimorbidity), which are often not taken into account by the guidelines.[9,10,12] There are no studies to-date examining the association of multimorbidity on treatment with ICI among older individuals with late-stage melanoma. Presence of multimorbidity leads to less aggressive treatment with existing modalities (such as chemotherapy and radiation) due to fear of worsening other conditions.[13–15] Older patients with multimorbidity are the norm rather than exception in clinical practices.[16] Therefore, evaluating the association of multimorbidity to ICI use in real-world setting may help healthcare providers personalize these treatments for their older patients.

In addition, disparities in the receipt of ICI are unknown. Studies on other cancers have shown some subgroups may be less likely to receive treatment. For example, age and racial disparities on treatment received was reported among older patients with late-stage pancreatic adenocarcinoma.[17] Patients below the age of 80 years and non-Hispanic Whites were more likely to receive treatment than those above 80 years of age and other race/ethnicity.[17] Similarly, a study among older patients with bladder cancer reported better survival among married patients than unmarried ones, because of greater likelihood of receiving treatment.[18] Underinsured patients with late-stage melanoma were more likely to receive treatment at hospitals which prescribed immunotherapy at a lower frequency.[19] With evident disparities in receipt of treatment, it is critical to know whether some subgroups lag in the diffusion of innovative therapies like ICIs, so that oncologists and patients alike can make informed decisions when considering ICIs as the treatment option. Therefore, the objective of this study is to examine the association of multimorbidity and other factors to ICI use that cover years from the initial introduction (i.e. 2011) to 2015 among older patients with late-stage melanoma.

2. Methods

2.1. Study design

This was a retrospective cohort design with a 12-month baseline (pre-diagnosis) and 12-month follow-up (post-diagnosis) period, anchored to an index date. Diagnosis date of late-stage (stage III/stage IV) melanoma diagnosis was the index date and was used to define pre- and post-diagnosis periods. Multimorbidity and all independent variables were assessed in the baseline period while treatments (chemotherapy, radiation, ICI) received were assessed in the follow-up period.

2.2. Data source

This study was conducted using the Surveillance, Epidemiology, and End Results (SEER) cancer registry linked with fee-for-service Medicare claims. Information on clinical variables related to cancer (such as stage of cancer at diagnosis) was obtained from SEER data, while information on healthcare encounters of beneficiaries when enrolled and using Medicare covered health services was obtained from Medicare claims. As the patients are deidentified by SEER-Medicare, this study was exempt from approval by the Institutional Review Board.

2.3. Study population

Incident melanoma diagnosis between 2011 and 2015 was identified using International Classification of Diseases (ICD)-O-3 site codes (C44.0 – C44.9) and ICD-O-3 histology codes (8720 – 8790). Late-stage (stage III/IV) of melanoma was identified based on the TNM classification using American Joint Committee on Cancer 7th Edition. The final cohort comprised of 4519 patients with late-stage melanoma following exclusion of those with local or regional (stage I/II) melanoma, non-incident melanoma, ages 66 years and below, not continuously enrolled in Medicare part A and part B during pre-index period, and diagnosed with late-stage cancer during autopsy.

2.4. Measures

2.4.1. Dependent variable: ICI use. The study outcome, ICI use, was identified in the post-diagnosis period. The ICIs approved for late-stage melanoma treatment include ipilimumab, nivolumab, and pembrolizumab, which were identified using healthcare common procedure coding system codes (J9228, J9299, J9271).

2.4.2. Independent variables. Multimorbidity: Presence of 2 or more chronic conditions in the pre-diagnosis period was defined as multimorbidity in this study. These conditions were obtained from a list of 21 chronic conditions developed by Multiple Chronic Conditions working group within the US Department of Health and Human Services Office of Assistant Secretary of Health (Supplemental Digital Content (Appendix 1, http://links.lww.com/MD/F724)). Pre-existing autoimmune diseases were also added to the list based on the current challenges with ICI use in patients with these conditions (Supplemental Digital Content (Appendix 2, http://links.lww.com/MD/F726)).[20] All these conditions were identified with ICD, 9th Edition.

Treatment with chemotherapy and radiation was also determined in the post-index period. Chemotherapy and radiation claims were identified using procedure codes, Healthcare common procedure coding system codes, and revenue center codes (see Supplemental Digital Content (Appendix 3, http://links.lww.com/MD/F728)). Overlapping procedure codes for chemotherapy and ICI (96413, 96415) were excluded to avoid confusion.

Biological factors consisted of age (66–69 years, 70–74 years, 75–79 years, and ≥80 years), sex (male/female), and race (white/non-white). Social factors included marital status (married/not married). Community resources included regions (Northeast, South, West, and North Central). Dual Medicare/Medicaid enrollment (yes/no) was used as a proxy for low economic status. Years of incident melanoma diagnosis (2012–2015) was used to control for changes in practice patterns.

2.5. Statistical analysis

Chi-square tests were used to identify significant unadjusted associations of individual characteristics to ICI use. Multivariable Logistic regressions were performed to determine the association

of multimorbidity, year of diagnosis, age, sex, race/ethnicity, marital status, dual eligibility, and region with ICI use. Parameter estimates are presented as adjusted odds ratios (AORs) after adjusting for all independent variables, with their corresponding 95% confidence intervals (CI); $P \leq .05$ was considered statistically significant. All analyses were conducted using SAS 9.4 (SAS Institute Inc.).

3. Results

The study population consisted of 4,519 older adults with late-stage melanoma and comprised predominantly of males (64.2%), Non-Hispanic Whites (96.1%) and those 70 years or older (70.4%). About 85% of the older adults had multimorbidity, 18% received any treatment, and 6% received ICI. In the study cohort, 5.5% of patients with multimorbidity and 6% of patients without multimorbidity received ICI. The characteristics of those who received and did not receive ICI differed by all variables except the presence of multimorbidity ($P = .62$) and race ($P = .29$) (Table 1).

Table 2 presents the unadjusted odds ratio, AORs, and 95% CIs of all independent variables included in the study from separate logistic regressions on ICI use. In the unadjusted regressions, year of diagnosis, age, sex, marital status, and dual eligibility were significantly associated with ICI use. In the adjusted analysis, patients in the lower age groups (66 to 69 years and 70 to 74 years) had significantly higher odds of receiving ICIs than those 80 years and above (AOR = 1.65, 95%CI = 1.15, 2.36; AOR = 1.81, 95%CI = 1.28, 2.54 respectively). Patients who were married (AOR = 1.92, 95%CI = 1.46, 2.52), resided in the Northeastern SEER regions (AOR = 1.75, 95%CI = 1.26, 2.41), and had dual eligibility (AOR = 2.42, 95%CI = 1.40, 4.19) were more likely to receive ICIs than the comparison groups: those who were not married, residing in SEER Western regions, and did not have dual eligibility. Patients diagnosed in 2012 (AOR = 0.42, 95%CI = 0.28, 0.63) were less likely to receive ICI than those diagnosed in 2015.

Multimorbidity was not significantly associated with ICI in fully adjusted models. In the fully adjusted model, sex, and race were not significantly associated with ICI use.

Table 1

Percent with immune checkpoint inhibitor (ICI) use by selected patient-level characteristics among older adults (age >65 years) with incident late-stage melanoma during 2012 and 2015.

Variables	ICI N (%)	No ICI N (%)	*P*-value
ALL	252 (5.6)	4,267 (94.4)	
Multimorbidity			
Yes	211 (5.5)	3,622 (94.5)	.620
No	41 (6.0)	645 (94.0)	
Year of diagnosis			
2012	35 (3.2)	1,060 (96.8)	.001***
2013	63 (5.8)	1,026 (94.2)	
2014	74 (6.4)	1,090 (93.6)	
2015	80 (6.8)	1,091 (93.2)	
Age			
66 to 69 years	62 (6.8)	851 (93.2)	<.001***
70 to 74 years	76 (7.6)	929 (92.4)	
75 to 79 years	45 (5.0)	860 (95.0)	
≥80 years	69 (4.1)	1,627 (95.9)	
Sex			
Female	72 (4.5)	1,545 (95.5)	.014*
Male	180 (6.2)	2,722 (93.8)	
Race			
Whites	239 (5.5)	4,103 (94.5)	.29
Non-Whites	13 (7.3)	164 (92.7)	
Marital Status			
Married	163 (7.3)	2,057 (92.7)	<.001***
Not married	89 (3.9)	2,210 (96.1)	
Dual Medicare/Medicaid eligibility			
Yes	17 (10.0)	153 (90.0)	.010*
No	235 (5.4)	4,114 (94.6)	
Regions			
Northeast	64 (7.9)	748 (92.1)	.019*
South	49 (5.1)	916 (94.9)	
North Central	24 (5.1)	451 (94.9)	
West	115 (5.1)	2,152 (94.9)	

Linked Surveillance, Epidemiology, and End Results and Medicare Claims Database.
Note: Based on 4,519 older adults with incident late-stage (Stage III/IV) melanoma continuously enrolled in Medicare Part A & B fee-for service programs 12 months prior to incident cancer diagnosis.
Significance: *.05< $P \leq$ .01; **.01 < $P \leq$.001; ***P< .001.

4. Discussion

The treatment landscape for late-stage melanoma remained unchanged for decades before the introduction of ICIs in 2011. The median overall survival with traditional treatments (chemotherapy and/or radiation) is 6 to 8 months.[21,22] Due to poor prognosis for survival, many patients may not receive treatment, as observed in this study. An overwhelming majority (82%) of the cohort did not receive any treatment for their late-stage melanoma. Post-late stage melanoma diagnosis treatment rates (18%) observed in this study is consistent with a published study (22%).[23] In this published study, the authors noted 22% initiated treatment after the disease progression while 51% started treatment before late-stage melanoma diganosis.[23]

Although ICIs have been around for nearly a decade, evidence on the treatment pattern in the real world is just emerging. Recent studies exploring the real-world treatment patterns among all adults for late-stage melanoma reported that only 34% to 37% of the patients received ICI as the first-line treatment, despite the recommendation by the NCCN guidelines.[24–26] The rates of treatment with ICI in our study is very low (6%). A plausible reason for the low rate can be due to the differences in population studied. Our study focused on older adults with 85% having pre-existing multimorbidity who may be at high risk for poor survival prognosis. As evidence is still emerging on the side effect profile of ICIs compared to existing modalities,[27] oncologists may be cautious in using ICI among older patients with late-stage melanoma.

This study observed that an overwhelming majority of patients had pre-existing multimorbidity, no different than other cancer types.[15,28] As RCTs of ICIs typically exclude patients with multimorbidity,[29] evidence on the association of multimorbidity to ICI use is not available. This is the first study to report the use of ICI among older patients with multimorbidity status. In this study, those with multimorbidity were as likely to receive ICI as those without, suggesting that multimorbidity was not a barrier in the receipt of ICI. While the rationale for this was not explored further, plausible reasons are discussed. Recent studies using SEER-Consumer Assessment of Healthcare Providers and Systems suggest that patients with multimorbidity and cancer have better communication with their providers and rated specialties better than those without multimorbidity.[30] It has also been reported that Medicare beneficiaries with multi-

Table 2

Unadjusted odds ratio (OR), adjusted odds ratios (AOR), and 95% confidence intervals (CI) from logistic regressions on immune checkpoint inhibitor use older adults (age >65 years) with incident late-stage melanoma during 2012 and 2015.

Variables	Unadjusted analysis			Fully Adjusted Analysis		
	OR	95%CI	Significance	AOR	95%CI	Significance
Multimorbidity						
Yes	0.82	[0.55, 1.22]		0.96	[0.67, 1.37]	
No	*(ref)*			*(ref)*		
Year of diagnosis						
2012	*(ref)*			*(ref)*		
2013	2.03	[1.30, 3.18]	**	1.82	[1.19, 2.78]	**
2014	1.98	[1.27, 3.09]	**	2.10	[1.39, 3.18]	***
2015	0.78	[0.45, 1.34]		2.38	[1.58, 3.59]	***
Age						
65 to 69 years	1.82	[1.19, 2.81]	**	1.63	[1.14, 2.34]	**
70 to 74 years	2.19	[1.46, 3.28]	***	1.79	[1.27, 2.52]	***
75 to 79 years	1.42	[0.90, 2.25]		1.18	[0.80, 1.74]	
≥80 years	*(ref)*			*(ref)*		
Sex						
Females	0.67	[0.48, 0.94]	*	0.78	[0.58, 1.04]	
Males	*(ref)*			*(ref)*		
Race						
Whites	*(ref)*			*(ref)*		
Non-whites	1.53	[0.79, 2.94]		1.17	[0.64, 2.15]	
Marital Status						
Married	1.99	[1.45, 2.73]	***	1.94	[1.48, 2.56]	***
Not married	*(ref)*			*(ref)*		
Dual Medicare/Medicaid eligibility						
Yes	1.99	[1.08, 3.66]	*	2.34	[1.35, 4.03]	**
No	*(ref)*			*(ref)*		
Region						
North central	0.65	[0.36, 1.17]		0.59	[0.36, 0.95]	*
West	0.72	[0.49, 1.06]		0.57	[0.42, 0.79]	***
South	0.64	[0.40, 1.02]		0.56	[0.38, 0.83]	**
Northeast	*(ref)*			*(ref)*		

Linked surveillance, epidemiology, and end results and medicare claims database.

Note: Based on 4,519 older adults with incident late-stage (Stage III/IV) melanoma continuously enrolled in Medicare Parts A and B fee-for-service programs 12 months prior to incident cancer diagnosis.

* $0.05< P \leq .01$.

** $0.01 < P \leq .001$.

*** $P<.001$.

Ref = reference group.

morbidity are equally likely to trust their doctors for their care,[31] suggesting that multimorbidity may not be a barrier to novel life-saving therapies.

This is the first study to the best of our knowledge that explored the factors associated with ICI use among older patients with late-stage melanoma. In this study, patients between the ages of 66 and 74 years were more likely to receive ICIs compared to patients 80 years and older. However, published studies did not find additional adverse events or difference in overall survival in patients between 80 to 100 years versus those between 65 to 79 years, when treated with ICIs.[10] Oncologists may exercise caution in active treatment of cancer among old-old (age > 80 years), because side effects can occur more often and in greater severity in this age group.[28,32,33] Furthermore, higher rates of pre-existing chronic conditions in this age group may also warrant cautious active cancer treatment. In our study, nearly 90% of those 80 years or older had pre-existing multimorbidity compared to only 82% among 65 to 79 years. Due to small cell sizes, we were unable to empirically test the interaction of old-old with multimorbidity on ICI use in our study.

Social support, measured with the proxy (i.e. marital status), was significantly associated with ICI use in this study. Presence of social support have shown lesser psychological distress among patients with cancer and more enthusiasm about getting treatment, even if the disease is terminal.[34,35] Therefore, these patients are more accepting of newer treatments. It is plausible that shared decision making with the patient and their caregivers/support system may increase the use of novel therapies in real-world settings.

Regional variations were also observed in our study, with older patients residing in Northeastern SEER regions having higher rates of ICI use. The reasons for differential adoption of newer treatments across the US regions is complex. Although to date, no study has examined regional disparities in ICI use among late-stage melanoma patients, few reasons for regional disparities based on evidence from the adoption of new medical treatments and new technologies are speculated here. The US states with higher population density may also have greater number of highly skilled professionals. In addition, these states tend to have policies that provide more opportunities to capitalize on innovations and are more likely to adopt innovations faster.[36,37] Based on these factors, states in the Northeastern region including New York, Connecticut, and Massachusetts, had the highest innovation scores compared to other US states.[36] In addition, key opinion leaders, who also lead many RCTs, play an

important role in the diffusion of innovation.[38] A study reported that such opinion leaders were based in urban areas, most of them in the Northeastern regions such as New York City and Boston.[38] These leaders encouraged use of innovative therapies in real-world settings.[38] Healthcare providers in various US regions should, therefore, evaluate the political influences in driving their prescribing practices and work with local opinion leaders in finding ways to improve adoption of newer therapies among patients.

In this study, dual Medicaid/Medicare eligibility was positively associated with ICI use. Previous studies have reported that dually eligible beneficiaries are less likely than Medicare-only beneficiaries to receive prostate or breast cancer treatment.[39] In a study of lung cancer patients, dual eligibility status was associated with longer duration of treatment.[40] Recent studies on late-stage melanoma reported that patients with Medicaid were less likely to receive ICIs and those with Medicare were as likely to receive ICIs as patients with commercial insurance.[41–43] Thus, the receipt of ICI may be driven more by Medicare than Medicaid.

Year of diagnosis was significantly associated with ICI use, with those diagnosed in earlier years being less likely to use ICIs. This may be because of few completed RCTs at the time and only 1 ICI (ipilimumab) approved for the treatment before 2014. Therefore, the data to support the safety and efficacy of ICI had not been widely been disseminated. In addition, the diffusion of innovation takes substantial time.[8] Rather than rely on communication of a medical innovation, most physicians adopted the innovation after watching their colleagues use them.[44] This is especially true when contemplating use in populations excluded in the RCTs,[44] such as older patients with multimorbidity. Although the use of ICI as first-line treatment in late-stage melanoma was added in NCCN guideline in 2012, studies on the use of ICI in real-world settings remain limited.

The findings of this study should be interpreted considering its limitations. First, the reasons for not receiving any treatment in older patients was unknown. Though disparities in ICI use were observed, we are unable to evaluate whether these disparities are due to patient preferences or shared decision-making of providers and patients. Such information could direct healthcare providers on measures that can be taken to enhance the adoption of ICIs. Second, individual-level socioeconomic factors, such as education and income, which may be associated with ICI use, were not available to us. Third, information on severity of co-existing illnesses may have provided insights into whether the intake is low because of competing demands that may confer high mortality risk and may have precluded the use of ICI. Despite these limitations, the study has several strengths. No study to-date has focused on treatment of older adults with multimorbidity and late-stage melanoma. With a high prevalence, oncologists are bound to encounter such patients on a daily basis. This study provides oncologists with strong evidence on the current treatment landscape among older adults with multimorbidity. In addition, this study examined the factors associated with ICI use. In the era of personalized medicines, patient-level factors play a critical role in treatment decisions. This study sheds light on various factors that will help healthcare providers in reaching a successful treatment goal with their older patients.

The findings from this study suggest that despite evidence of improved survival benefits over chemotherapy, the adoption of ICI among older patients remain low. This study revealed disparities in ICI use even after 5 years since ICI approval and introduction in the US markets. However, multimorbidity was not a barrier to ICI use suggesting that future research is needed on low uptake of ICI in older patients with multimorbidity.

Author contributions

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