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Multimorbidity, Immune Checkpoint Inhibitor Use, and Healthcare Expenditures among Older Patients with Late-stage Melanoma

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Multimorbidity, Immune Checkpoint Inhibitor Use, and Healthcare Expenditures among Older Patients with Late-stage Melanoma

Pragya Rai

Dissertation submitted
to the School of Pharmacy
at West Virginia University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in
Health Services and Outcomes Research

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Morgantown, West Virginia
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ABSTRACT

Multimorbidity, Immune Checkpoint Inhibitor Use, and Healthcare Expenditures among Older Patients with Late-stage Melanoma

Pragya Rai

With decades of unchanged cancer care with no added survival benefit, immune checkpoint inhibitors (ICI) changed the treatment landscape of late-stage melanoma in 2011. A key factor in determining the use of ICIs is the presence of pre-existing chronic conditions, which can influence the outcome. However, the prevalence of multimorbidity (defined as presence of two or more chronic conditions) among older patients with late-stage melanoma remains unknown. It also remains unknown if the presence of multimorbidity factors into the use of ICIs. Hospital-related factors associated with ICI use have been studied. Yet, patient-level factors, such as age, sex, marital status, which may play a more crucial role in the use of ICIs, remain unknown. Furthermore, ICI use may exacerbate healthcare expenditures for an already expensive condition, i.e., late-stage cancer. There are no studies exploring the effects of ICI on healthcare expenditures among the elderly. Therefore, this study had three main objectives (1) to examine the prevalence and type of pre-existing multimorbidity and the associated risk factors, (2) to assess the association of multimorbidity and other risk factors on ICI use, and (3) to assess the impact of ICI and multimorbidity on healthcare expenditures among older patients with late-stage melanoma. Retrospective cohort studies were conducted using Surveillance, Epidemiology, and End Results cancer registry linked with fee-for-service Medicare claims for older (>66 years) patients with a 12-month pre-index and 12-month post-index period. Index date was the date of incident stage III/stage IV melanoma diagnosis between 2011 and 2015. Logistic regression was used to examine the associations of multimorbidity or ICI use to various patient-level factors. Generalized linear mixed models with gamma distribution and log-link was used to analyze adjusted relationships between ICI/multimorbidity and healthcare expenditures. In the first aim, an overwhelming majority (85%) of older adults with late stage melanoma had pre-existing multimorbidity. The second aim concluded that only 6% of older adults with late-stage melanoma received ICI. Multimorbidity was not significantly associated with ICI use. Factors positively associated with ICI use were lower age, social support in the form of spouse, residence in the Northeastern regions, and had dual eligibility compared to their counterparts. This study concluded that patient-level factors may play a significant role in decisions towards treatment of late-stage melanoma with ICI, regardless of multimorbidity. The third study reported that the average total, outpatient, home health, and inpatient healthcare expenditures in the pre-index period were significantly ($p < 0.001$) lower than the expenditures in the post-index period. In addition, regardless of multimorbidity, the high expenditures in post-index period were influenced by the use of ICI. Therefore, ICI use was significantly associated with healthcare expenditures. In summary, multimorbidity is a growing concern for oncologists, especially among the elderly. The high prevalence of multimorbidity among elderly in our study points to the fact that multimorbidity should be factored into cancer care. Since multimorbidity is not included in cancer care guidelines, it does not play a role in receipt of ICI among older patients. However, the use of ICI significantly increases healthcare expenditures. To reduce costs, newer payment models that focus on value are being developed and tested. Future studies need to examine whether such models can achieve the triple aims of “better health, better value, and lower costs.”

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LIST OF ABBREVIATIONS

ACS	American Community Survey
AD	Autoimmune diseases
AHRF	Area Health Resource File
AOR	Adjusted odds ratio
CI	Confidence interval
CMS	Centers for Medicaid and Medicare Services
CVD	Cardiovascular diseases
GLM	Generalized linear models
GLMM	Generalized linear mixed models
HCPCS	Healthcare common procedure coding system
ICD	International Classification of Diseases
ICI	Immune checkpoint inhibitors
irAE	Immune-related adverse events
MHC	Mental health conditions
NCCN	National Cancer Comprehensive Network
OCM	Oncology Care Model
OR	Odds ratio
PHC	Physical health conditions
RCT	Randomized clinical trials
SEER	Surveillance, Epidemiology, and End Results
US	United States

CHAPTER 1

1. BACKGROUND AND SIGNIFICANCE

1.1. Introduction

Melanoma Prevalence and Incidence

Melanoma is a type of skin cancer which arises from uncontrollable proliferation of melanocytes.¹ Historically a rare cancer, its incidence has risen faster than any other cancer.¹ This rise in incidence has been primarily attributed to tanning beds, though other risk factors such as sun exposure and other environmental factors cannot be ruled out.^{1,2} The incidence rose from 1 in 1,500 in 1935 to 1 in 30 in 2015.³ In 2020, approximately 100,000 Americans will be diagnosed with melanoma.^{4,5} This rise in incidence has made melanoma the fifth most common cancer in the United States (US).⁵ If caught early, prognosis of melanoma is favorable.^{3,6} However, once melanoma has metastasized, treatment becomes difficult with a grim long-term prognosis; median overall survival rates range from 6 to 8 months.^{7,8} Further, the 1- and 2-year survival rates for patients with metastatic melanoma were 23% and 9% respectively.⁹

Melanoma in the elderly

Globally, the greatest burden of melanoma falls on residents of Australia, Europe, New Zealand, the elderly and male population.¹⁰ The incidence in the older population continues to rise in the US while the incidence in younger population appears to be leveling off.¹¹ Nearly 50% of all melanoma deaths in the US occur in white men older than 50 years.¹¹ One of the reasons for higher death rates among the older population (>65 years) is immunosenescence, which means as we age, our immune system declines.¹¹ Therefore, older patients have reduced capacity to fight infections and malignancy. Another reason for the high mortality rate among the elderly is that several poor prognostic factors, including non-superficial spreading histology,

higher Clark invasion level, lower Breslow thickness, and presence of ulceration, were significantly observed in the elderly.

In addition, as patients age, the factors of primary melanoma become more advanced and melanoma is more likely to develop poorer histological features.¹² Therefore, older patients are more likely to be diagnosed with late-stage (Stage III/IV) melanoma.¹² A study noted that older patients had higher primary tumor stage, higher Breslow thickness, ulceration, and poorer survival compared to younger (18-64 years) patients.¹² Therefore, this dissertation will focus on older patients with late-stage melanoma.

Treatment of late-stage melanoma

Once melanoma has been diagnosed, there are multiple options for treatment. Prior to 2011, management of metastatic melanoma included single-agents (alkylating agents, microtubule disrupting agents, platinum analogs, and nitrosoureas), as well as combination chemotherapy along with surgery and radiation therapy.^{13,14} However, these therapies did not significantly improve survival and were often associated with high toxicity.¹⁴⁻¹⁶ This led to the advent of immune checkpoint inhibitors (ICI; including ipilimumab, nivolumab, and pembrolizumab) since 2011, which have significantly improved survival with less toxic side effects.^{17,18} A departure from chemotherapy, ICIs work by energizing the immune system of the body to fight off the cancer cells.^{17,18} Recent data of 5.3 years median follow-up for ipilimumab, an anti-CTLA-4 agent, yielded significantly better distant metastasis free survival compared to standard chemotherapy, with no additional toxicities reported since the initial report at 2.3 years.^{19,20} Even superior overall survival, progression free survival, objective response rates, and better safety profile were observed with anti-PD-1/PD-L1 agents (nivolumab and pembrolizumab).²⁰⁻²² This led many researchers to explore the efficacy of combination ICI.

Early data from ongoing randomized clinical trials (RCTs) have shown durable response with combination ipilimumab and nivolumab.²³ Such promising results from RCTs led to the integration of ICI (monotherapy or combination) as the first-line treatment for metastatic melanoma.^{24,25}

Multimorbidity

People often live with two or more chronic conditions. Aging population and increase in life expectancy means that the number of people living with increasing number of chronic conditions will continue to rise.²⁶ This “multimorbidity” or the coexistence of two or more chronic conditions in the same individual will have an impact on their safety in primary and specialty care. The safety concerns arise due to multiple reasons, including²⁶

- polypharmacy, which may lead to poor medication adherence and adverse drug events,
- complex management regimens,
- more frequent and complex interactions with health care services leading to greater susceptibility to failures of care delivery and coordination,
- the need for clear communication and patient-centered care due to complex patient needs,
- demanding self-management regimens and competing priorities, and
- more vulnerability to safety issues due to poor health, advanced age, cognitive impairment, limited health literacy, and comorbid depression or anxiety.

Therefore, recent years has seen an increase in research on multimorbidity to alleviate the safety concerns for such individuals.

Multimorbidity in the elderly

Studies have shown that prevalence of multimorbidity is on the rise worldwide. A study conducted in one developed country reported that almost 25% of the entire population has multimorbidities.²⁶ Recent literature has shown high levels of multimorbidity in low- and middle-income countries.²⁶ Similar trend has also been observed in high-income countries. For example, in Sweden, the prevalence of multimorbidity was 56.3% among adults aged 35 to 75 years.²⁷ In the United States (US), one in four adults were reported to have multimorbidity, with 68% of the elderly individuals having two or more chronic conditions and 36% having four or more chronic conditions.²⁸ Another study reported similar findings among Medicare beneficiaries: 62% aged 65 to 74 years, 75.7% aged 75 to 84 years, and 81.5% aged 85 years and above had multimorbidity.²⁹ In addition, female Medicare beneficiaries had higher prevalence of multimorbidity compared to males.²⁹

Such high prevalence has serious consequences on health outcomes of the elderly. Studies have shown that multimorbidity is associated with an increased risk of death, disability, poor functional status, poor quality of life, adverse drug events, and other adverse outcomes.^{29–31} Despite efforts to reduce multimorbidity among the elderly, the condition remains rampant. Therefore, studies as this are needed to provide information on the impact of multimorbidity on newly diagnosed conditions, such as cancer.

Late-stage melanoma and multimorbidity

Prevalence of multimorbidity among older patients with late-stage melanoma

The prognosis, treatment, and health outcomes (including survival) of patients with late-stage melanoma depends on a number of factors, including age, tumor characteristics, and presence or absence of comorbidities.^{29,32} The presence of comorbidities influence cancer

detection, treatment, and progression of cancer. This in turn can affect the prognosis and long-term survival of the patients. Patients with comorbidities are at higher risk of complications and lower performance status, may have decreased quality of life, and may face more life-threatening conditions. Despite the importance of considering comorbidities in treatment and prognosis of melanoma, the prevalence of comorbidities has received little attention.

There are few studies on the impact of comorbidities of melanoma stage of diagnosis, treatment, and health outcomes. These studies reported that the prevalence of chronic conditions varies from 19% to 80% among adult patients with malignant melanoma.^{25,33–36} These studies did not focus on late-stage melanoma because of poor survival among those patients. However, the advent of ICIs may result in an increase in late-stage melanoma survivors. Therefore, identifying prevalent conditions in patients with late-stage melanoma will allow healthcare professionals to tailor their long-term care for each individual.

Moreover, the studies do not usually include mental health conditions. Literature also suggests that those with mental health conditions may have barriers to cancer care.³⁷ However, most studies on patients with cancer have focused only on anxiety and depression; the presence of other mental health conditions, such as dementia, can also lead to less-aggressive cancer treatment because of compromised informed consent and adverse effects.^{38–41} Therefore, estimating the prevalence of any type of multimorbidity can be useful to the providers as well as patients.

In addition, one of the conditions worrisome for oncologists is autoimmune disease. This is because ICI therapy can induce autoimmune side effects affecting almost any organ system, specifically aberrant activation of immune cells against self-antigens, referred to as “immune-related adverse events (irAE)”.⁴² Patients with pre-existing autoimmune diseases may be at a

greater risk for developing irAEs.⁴³ Therefore, these patients were largely excluded from RCTs of ICI. However, a recent study reported that the prevalence of autoimmune diseases has been increasing from 17.1% in 2004 to 28.3% in 2014.³⁶ Although autoimmune diseases are more frequent in the older patients, occurrence of autoimmune disease multimorbidity remains unknown. *Therefore, a study which included a comprehensive list of mental health conditions and autoimmune diseases is necessary because studies often include only limited mental health conditions and no autoimmune diseases. In addition, examining factors (i.e., risk profile) other than age that may be associated with multimorbidity can help in assessing disease burden, surveillance, treatment decisions, and survivorship plans of patients with late-stage melanoma, justifying rationale for Aim 1.*

Factors associated with ICI use among older patients with late-stage melanoma

Since the approval of ICI in 2011, literature on the improved survival associated with ICIs have increased exponentially. It stands to reason that the use of ICI in real-world setting may be commonplace. However, that is not the case; adoption of ICIs has been slow. We speculate few reasons for this slower diffusion of innovation. First, with their strict inclusion and exclusion criteria, RCTs of ICIs did not provide robust evidence on the use and impact of ICI among the elderly. Additionally, multimorbidity is prevalent among the older patients. Layering the management of melanoma onto the management of a patient with multimorbidity further compounds the complexity of care. The interplay between treatment approaches used for melanoma care and those used for multimorbidity can be complicated. In patients with pre-existing multimorbidity, a new diagnosis of cancer adds a new dynamic, with the primary care physicians and other specialists shifting into supportive roles, to deliver non-cancer care in the

context of cancer treatment.^{44,45} With lack of evidence from RCTs, decision-making on choosing ICI treatment for care may become difficult.

In addition, certain patient-level factors may be considered as a source of slower adoption of newer therapies. 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.⁴⁶ Patients below the age of 80 years and White non-Hispanics were more likely to receive treatment than those above 80 years of age and other race/ethnicity.⁴⁶ 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.⁴⁷ Financial aspects potentially affecting the care setting for late-stage melanoma patients may also be a potential reason.⁴⁸ Insured patients are more likely to receive ICIs compared to uninsured or underinsured patients.⁴⁹ *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, thus justifying rationale for Aim 2.*

Healthcare expenditure associated with ICI among older patients with multimorbidity and late-stage melanoma

The economic burden associated with cancer is substantial. There is robust evidence that cancer increases healthcare expenditures. The costs differ by type and stage of cancer. Therefore, although the cost of malignant melanoma is the lowest compared to other cancers, metastasis of melanoma significantly increases healthcare expenditures.^{50–52} In fact, 55% of the annual direct cost for treating melanoma arose from late-stage melanoma and one-third of the total cost was related to the end-of life melanoma treatment.⁵³ The annual treatment costs ranged

from \$44.9 million among Medicare patients with existing melanoma to \$932.5 million among newly diagnosed cases across all groups.⁵⁴ Among Medicare beneficiaries, the average per-patient melanoma charges were \$2,194 during the initial four months of treatment and increased to \$3,933 during the terminal six months of treatment in 2010.⁵⁵

Such costs are bound to increase with time due to inflation. However, recent years has seen a substantial increase in cancer-related healthcare costs. The high healthcare expenditures for late-stage melanoma may be driven by many factors such as high cost of ICIs, the associated administration costs for these drugs, and supporting care (monitoring and testing).⁵⁶ One of the concerns are the high costs of ICIs. According to Dr. Leonard Saltz, the costs of newer therapies “*approximately 4,000 times the cost of gold*”.⁵⁷ He calculated that the cost for a typical patient receiving the CheckMate067 combination (ipilimumab and nivolumab) would have been \$295,566.⁵⁷ With a 20% co-pay, the out-of-pocket cost to the patients would have totaled \$60,000. In addition, serum biomarker testing and enzyme level monitoring are common before and during treatment of late-stage melanoma.⁵⁸ These functions also factor into the cost of melanoma care. Therefore, this amounted to \$174 billion for treating late-stage melanoma for one year only.⁵⁷

Further, the presence of multimorbidity may further exacerbate the costs. Healthcare resource utilization is high among patients with multimorbidity, with frequent visits to specialists and higher hospitalization rates. Therefore, there was a positive associated between multimorbidity and healthcare costs, with an average increase of \$1,774 in total costs for each body system affected by chronic conditions.⁵⁹ It is reasonable that older adults with multimorbidity treated with ICIs will therefore incur the highest healthcare expenditures.

It should be kept in mind that almost no patients pay for their treatments. Rather, the society collectively pay the price for the expensive therapies. When an individual gets a treatment, others pay through insurance premiums and/or taxes that support Medicare, Medicaid, or other government programs. Therefore, when medical costs increase, so do the insurance premiums. These rising premiums may in turn harm the very people who need it the most, by reducing their access to care because they may be unable to purchase coverage. *Examining the healthcare expenditures and the reason behind the increase will allow various stakeholders- healthcare professionals, payers, organization- to identify and condemn practices with unreasonable costs, thus justifying the rationale for Aim 3.*

1.2. Innovation

a) Comprehensive evaluation of chronic conditions among older patients with late-stage melanoma: This is the first study to include a comprehensive list of physical and mental health conditions when evaluating the prevalence of multimorbidity. In addition, the updated list includes the autoimmune diseases based on the current challenges with ICI use.

b) Novel factors of ICI adoption: Studies have evaluated the role of healthcare practices in adopting ICIs. However, patient-level factors have not been evaluated. As shared decision-making is common practice, patient-level factors that influence the adoption of newer therapies might provide oncologists with leads to make headway on improving uptake of ICIs.

c) Fill a significant knowledge gap in literature: Given that no studies have examined multimorbidity among older patients with late-stage melanoma, the proposed study will fill an important knowledge gap in the literature by identifying the prevalence of various chronic conditions in such patients.

1.3. Specific Aims

Aim 1.1: Estimate the prevalence and type of multimorbidity prior to the diagnosis of late-stage melanoma

Aim 1.2: Evaluate the association of patient-level factors to multimorbidity in older patients with late-stage melanoma

Hypothesis 1.2: In the fully adjusted model which will include all the independent variables, age will be significantly associated with multimorbidity among older patients with late-stage melanoma.

Aim 2: Examine the association of multimorbidity and other factors to ICI use that cover years from the initial introduction in 2011 to 2015 among older patients with late-stage melanoma

Hypothesis 2: In the fully adjusted model, year of diagnosis, age, marital status, dual eligibility, and region of residence will be significantly associated with ICI use among older patients with late-stage melanoma.

Aim 3.1: Estimate the impact of ICI use on healthcare expenditures during pre- and post-late-stage melanoma diagnosis periods among older patients with late-stage melanoma

Hypothesis 3.1: ICI use will be associated with high expenditures throughout the treatment period compared to those without ICI use.

Aim 3.2: Estimate the impact of ICI-multimorbidity interaction on healthcare expenditures during pre- and post-late-stage melanoma diagnosis periods among older patients with late-stage melanoma

Hypothesis 3.2: Patients who used ICI and had multimorbidity will have higher expenditures throughout the treatment period compared to ICI non-users and those without multimorbidity.

1.4. Approach

Conceptual Frameworks Used to Guide the Selection of Variables

A conceptual framework was created by adapting determinants of health outcomes and chronic disease model and Andersen's healthcare utilization model.^{60,61} According to these

models, outcomes such as presence of multimorbidity, receipt of novel therapies (ICI), and consequently healthcare expenditures are based on the presence or absence of multiple

factors. These factors included biological factors, social factors, community resources, socio-economic status, and year of diagnosis. Biological factors consisted of age (66-69, 70-74, 75-79, 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 Northcentral). Dual Medicare/Medicaid enrollment (yes/no) was a proxy for low economic status. Years of incident melanoma diagnosis (2012-2015) was used to control for changes in

practice patterns. Aim 3 also included healthcare utilization (visits to primary care physician and oncologists).

Data sources

Data from multiple sources were used to accomplish the study aims.

Surveillance, Epidemiology, and End Results (SEER): SEER is a cancer registry and provides data on clinical variables related to cancer. SEER data consists of various files, which contain information on patients and cancers. Patient Entitlement and Diagnosis Summary File provides information for each person's date of birth, sex, race, and state of residence. This file also includes information on Medicare eligibility, reason for Medicare entitlement, and health maintenance organization (HMO) enrollment by month. In addition, these files also contain geographically-based (ZIP code and census tract level) socioeconomic information. The file contains exhaustive information on cancer, such as diagnosis date, cancer stage, tumor size, number of positive lymph nodes, and tumor histology.

SEER-Medicare Claims: Medicare Enrollment File: Medicare is the federally funded program that provides health insurance to the elderly, persons with end-stage renal disease, and some disabled. For persons aged 65 and over, nearly 90% are Medicare eligible. Medicare claims provides information on Part A coverage (hospital, skilled nursing facility, hospice and some home healthcare), Part B coverage (physician and outpatient services), Part C (HMO enrollment, most of whom have fee-for-service coverage), and Part D (prescription drug) coverage. Medicare claims database is the best source of information to estimate Medicare payments among the elderly for cancer and other disease states. To link SEER with Medicare data, identifiers contained in the Medicare's master enrollment file is matched with individual identifiers for all persons in their files.

American Community Survey (ACS) Census Tract Files: The ACS census tract and census zip code files were linked to PEDSF files by geographic codes, such as, state and county. These files provided information on the census tract median household income and education level.

Area Health Resource File (AHRF): The AHRF is a publicly available data file provided by Department of Health and Human Services and contains county, state and national files. The AHRF provides more than 6,000 variables for each of the nation's counties. The AHRF contains information such as health facilities, health professions, and socioeconomic and environmental characteristics. The basic file contains geographic codes and descriptors that may be used to link it to other files and to aggregate counties into various geographic groupings. This study used the AHRF variables to measure health care infrastructure that can influence the detection of multimorbidity, ICI use and expenditures.

CHAPTER 2

2. PREVALENCE AND RISK FACTORS FOR MULTIMORBIDITY IN ELDERLY US PATIENTS WITH LATE-STAGE MELANOMA

2.1. Abstract

Introduction: Presence of multimorbidity can affect prognosis, treatment, and outcomes of individuals with cancer. However, the prevalence and factors associated with multimorbidity among older late-stage melanoma is not well studied. We estimated the prevalence of any type of pre-existing multimorbidity (autoimmune disorder (AD), physical health conditions (PHC), and mental health conditions (MHC)) among older adults with late-stage melanoma in the United States. We further examined the association of patient-level factors to multimorbidity in late-stage melanoma.

Methods: We derived data on older fee-for-service Medicare beneficiaries (age ≥ 66 years) diagnosed with late-stage melanoma between 2011 and 2015 ($N = 4,519$) from the linked Surveillance, Epidemiology, and End Results cancer registry and Medicare claims. We defined multimorbidity as the prevalence of two or more chronic conditions prior to the diagnosis of melanoma. We used unadjusted and adjusted logistic regressions to examine the association of patient-level factors to multimorbidity.

Results: An overwhelming majority (85%) of older patients with late-stage melanoma had multimorbidity. Pre-existing PHC multimorbidity (84%) was the most prevalent, followed by AD (12%), and MHC (6%). Age and region were associated with any and PHC multimorbidity. Sex, marital status, and region were factors associated with pre-existing AD while sex, marital status, and dual eligibility were associated with MHC multimorbidity.

Conclusions: Pre-existing multimorbidity was highly prevalent among older individuals with late-stage melanoma; prevalence rates and factors associated with multimorbidity varied by type of chronic conditions. This highlights the need for developing systematic approaches to optimizing care of older patients with late-stage melanoma and multimorbidity.

2.2. Introduction

Melanoma is a form of skin cancer with an alarmingly-rising incidence in the United States (US), making it the fifth most common cancer, with the highest occurrence among the elderly (≥ 65 years).^{2,62,63} Although melanoma accounts for 2% of all skin cancers, late-stage melanoma is the most lethal, accounting for 90% of deaths.² A key factor for treatment of patients with melanoma is having a pre-existing chronic condition. Pre-existing chronic conditions are highly prevalent in all cancers and have been shown to affect cancer stage at diagnosis, treatment, and outcomes; melanoma being no exception.^{32,64} The prevalence of chronic conditions in patients with melanoma varies from 19% to 80%.^{33,34} The presence of additional chronic conditions prevents physicians from aggressively treating melanoma, thereby increasing the risk of mortality.^{33,34}

As patients age, the number of chronic conditions increases.²⁹ Some studies focused on the presence of multimorbidity, defined as the presence of two or more chronic conditions, among patients with breast, bladder, and colorectal cancers.^{65–68} These studies also documented high prevalence of multimorbidity and associated adverse outcomes. However, to date no study has exclusively examined multimorbidity in patients with late-stage melanoma perhaps due to the poor survival of these patients. Studies of multimorbidity among late-stage melanoma patients are important and needed for reasons stated below.

Immune checkpoint inhibitors (ICI) have changed the treatment landscape of late-stage melanoma, with significant improvements in survival.^{6,69} However, pre-existing multimorbidity may compete with cancer care because cancer treatment needs to focus not only on mortality but also treatment complications and quality of life.⁷⁰ For example, ICIs affect the immune system.¹⁸ Patients with pre-existing autoimmune diseases (AD) have weaker immune systems, and this may deter their treatment with ICI, due to fears of higher mortality and worse quality of life post-treatment.^{42,71} As ICIs are often used in cancer patients with pre-existing AD seeking care in the real-world settings,^{42,43,72} it is critical to assess the prevalence of pre-existing AD in the elderly. Furthermore, literature also suggests that those with mental health conditions (MHCs) may have barriers to cancer care.³⁷ However, most studies on patients with cancer have focused only on anxiety and depression; the presence of other MHCs, such as dementia, can also lead to less-aggressive cancer treatment because of compromised informed consent and adverse effects.³⁸⁻⁴¹ Therefore, estimating the prevalence of any type of multimorbidity can be useful to the providers as well as patients. Including a comprehensive list of MHCs and ADs is necessary because studies often include only limited MHCs and no ADs. In addition, examining factors (i.e. risk profile) other than age that may be associated with multimorbidity can help in assessing disease burden, surveillance, treatment decisions, and survivorship plans of patients with late-stage melanoma.

Therefore, the objectives of the current study are to estimate the prevalence and type of multimorbidity prior to the diagnosis of late-stage melanoma and assess the association of patient-level factors to multimorbidity in older patients with late-stage melanoma.

2.3. Methods

Study Design

We adopted a retrospective cohort design. The cohort consisted of older adults with incident late-stage (stage III/IV) melanoma diagnosis based on the American Joint Committee on Cancer 7th Edition. Index date was defined as the date of incident late-stage melanoma diagnosis. Pre-index period was defined as 12 months before incident melanoma diagnosis. Multimorbidity, type of multimorbidity, and all independent variables were assessed during the pre-index period. The study was exempted by West Virginia University Institutional Review Board.

Data Source

Surveillance, Epidemiology, and End Results (SEER) cancer registry and Medicare claims files were used. The SEER data provided information on clinical variables related to cancer (example: stage of cancer at diagnosis); Medicare claims provided information on healthcare encounters of the beneficiaries when enrolled and using Medicare covered health services.

Study Population

We identified 41,848 individuals with incident melanoma diagnosis between 2011 and 2015 using ICD-O-3 site (C44.0 - C44.9) and histology (8720 – 8790) codes. Following the exclusion of those with local or regional (stage I/II) melanoma, non-incident melanoma, below the age of 66 years, not continuously enrolled in Medicare part A and Part B during the pre-index period, and diagnosed with late-stage cancer during autopsy, the final analytical cohort comprised 4,519 individuals with late-stage melanoma.

Measures

Dependent variables: Any, PHC, MHC, and AD multimorbidity

Multimorbidity was defined as the presence of ≥ 2 chronic conditions prior to the diagnosis of incident late-stage melanoma. We used the list of chronic conditions developed by the Multiple Chronic Conditions working group within the US Department of Health and Human Services Office of Assistant Secretary of Health.⁷³ The list was developed based on the conditions that met the definition of chronicity, are prevalent, and are potentially amenable to public health. Based on the current challenges with ICIs, pre-existing AD was added, which were identified from a list of 131 conditions provided by the American Autoimmune-Related Disease Association (Appendix 7.1).⁷⁴ All these conditions were identified with International Classification of Diseases (ICD), 9th Edition.

Physical Health Conditions (PHC) consisted of pre-existing AD, arthritis, asthma, coronary artery disease, cardiac arrhythmias, diabetes, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), hepatitis, hyperlipidemia, hypertension, human immunodeficiency virus, obesity, osteoporosis, and stroke.

To explore the PHC most prevalent among those with multimorbidity, we created a taxonomy of PHC. The groups were: cardiovascular diseases (CVD - coronary artery disease, cardiac arrhythmias, congestive heart failure, and hypertension), endocrine diseases (diabetes, hyperlipidemia, and obesity), musculoskeletal diseases (arthritis, osteoporosis, and pre-existing AD), and respiratory diseases (asthma and COPD).

Mental health conditions (MHC) consisted of anxiety, bipolar disorder, depression, psychoses, schizophrenia, and substance abuse.

We also added PHC groups (CVD, endocrine, musculoskeletal, and respiratory diseases) and MHCs to explore any multimorbidity using combinations of dyads (e.g. CVD /endocrine diseases, MHC/respiratory diseases) and triads (e.g. CVD/endocrine diseases/MHC).

Indices of pre-existing conditions for each of the categories (PHC, MHC, and AD) were also created. These were derived by counting the number of conditions in each of the groups; PHC index ranged from 0-13, MHC index from 0-5, and AD index from 0-6.

Independent variables

These were identified at the pre-index period and included biological and social factors, community resources, socio-economic status, and year of diagnosis. Biological factors consisted of age (66-69, 70-74, 75-79, 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 Northcentral). 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.

Statistics

Chi-square tests were used to identify significant unadjusted associations of individual characteristics to multimorbidity. Multivariable logistic regressions were performed to determine the factors associated with multimorbidity. Parameter estimates are presented as adjusted odds ratios (AORs) after adjusting for all independent variables, with their corresponding 95% confidence intervals (CI); $p \leq 0.05$ was considered statistically significant. All analyses were conducted using SAS 9.4 (SAS Institute Inc.).

2.4. Results

The study population was predominantly male (64.2%), White (96.1%) and ≥ 70 years (70.4%). The mean number of chronic conditions (including PHCs, MHCs and ADs) was 4.26 with median of 4.0. The mean number of PHCs was 3.98 with median of 4.0. The prevalence of any PHC was 92.3%; MHC was 20.8% and AD was 28.7%. The most prevalent pre-existing condition was CVD (78%) followed by endocrine diseases (72%).

Multimorbidity patterns

Multimorbidity was highly prevalent (85%) in the US elderly with late-stage melanoma. The prevalence of multimorbidity varied by type of chronic conditions: 84% had PHC multimorbidity, 12% had AD multimorbidity, and 6% had MHC multimorbidity.

Among those with any multimorbidity, the most prevalent dyad combination was endocrine and musculoskeletal diseases combination (21.7%) followed by CVD and endocrine disease combination (20.3%). Among triads, CVD, endocrine, and musculoskeletal disease combination (22.6%) was the most prevalent followed by endocrine, MHC, and musculoskeletal disease combination (7%).

Factors associated with any multimorbidity

In unadjusted analyses, characteristics of individuals with and without multimorbidity differed by age and region (Table 2.1). A significantly higher proportion of Medicare beneficiaries aged ≥ 80 years had multimorbidity compared to those in the age group 65-69 years (89.4% versus 77.1%, $p < .0001$). Multivariable logistic regression on any multimorbidity showed similar results (Table 2.1). Older adults in the age group 70-74 years (AOR, 1.41; 95%CI, 1.12, 1.76), 75-79 years (AOR, 1.84; 95%CI, 1.44, 2.35) and ≥ 80 years (AOR, 2.55; 95%CI, 2.04, 3.18) were more likely to have pre-existing multimorbidity compared to those in

the age group 65-69 years. Older adults residing in the Northcentral (AOR, 0.69; 95%CI, 0.49, 0.96) and Western (AOR, 0.65; 95%CI, 0.51, 0.83) SEER regions were less likely to have any multimorbidity compared to residents in the Northeastern parts.

Factors associated with PHC multimorbidity

In unadjusted analyses, characteristics of individuals with and without PHC multimorbidity differed by age and region (Table 2.2). Individuals with PHC multimorbidity had significantly higher proportion of those aged ≥ 70 years and residing in Northeastern regions compared to those without PHC multimorbidity. Multivariable logistic regression on PHC multimorbidity showed similar results (Table 2.3). Older adults in the age group 70-74 years (AOR, 1.42; 95%CI, 1.13, 1.77), 75-79 years (AOR, 1.81; 95%CI, 1.42, 2.30) and ≥ 80 years (AOR, 2.47; 95%CI, 1.99, 3.06) were more likely to have pre-existing multimorbidity compared to those in the age group 65-69 years. Older adults residing in the Northcentral (AOR, 0.65; 95%CI, 0.47, 0.90) and Western (AOR, 0.67; 95%CI, 0.53, 0.85) SEER regions of the US were less likely to have PHC multimorbidity compared to residents in the Northeastern region.

Factors associated with AD multimorbidity

In unadjusted analyses, characteristics of individuals with and without AD multimorbidity differed by sex and region (Table 2.2). A significantly higher proportion of females and residing in Northcentral SEER regions compared had AD multimorbidity compared to men and those residing in Northeastern regions. Multivariable logistic regression on AD multimorbidity (Table 2.3) confirmed unadjusted associations; females (AOR, 1.81; 95%CI, 1.48, 2.22) were nearly two times as likely to have AD multimorbidity compared to older males. Unmarried older adults (AOR, 0.79; 95%CI, 0.65, 0.97) and those residing in southern SEER

regions (AOR, 0.58; 95%CI, 0.42, 0.80) were less likely to have AD multimorbidity compared to married elderly and residents in the Northeastern regions.

Factors associated with MHC multimorbidity

In unadjusted analyses, characteristics of individuals with and without MHC multimorbidity differed by sex, marital status, and dual eligibility (Table 2.2). Elderly with MHC multimorbidity had significantly higher proportion of females, unmarried, and lower income status. Multivariable logistic regression on MHC multimorbidity showed similar results (Table 2.3). Older females (AOR, 1.88; 95%CI, 1.46, 2.44) and those not married (AOR, 1.85; 95%CI, 1.41, 2.44) were more likely to have MHC multimorbidity compared to older males and those married. Older adults with lower income status (AOR, 3.33; 95%CI, 2.14, 5.19) were three times more likely to have MHC multimorbidity compared to those with higher income status.

2.5. Discussion

There is sparse information on prevalence of multimorbidity among individuals with melanoma, with no studies focusing on the elderly with late-stage melanoma. This is the first study to explore the prevalence and factors associated with the presence and type of multimorbidity among older adults with late-stage melanoma in the US. We found that 4 in 5 older adults with late-stage melanoma had pre-existing multimorbidity. Our estimates are higher than those found in non-US studies. For example, a Danish study reported multimorbidity in 9% of patients with melanoma.³³ This study included adults (>18 years) and all stages of melanoma. In contrast, a German study reported multimorbidity in 57% of patients with melanoma. The difference in estimated prevalence rates among these studies may be due to the differences in the study population (all stages as opposed to late-stage and older adults as opposed to adults 18 years or older) and time-period (pre-existing versus co-existing conditions).

The most common comorbid conditions in our study were CVD, endocrine, and musculoskeletal diseases or a combination of the three in dyads and triads. This is not surprising given that CVD, endocrine, and musculoskeletal diseases are highly prevalent in older adults.^{75,76} These diseases and cancer share modifiable risk factors, with some studies stating a bidirectional relationship between them.⁷⁷⁻⁷⁹ As heart disease, diabetes, and malignant cancers are among the top five leading causes of age-adjusted mortality,⁸⁰ healthcare providers managing patients with late-stage melanoma may need to routinely monitor for the presence of these conditions and coordinate their care with the primary care physicians.

Among risk factors for any multimorbidity, age is well-established, with studies reporting that the number of chronic conditions increases with age,^{29,33} a trend noted in our study as well. Increasing number of chronic conditions led to late-stage cancer detection, as both the patient and the physician were distracted by the pre-existing conditions.⁸¹ Adding increasing age to the mix resulted in less aggressive treatment and a dismal chance of entering a clinical trial, as physicians had to grapple with physical frailty and polypharmacy as well in these patients.^{33,81} Therefore, oncologists should optimize the treatment of aging patients with multimorbidity to improve their outcomes.

Regions, namely Northcentral and Western SEER regions, were associated with lower odds of having multimorbidity. There are no exhaustive studies on SEER geographical disparities in late-stage melanoma cancer patients, and further research is needed to explain these results.

Our study also examined type of multimorbidity in terms of PHC, AD, and MHC. Risk factors for PHC multimorbidity were similar to any multimorbidity, perhaps because PHC was more prevalent than MHC, making up the bulk of multimorbidity index. Among the PHC, we

further explored the prevalence of pre-existing AD among older patients. In 2014, the prevalence of pre-existing AD among individuals with metastatic melanoma was 20%.^{36,82} Our study echoed those findings among the elderly as well. Similar to a previous study on patients with metastatic melanoma and AD, our study also notes sex and region as a risk factor for AD multimorbidity.³⁶ In addition, this study also notes the presence of social support in the form of spouses as a risk factor for AD multimorbidity. Spouses are an important source of social support for patients with any chronic condition.⁸³ Therefore, patients with multiple AD are more dependent on that social support to manage their conditions.⁸³ Oncologists should consider these risk factors when deciding if a drug acting via the immune system is the best course of treatment for older patients.

Consistent with other studies, we observed 30% of older adults with late-stage melanoma were diagnosed with any MHC.^{84,85} Similar levels of MHC were also found in individuals with late-stage breast,³⁸ colorectal,³⁹ and prostate cancer.⁴⁰ Sex as a risk factor was also observed with MHC multimorbidity, perhaps because MHC are more prevalent in females compared to males.^{86,87} In addition, lack of social support was a risk factor for MHC multimorbidity. Social deprivation is a known risk factor for MHC among patients with cancer.^{88,89} We also observed that dual eligibility was a risk factor for having MHC multimorbidity. Individuals with melanoma having Medicaid had worse prognosis compared to uninsured and non-Medicaid individuals, pointing to the importance of socioeconomic status in melanoma care.⁹⁰ These risk factors should be assessed in order to reduce further psychological distress and devise appropriate follow-up interventions.

2.6. Strengths and limitations

The present study has several limitations. First, SEER does not contain information on individual behavior such as smoking status, alcohol consumption, or functional status, all of which can further affect the risk of having multimorbidity. Second, we did not have access to individual-level socioeconomic factors, such as education and income. Third, we could not determine the severity of the conditions. Despite these limitations, this study has several strengths. Although few studies on comorbid conditions in individuals with melanoma exist, they did not focus on late-stage melanoma, perhaps because the prognosis was poor with low chances of survival.⁹¹ Therefore, prognostic burden of multimorbidity in such individuals was deemed less important.⁹¹ However, newer therapies such as ICIs will improve survivorship of patients with late-stage melanoma. Therefore, information on the prevalence and type of multimorbidity in such individuals can help both physicians and patients in choice of cancer treatment, survivorship plans, and quality of life care. We included an exhaustive list of PHC and MHC, including pre-existing AD.

2.7. Conclusions

Nearly 4 in 5 older adults with late-stage melanoma had any multimorbidity. The prevalence of multimorbidity varied by type of conditions with lowest in MHC and highest in PHC. One in 10 older adults with late-stage melanoma had AD multimorbidity, suggesting challenges to the management and decisions for treatment. Cardiovascular, endocrine, and musculoskeletal diseases were the most commonly occurring comorbid conditions, which share risk factors with cancer. While the risk factors for any multimorbidity were age and region, they varied depending on the type of multimorbidity. Therefore, surveillance of type of

multimorbidity in clinical care should routinely be conducted to properly decide the treatment and follow-up care among older patients with late-stage melanoma.

Table 2.1
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
Linked Surveillance, Epidemiology, and End Results and Medicare Claims Database

Variables	ICI	No ICI	p-value	Significance
	N (%)	N (%)		
ALL	252 (5.6)	4,267 (94.4)		
Multimorbidity				
Yes	211 (5.5)	3,622 (94.5)	0.62	
No	41 (6.0)	645 (94.0)		
Year of diagnosis				
2012	35 (3.2)	1,060 (96.8)	0.0008	***
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)	0.0004	***
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)	0.014	*
Male	180 (6.2)	2,722 (93.8)		
Race				
Whites	239 (5.5)	4,103 (94.5)	0.29	
Non-Whites	13 (7.3)	164 (92.7)		
Marital Status				
Married	163 (7.3)	2,057 (92.7)	<0.0001	***
Not married	89 (3.9)	2,210 (96.1)		
Dual Medicare/Medicaid eligibility				
Yes	17 (10.0)	153 (90.0)	0.0104	*
No	235 (5.4)	4,114 (94.6)		
Regions				
Northeast	64 (7.9)	748 (92.1)	0.0186	*
South	49 (5.1)	916 (94.9)		
North Central	24 (5.1)	451 (94.9)		
West	115 (5.1)	2,152 (94.9)		

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. *0.05 < p ≤ 0.01; **0.01 < p ≤ 0.001; *** p < 0.001

Table 2.2
Percent with Type of Multimorbidity by Selected Patient-level Characteristics
Older Adults (age ≥65 years) with Incident Late-stage Melanoma during 2011 and 2015
Linked Surveillance, Epidemiology, and End Results and Medicare Claims Database

	PHC Multimorbidity		AD Multimorbidity		MHC Multimorbidity	
	% Yes	% No	% Yes	% No	% Yes	% No
Year of diagnosis						
2012	83.7	16.3	10.4	89.6	5.0	95.0
2013	82.8	17.2	9.6	90.4	5.1	94.9
2014	85.8	14.2	9.1	90.9	6.4	93.6
2015	83.0	17.0	10.7	89.3	6.9	93.1
Age^a						
65 to 69 years	76.0	24.0	8.8	91.2	6.6	93.4
70 to 74 years	81.9	18.1	9.6	90.4	5.8	94.2
75 to 79 years	85.2	14.8	9.8	90.2	6.0	94.0
≥80 years	88.6	11.4	10.9	89.1	5.5	94.5
Sex^{b,c}						
Female	84.2	15.8	13.2	86.8	8.8	91.2
Male	83.7	16.3	8.1	91.9	4.2	95.8
Race						
White	83.9	16.1	10.1	89.9	5.9	94.1
Non-Whites	83.1	16.9	6.8	93.2	5.6	94.4
Marital status^c						
Married	84.2	15.8	10.4	89.6	3.9	96.1
Not married	83.6	16.4	9.5	90.5	7.8	92.2
Region^{a,b}						
Northeast	87.4	12.6	11.9	88.1	6.3	93.7
South	85.7	14.3	7.2	92.8	6.0	94.0
North central	82.5	17.5	13.5	86.5	8.0	92.0
West	82.1	17.9	9.7	90.3	5.2	94.8
Dual Medicare/Medicaid Enrollment ^c						
Yes	86.5	13.5	9.4	90.6	17.1	82.9
No	83.8	16.2	10.0	90.0	5.4	94.6

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.

AD: Autoimmune diseases; MHC: Mental health conditions; PHC: Physical health conditions

^a represents significant group differences in presence or absence of PHC multimorbidity; ^b represents significant group differences in presence or absence of AD multimorbidity; ^c represents significant group differences in presence or absence of MHC multimorbidity based on chi-square tests.

Table 2.3
Adjusted Odds Ratios (AOR) and 95% Confidence Intervals (CI) from
Separate Multivariable Logistic Regressions on Type of Multimorbidity
Older Adults (age ≥65 years) with Incident Late-stage Melanoma during 2011 and 2015
Linked Surveillance, Epidemiology, and End Results and Medicare Claims Database

	PHC Multimorbidity			AD Multimorbidity			MHC Multimorbidity		
	AOR	95% CI	Prob	AOR	95% CI	Prob	AOR	95% CI	Prob
Year of diagnosis									
2012	1.00	[0.80 , 1.26]		0.95	[0.73 , 1.25]		0.73	[0.51 , 1.05]	
2013	0.95	[0.76 , 1.19]		0.88	[0.67 , 1.17]		0.75	[0.53 , 1.08]	
2014	1.21	[0.96 , 1.52]		0.82	[0.62 , 1.08]		0.96	[0.69 , 1.34]	
2015	[ref]			[ref]			[ref]		
Age									
65 to 69 years	[ref]			[ref]			[ref]		
70 to 74 years	1.42	[1.13 , 1.77]	0.002	1.11	[0.81 , 1.52]		0.92	[0.63 , 1.35]	
75 to 79 years	1.81	[1.42 , 2.30]	<0.001	1.16	[0.84 , 1.59]		0.95	[0.65 , 1.40]	
≥80 years	2.47	[1.99 , 3.06]	<0.001	1.22	[0.92 , 1.62]		0.74	[0.53 , 1.04]	
Sex									
Female	1.02	[0.86 , 1.21]		1.81	[1.48 , 2.22]	<0.001	1.88	[1.46 , 2.44]	<0.001
Male	[ref]			[ref]			[ref]		
Race									
White	[ref]			[ref]			[ref]		
Non-Whites	1.03	[0.68 , 1.55]		0.62	[0.34 , 1.14]		0.63	[0.32 , 1.24]	
Marital status									
Married	[ref]			[ref]			[ref]		
Not married	0.91	[0.77 , 1.07]		0.79	[0.65 , 0.97]	0.03	1.85	[1.41 , 2.43]	<0.001
Region									
Northeast	[ref]			[ref]			[ref]		
South	0.89	[0.68 , 1.18]		0.58	[0.42 , 0.80]	0.001	0.93	[0.62 , 1.38]	
North central	0.65	[0.47 , 0.90]	0.009	1.13	[0.80 , 1.59]		1.42	[0.91 , 2.21]	
West	0.67	[0.53 , 0.85]	0.001	0.82	[0.63 , 1.06]		0.79	[0.56 , 1.12]	
Dual Medicare /Medicaid Enrollment									
Yes	1.31	[0.82 , 2.07]		0.99	[0.58 , 1.69]		3.33	[2.14 , 5.19]	<0.001
No	[ref]			[ref]			[ref]		

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.

AD: Autoimmune diseases; MHC: Mental health conditions; PHC: Physical health conditions; Prob: Probability

CHAPTER 3

3. FACTORS ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITOR USE AMONG OLDER PATIENTS WITH LATE-STAGE MELANOMA

3.1. Abstract

Background: 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 elderly 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.

Methods: 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 two 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.

Results: 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.

Conclusions: In the real-world clinical practice, only one 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.

3.2. Introduction

Newer therapies, namely immune checkpoint inhibitors (ICIs) with a unique mechanism of action and unknown side effect profile,⁹² have significantly increased the survival prognosis for adults with late-state melanoma.^{19,22,93} 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.^{42,93} These recommendations were based on the evidence presented in randomized clinical trials (RCTs), which have strict inclusion and exclusion criteria.^{19,20,72} These stringent criteria, while beneficial to ensure patient safety, 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.⁹⁴ One of the patient subpopulations where evidence on use of ICI is lacking is the elderly. Although utility of ICI in elderly patients with late-stage melanoma is debated, data from studies have shown that these therapies are well tolerated in the elderly.⁹⁵⁻⁹⁷ Older patients are also known to have multiple chronic conditions (also known as multimorbidity), which are often not taken into account by the guidelines.^{95,96,98} 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.^{32,33,35}

Older patients with multimorbidity are the norm rather than exception in clinical practices.²⁹

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.⁴⁶ Patients below the age of 80 years and White non-Hispanics were more likely to receive treatment than those above 80 years of age and other race/ethnicity.⁴⁶ 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.⁴⁷ Underinsured patients with late-stage melanoma were more likely to receive treatment at lower immunotherapy prescribing hospitals.⁴⁸ 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.

3.3. Methods

Study Design

This was a retrospective cohort design with a 12-month baseline (pre-diagnosis) and 12-month follow-up (post-diagnosis) period. Diagnosis date of late-stage (stage III/stage IV) melanoma diagnosis 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.

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.

Study Population

Incident melanoma diagnosis between 2011 and 2015 was identified using 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 4,519 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.

Measures

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 (HCPCS) codes (J9228, J9299, J9271).

Independent variables

Multimorbidity: Presence of two or more chronic conditions in the pre-diagnosis period was defined as multimorbidity in this study. These conditions were obtained from a list of 18 chronic conditions developed by Multiple Chronic Conditions working group within the US Department of Health and Human Services Office of Assistant Secretary of Health. Pre-existing autoimmune diseases were also added to the list based on the current challenges with ICI use in patients with these conditions.⁷³ All these conditions were identified with International Classification of Diseases (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, HCPCS codes, and revenue center codes (see Appendix 7.2). 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.

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); $p \leq 0.05$ was considered statistically significant. All analyses were conducted using SAS 9.4 (SAS Institute Inc.).

3.4. Results

The study population 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 ($p=0.62$) and race ($p=0.29$) (Table 3.1).

Factors associated with ICI use: Unadjusted Logistic Regression on ICI use

Table 3.2 presents the unadjusted odds ratio (OR), 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.

Factors associated with ICI use: Multivariable Logistic Regression on ICI use

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.

3.5. 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.^{99,100} 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%).¹⁰¹ In this published study, the authors noted 22% initiated treatment after the disease progression while 51% started treatment before late-stage melanoma diagnosis.¹⁰¹

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 34-37% of the patients received ICI as the first-line treatment, despite the recommendation by the NCCN guidelines.^{25,102,103} 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,¹⁰⁴ 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.^{32,105} As RCTs of ICIs typically exclude patients with multimorbidity,¹⁰⁶ 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.¹⁰⁷ It has also been reported that elderly Medicare beneficiaries with multimorbidity are equally likely to trust their doctors for their care,¹⁰⁸ 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 the elderly with late-stage melanoma. In this study, compared to patients 80 years and older, those between the ages of 66 and 74 years were more likely to receive ICIs. 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.⁹⁶ 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.^{105,109,110} 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.

In this study, social support, measured with the proxy (i.e. marital status), was significantly associated with ICI use. 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.^{111,112} 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.^{113,114} 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.¹¹³ In addition, key opinion leaders, who also lead many RCTs, play an important role in the diffusion of innovation.¹¹⁵ 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.¹¹⁵ These leaders encouraged use of innovative therapies in real-world settings.¹¹⁵ 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.¹¹⁶ In a study of lung cancer patients, dual eligibility status was associated with longer duration of treatment.¹¹⁷ 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.^{118–120} 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 one ICI (ipilimumab) approved for the treatment before 2014. Therefore, the data to support the safety and efficacy of ICI had not been widely disseminated. In addition, the diffusion of innovation takes substantial time.⁹⁴ Rather than rely on communication of a medical innovation, most physicians adopted the innovation after watching their colleagues use them.¹²¹ This is especially true when contemplating use in populations excluded in the RCTs,¹²¹ 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.

3.6. Strengths and limitations

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.

3.7. Conclusions

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 five 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.

TABLES

Table 3.1
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
Linked Surveillance, Epidemiology, and End Results and Medicare Claims Database

Variables	ICI	No ICI	p-value	Significance
	%	%		
ALL	5.6	94.4		
Multimorbidity				
Yes	5.5	94.5	0.62	
No	6.0	94.0		
Year of diagnosis				
2012	3.2	96.8	0.0008	***
2013	5.8	94.2		
2014	6.4	93.6		
2015	6.8	93.2		
Age				
66 to 69 years	6.8	93.2	0.0004	***
70 to 74 years	7.6	92.4		
75 to 79 years	5.0	95.0		
≥80 years	4.1	95.9		
Sex				
Female	4.5	95.5	0.014	*
Male	6.2	93.8		
Race				
Whites	5.5	94.5	0.29	
Non-Whites	7.3	92.7		
Marital Status				
Married	7.3	92.7	<0.0001	***
Not married	3.9	96.1		
Dual Medicare/Medicaid eligibility				
Yes	10.0	90.0	0.0104	*
No	5.4	94.6		
Regions				
Northeast	7.9	92.1	0.0186	*
South	5.1	94.9		
North Central	5.1	94.9		
West	5.1	94.9		

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. *0.05 < p ≤ 0.01; **0.01 < p ≤ 0.001; *** p < 0.001

Table 3.2
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
Linked Surveillance, Epidemiology, and End Results and Medicare Claims Database

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)		

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 ≤ 0.01; **0.01 < p ≤ 0.001; *** p < 0.001

Abbreviations: ref = Reference group

CHAPTER 4

4. IMMUNE CHECKPOINT INHIBITOR USE, MULTIMORBIDITY, AND HEALTHCARE EXPENDITURES AMONG OLDER ADULTS WITH LATE-STAGE MELANOMA

4.1. Abstract

Background: The objective of this study is to assess the impact of immune checkpoint inhibitors (ICI) and multimorbidity on healthcare expenditures among older patients with late-stage melanoma.

Methods: A retrospective longitudinal cohort study using Surveillance, Epidemiology, and End Results linked with Medicare claims was conducted. Generalized linear mixed models were used to analyze adjusted relationships of ICI, multimorbidity, and ICI-multimorbidity interaction on average healthcare expenditures.

Results: Patients who received ICI and those who had multimorbidity had significantly higher average total healthcare expenditures compared to ICI nonusers and no multimorbidity. In the fully adjusted model using ICI-multimorbidity interaction, no excess cost was added by multimorbidity.

Conclusion: Use of ICIs, regardless of multimorbidity, is associated with increased healthcare expenditures.

4.2. Introduction

Cancer exerts a substantial burden on the morbidity and mortality of patients.^{122,123} In addition, cancer exerts a significant economic burden on not only the patients, but also on payers and society as well.⁵⁰ Cancer is one of the top five most expensive chronic conditions.⁵⁰ There is robust evidence showing that cancer substantially increases healthcare expenditures.^{124–127} For

example, it has been reported that adults with cancer have four times higher expenditures compared to those without cancer.^{51,127} Furthermore, the healthcare cost of cancer differs by the type and stage of cancer. Healthcare costs were highest for cancers with poor survival rates such as brain cancers and lowest for cancers with high survival rates, such as melanoma.⁵¹ However, the cost increases substantially when the cancer metastasizes.^{50–52} For example, 55% of the annual direct costs for treating melanoma were related to treating late-stage melanoma.⁵³

While many factors can influence healthcare costs among cancer patients, expensive drugs approved for cancer, the administration of these drugs, and supportive care (monitoring, surveillance, and management of side-effects such as kidney infections, pneumonia through frequent medical office visits and sometimes hospitalizations) are some of the main factors.⁵⁶ For example, in metastatic melanoma patients initiated on an immune therapy agent ipilimumab, the average all-cause healthcare expenditures for a treatment episode was estimated to be \$153,062.¹²⁸ The immune checkpoint inhibitors (ICIs) were first approved for the treatment of late-stage melanoma nine years ago after their success in improving survival was established by randomized clinical trials (RCTs).⁹² However, the high cost of ICIs may hinder their widespread adoption in real-world clinical settings. The average wholesale price in 2015 of a single dose for a 70 kg patient was \$5,732 for nivolumab, \$33,162 for ipilimumab, and \$35,073 for the combination therapy.¹²⁹ As these drugs need to be administered by healthcare professionals in outpatient settings, the total costs are even higher.¹³⁰ This is compounded by the fact that an optimum dose for ICIs remains unknown which entails continuous use of ICI until regression of the tumor or appearance of adverse events.^{20,21,23} Oncologists estimated that treatment cost for the highest and most often administered dose, 26 courses of an ICI can be as high as \$1,009,944 with a 20% copay.⁵⁷

Thus, a vast majority of patients cannot afford ICI treatment unless covered by health insurance.^{48,120,131,132} In the United States (US), insurance and type of insurance coverage are often associated with prognosis, treatment and survival of cancer patients. Specifically, using the National Cancer Database, Jain and coauthors (2020) reported that the stage of diagnosis and receipt of ICIs were associated with insurance status.¹³³ A high proportion of individuals with late-stage melanoma were on Medicare and were as likely as those with commercial insurance to receive ICI.^{48,49} These findings suggest that Medicare may bear a disproportionate share of late-stage melanoma expenditures. Furthermore, older Medicare beneficiaries (age > 65 years) are of particular interest for several reasons; 96% are covered by Medicare; higher incidence of better cancer/late-stage melanoma is observed among these patients, and Medicare patients are facing an evolving payment landscape, such as Oncology Care Model (OCM), aimed towards improving cancer care continuum while reducing costs in older patients.^{10,134–136}

The newer payment models also include patients in high-risk groups, such as those with multimorbidity.¹³⁶ This is because 68% of the Medicare population reported having multimorbidity and resulted in 80% of Medicare payments.^{29,137–139} Expert and systematic reviews have concluded that patients with multimorbidity have higher costs compared to those without multimorbidity.^{28,140} Patients with multimorbidity and cancer have higher expenditures compared to those without any multimorbidity.^{141,142} Furthermore, multimorbidity is highly prevalent in older adults with late-stage melanoma.¹⁴³ If ICI are added to this mix, patients with multimorbidity and ICI may have even higher costs than those without multimorbidity and ICI. Therefore, the objectives of this study are (a) to estimate the impact of ICI use and (b) to assess the impact of the interaction of ICI and multimorbidity on healthcare expenditures among older patients with late-stage melanoma. We hypothesize that ICI use will be associated with high

expenditures throughout the treatment period compared to those without ICI use, and those with multimorbidity and ICI will have even higher costs than those without multimorbidity and ICI.

4.3. Methods

Study design

A retrospective observational longitudinal cohort design with a 12-month baseline (pre-index) and a 12-month follow-up (post-index) period was used; incident diagnosis of late-stage (stage III/IV) melanoma diagnosis was defined as the index date. Independent variables were assessed in the baseline period while treatments (chemotherapy, radiation, ICI) received were assessed in the follow-up period. Healthcare expenditures were measured every 120 days (t_1 , t_2 , t_3 , t_4 , t_5 , and t_6) during the 24-month observation period to ensure robust findings by reducing the “signal-to-noise” ratio¹⁴⁴ (Figure 4.1).

Data Sources

Surveillance, Epidemiology, and End Results (SEER) cancer registry linked with fee-for-service Medicare claims was used as the data source. Information on clinical variables related to cancer (such as stage of cancer at diagnosis) was obtained from the SEER data. Information on healthcare encounters of beneficiaries when enrolled and using Medicare covered health services including Medicare payments, and provider settings was obtained from Medicare claims.

Study Population

The study population was comprised of older (>65 years) adults diagnosed with incident melanoma between 2012 and 2015, identified using ICD-O-3 site codes (C44.0 – C44.9) and ICI-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. After excluding patients with local or regional (stage I/II) melanoma, non-incident melanoma, ages

66 years and below, not continuously enrolled in fee-for-service Medicare part A and part B during the observation period, and diagnosed with late-stage cancer during autopsy, the final cohort consisted of 4,519 patients.

Measures

Dependent variable: Total and Type of Healthcare expenditures

Total healthcare expenditures consisted of the sum of Medicare payments for inpatient, outpatient services (including carrier claims) for any care, home health care, and durable medical equipment. We also analyzed type of healthcare expenditures by site of care (inpatient and outpatient, and home healthcare). All healthcare expenditures were adjusted by the Consumer Price Index for medical services¹⁴⁵ and expressed in 2016 USD.

Independent variables

The use of ICI (yes/no) was identified in the post-diagnosis period. The three ICIs approved for late-stage melanoma treatment, ipilimumab, nivolumab, and pembrolizumab, were identified using healthcare common procedure coding system (HCPCS) codes (J9228, J9299, J9271). Overlapping procedure codes for chemotherapy and ICI (96413, 96415) were excluded to ensure that chemotherapy was not misclassified as ICI.

Multimorbidity (yes/no) was defined as the presence of two or more chronic conditions in this study. These conditions were obtained from a list of 18 chronic conditions developed by Multiple Chronic Conditions working group within the US Department of Health and Human Services Office of Assistant Secretary of Health.⁴¹ Pre-existing autoimmune diseases were added to the list based on the current challenges with ICI use in patients with these conditions.⁴² All the chronic conditions were identified with International Classification of Diseases (ICD), 9th Edition.

To examine the effects of ICI-multimorbidity interaction on cost, an ICI-multimorbidity interaction term was created, which was categorized into 4 groups: ICI and multimorbidity, ICI and no multimorbidity, No ICI and multimorbidity, and No ICI and no multimorbidity.

Other independent variables included biological factors, social factors, community resources, economic status, and year of diagnosis. 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). Oncologist visits (yes/no) and primary care physician visits (yes/no) were measured every 120 days. 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.

Statistical Analyses

Unadjusted subgroup differences in time-invariant characteristics between ICI users were tested with chi-square statistics. The associations of ICI and multimorbidity to healthcare expenditures were tested within the framework of Generalized Linear Models (GLM) with gamma distribution and log-link. This specification was chosen for GLM because of several reasons: (a) GLM does not require normal distribution of errors, (b) better aligns the variance function to the mean function, and (c) does not require smearing correction, which can be easily converted to original dollars.⁴³ Modified Park test confirmed the choice of gamma distribution with log-link was selected. As healthcare expenditures were measured every 120 days during the pre- and post-index periods, each individual had six observations. However, these observations were not independent and therefore generalized linear mixed models (GLMMs) with gamma distribution and log-link was used to analyze adjusted relationships between ICI and non-ICI user groups and ICI-multimorbidity interaction. The GLMMs included all independent variables

and time. Both unadjusted and adjusted models used GLMMs. Adjusted GLMMs included a time squared as one of the independent variables, to control for the non-linear relationship of healthcare expenditures over time. All analyses were conducted on STATA (StataCorp 2015).

4.4. Results

The study population was comprised of predominantly of males (64.2%), Non-Hispanic Whites (96.1%) and those 70 years or older (70.4%). Most older patients with late-stage melanoma had multimorbidity (85%) and 6% received ICI. The mean time from index date to ICI initiation was 48 days. The characteristics of the study population are presented in Appendix 7.3.

Overall healthcare expenditures

The average total, outpatient, home health, and inpatient healthcare expenditures in the pre-index period (t_1 , t_2 , and t_3) were significantly ($p < 0.001$) lower than the expenditures in the post-index period (t_4 , t_5 , and t_6) (Figure 4.2). All healthcare expenditures in the 120-day post-late-stage melanoma diagnosis period (t_4) were significantly higher compared to other pre- and post-index time periods (t_1 , t_2 , t_3 , t_5 and t_6).

Healthcare expenditures among ICI users and non-users

The average total, outpatient, home healthcare, and inpatient healthcare expenditures were significantly higher among ICI users compared to non-ICI users. Among ICI users, the average total and inpatient expenditures were significantly higher in t_4 (representing 120 days after cancer diagnosis) compared to other time periods (t_1 , t_2 , t_3 , t_5 and t_6) while average outpatient and home healthcare expenditures did not differ significantly in t_4 and t_5 and t_4 and t_6 time periods, respectively. Among non-ICI users, average total, outpatient, home healthcare, and inpatient expenditures were significantly higher in t_4 compared to other time periods.

Healthcare expenditures among those with and without multimorbidity

The average total, outpatient, home healthcare, and inpatient healthcare expenditures were significantly higher among those with multimorbidity compared to those without multimorbidity. Compared to t_4 , the average total, outpatient, home healthcare, and inpatient expenditures were significantly lower in other time periods (t_1 , t_2 , t_3 , t_5 and t_6) among those with multimorbidity. The average home healthcare expenditure did not significantly differ in t_4 and t_6 time periods among those without multimorbidity.

Healthcare expenditures and ICI-multimorbidity interaction

The average total, outpatient, home healthcare, and inpatient healthcare expenditures were significantly higher among ICI users and with multimorbidity group compared to ICI non-users and without multimorbidity. Average total expenditures by the ICI-multimorbidity groups are displayed in Figure 4.3. Compared to t_4 , the average total, outpatient, home healthcare, and inpatient expenditures were significantly lower in other time periods (t_1 , t_2 , t_3 , t_5 and t_6) among ICI users and with multimorbidity.

Adjusted associations of ICI and multimorbidity to total healthcare expenditures

Table 4.1 presents the unadjusted and adjusted parameters of GLMM on average total healthcare expenditures. The unadjusted and fully adjusted models showed similar results. In the model that was adjusted for time and time-squared, those with ICI had significantly higher average expenditures than those without ICI ($\beta=1.34$, $SE=0.52$, $p < 0.001$). When adjusted for multimorbidity, ICI users and those with multimorbidity had higher average expenditures compared to ICI non-users or no multimorbidity. In the fully adjusted model, the average total expenditure significantly increased with time ($\beta=0.49$, $SE=0.04$, $p < 0.001$). Patients who received ICI ($\beta=0.91$, $SE=0.07$, $p < 0.001$) and those who had multimorbidity ($\beta=0.72$, $SE=0.07$,

$p < 0.001$) had significantly higher average total expenditures compared to those who did not receive ICI or did not have multimorbidity.

Other variables with significant findings were age, dual eligibility, and visits to oncologists and primary care physicians. Significantly higher average total expenditures were reported in patients aged 75 to 79 years ($\beta=0.17$, $SE=0.07$, $p = 0.015$) and 80 years and older ($\beta=0.26$, $SE=0.06$, $p < 0.001$) compared to those aged between 65 and 69 years, who were dual eligible ($\beta=0.28$, $SE=0.11$, $p = 0.011$) versus those who were not, who had visited oncologists ($\beta=1.75$, $SE=0.05$, $p < 0.001$) versus no oncologist visits, and who had visited primary care physician ($\beta=1.38$, $SE=0.05$, $p < 0.001$) versus no primary care physician visits.

We also conducted GLMM on average total expenditures by ICI-multimorbidity interaction. In the fully adjusted model, compared to no ICI/no multimorbidity, average total expenditures were significantly higher in all other groups, namely in patients who used ICI and had multimorbidity ($\beta=17889.18$, $SE=1260.794$, $p < 0.001$), who used ICI but did not have multimorbidity ($\beta=16178.22$, $SE=2951.45$, $p < 0.001$), and who did not use ICI but had multimorbidity ($\beta=1510.35$, $SE=368.74$, $p < 0.001$). The contrast in average healthcare expenditures was examined by ICI use and multimorbidity by using ICI-no multimorbidity as the comparator group (Table 1). In the fully adjusted model, the average total healthcare expenditure significantly increased with time ($\beta=0.50$, $SE=0.04$, $p < 0.001$). Patients who were non-ICI users and had multimorbidity ($\beta=-0.73$, $SE=0.14$, $p < 0.001$) and non-ICI users and with no multimorbidity ($\beta=-1.51$, $SE=0.15$, $p < 0.001$) had significantly lower costs compared to patients who were ICI users and had no multimorbidity. However, there was no significant difference between patients who were ICI users and had multimorbidity and patients who were

ICI users and had no multimorbidity. Other variables with significant findings were same as above.

Adjusted relationships between ICI, multimorbidity, and type of healthcare expenditures

The relationship between ICI and multimorbidity by type of expenditures (outpatient, home healthcare, and inpatient) was further explored. The findings for average outpatient expenditures were similar to total expenditures (Appendix 7.4).

While patient with multimorbidity had significantly higher average home healthcare and inpatient expenditures compared to those without multimorbidity, ICI use was not significantly associated with those expenditures (Appendix 7.5 and Appendix 7.6, respectively). Similarly, the unadjusted and adjusted models of the effect of ICI and multimorbidity interaction on average home healthcare and inpatient expenditures were similar. In the fully adjusted model, the average home healthcare ($\beta=0.19$, $SE=0.06$, $p = 0.002$) and inpatient expenditure ($\beta=1.56$, $SE=0.22$, $p < 0.001$) significantly increased with time. However, no significant difference was observed among the ICI and multimorbidity groups.

4.5. Discussion

This study confirms previous findings and also presents some new findings. First, this study reports that average healthcare expenditures significantly increased after a terminal cancer, i.e., late-stage melanoma, diagnosis, which is in line with published studies. Cancer diagnosis exerts a huge financial burden on patients, payers, and healthcare systems, with four times higher costs in cancer cohort compared to the non-cancer cohort.^{3,7} Late-stage cancers tend to be more expensive than early-stage cancers.^{4,8,44,45} Although costs of early-stage versus late-stage melanoma were not compared, these findings still relay that late-stage melanoma diagnosis among older patients places enormous burden on the payers. These findings have implications

for the new OCM that are being experimented by the CMS. Under the OCM providers are expected to “provide higher quality, more highly coordinated oncology care at the same or lower cost to Medicare”.²⁹ The OCM organizes care around six-month episodes.²⁹ By providing information on total healthcare expenditures by time periods, our cost estimates can serve as benchmarks for episode-driven payments.

Second, this study found that ICI use is associated with higher average healthcare expenditures among older Medicare beneficiaries with late-stage melanoma. This is the first study to the best of our knowledge to assess the association of ICI use on healthcare expenditures among older adults with late-stage melanoma. Despite having similar expenditures during the pre-index periods (t_1 , t_2 , and t_3), use of ICI significantly increased post-index date (t_4 , t_5 , and t_6) expenditures. As seen in our study, outpatient expenditures were the major drivers of healthcare expenditures, contributing to 83% of the total expenditures. This study also found that ICI use was not associated with inpatient expenditures. Taken together these findings suggest that healthcare costs of ICI users may be driven by supportive care. Reasons for these findings are speculated as follows. It is reported that administration costs associated with ICIs are higher compared to other therapies.¹⁵ Intravenous infusion of ICI requires constant monitoring by a healthcare professional, which may lead to higher healthcare utilization.⁴⁶ Infusion reactions or immune-related adverse events may occur thereby increasing healthcare resource utilization.⁴⁶ Another possible reason could be the constant monitoring and testing of patients in the outpatient settings being treated with ICI.⁴⁶ Prior to and after infusion, late-stage melanoma patients are usually tested for serum biomarkers, enzyme level, and blood count.⁴⁶ The study findings confirm that cancer-related treatments have shifted from inpatient to outpatient settings.^{45,47}

Third, older Medicare beneficiaries with multimorbidity had higher average total expenditures compared to those without multimorbidity. Across a range of healthcare settings and population, disproportionately higher costs were accounted for in a small number of patients and multimorbidity was highly prevalent in those patients.⁴⁸ A majority of older adults with late-stage melanoma also had multimorbidity.³⁸ Therefore, higher total expenditures among older adults with multimorbidity corroborates findings from other studies.^{6,36} Many alternatives to traditional healthcare practices and payment models are being considered to account for the complex need of patients with multimorbidity.³⁵ Accountable Care Organizations and patient-centered medical homes over traditional practice models and bundled payment of services, which is more patient-centric than disease-centric, are a few such efforts.³⁵ Though there are numerous challenges to adopting such policies on a larger scale,³⁵ future studies need to explore whether these emerging models are effective in providing value-based care at lower costs for cancer patients in general and late-stage cancer patients in particular.

Fourth, the ICI-multimorbidity interaction revealed that multimorbidity did not play a significant role in the increase of expenditures. Rather, the high expenditures were due to the use of ICI. Although multimorbidity was associated with higher average expenditures in this study, the expenditures due to ICI use supersede those expenditures. The possible reasons for the increased average expenditures with ICI use are discussed above. These results further strengthen the need for newer payment models such as OCM, which focus on reducing cost of cancer care.

4.6. Strengths and Limitations

The findings of this study should be interpreted considering its limitations. First, Part D costs were not included. This is because patients with multimorbidity will have higher

prescription costs compared to those without multimorbidity. This may show even higher costs for patients with multimorbidity, which would be unrelated to cancer care. However, the current therapies for melanoma are covered under Part B. Therefore, melanoma-related treatment costs were adequately captured in this study. Second, information on severity of co-existing illnesses may have provided insights into cluster of conditions which may lead to higher healthcare expenditures. Third, the findings of this study cannot be generalized to all Medicare beneficiaries as the study population was limited to only those residing in SEER regions. Fourth, a 12-month follow-up period may not be adequately assessing the impact of various factors on healthcare expenditures. However, the mean overall survival for late-stage melanoma is approximately a year. Therefore, a 12-month follow-up period was chosen. Despite these limitations, the study has several strengths. This study adopted a longitudinal design and compared expenditures over time. Additionally, no study to-date has focused on impact of ICI on healthcare expenditures among older adults with multimorbidity and late-stage melanoma. This study provides payers with strong evidence on the influences of various factors on healthcare expenditures.

4.7. Conclusion

The results of this study illustrate that the healthcare expenditures were higher after a late-stage melanoma diagnosis. Use of ICIs and presence of multimorbidity were associated with higher expenditures. Outpatient expenditures contributed largely to the increase in total expenditures. However, the ICI-multimorbidity interaction revealed that ICI was the driving force behind the higher expenditures. Future studies are needed to explore healthcare utilization among older patients with multimorbidity and late-stage melanoma and explore its effect on healthcare expenditures.

FIGURE

Figure 4.1: Schematic of the study design. Each individual was observed for 24 months with a 12-month pre-index and 12-month post-index period. Healthcare expenditures and selected independent variables were measured repeatedly every 120 days during the pre-index (t_1 , t_2 , and t_3) and post-index (t_4 , t_5 , and t_6) periods, yielding a total of six repeated measures for every individual.

FIGURE

Figure 4.2: (a) Mean Total and Type of Healthcare Expenditures Over time; (b) Mean Total Healthcare Expenditures by ICI user status

Based on 6 repeated observation of 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.

Abbreviations: HHA, Home health care; ICI, Immune checkpoint inhibitors; USD, United States Dollars

FIGURE

Figure 4.3: Mean total healthcare expenditures by ICI-Multimorbidity groups during pre-index and post-index periods

Based on 6 repeated observation of 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. **Abbreviations:** ICI, Immune checkpoint inhibitors

TABLES

Table 4.1: Parameter estimates of select variables of GLMM on average total healthcare expenditures

Variables	No Interaction			With interaction		
	Unadjusted analysis					
	Beta	SE	Prob	Beta	SE	Prob
Time	0.83	0.04	<0.001	0.83	0.04	<0.001
ICI use				N/A		
Yes	1.34	0.52	<0.001			
No	(ref)					
Multimorbidity				N/A		
Yes	0.96	0.74	<0.001			
No	(ref)					
ICI-Multimorbidity Interaction	N/A					
Yes ICI and Yes Multimorbidity				0.19	0.10	0.051
Yes ICI and No Multimorbidity				(ref)		
No ICI and Yes Multimorbidity				-0.97	0.09	<0.001
No ICI and No Multimorbidity				-1.99	0.12	<0.001
Time squared	-0.15	0.01	<0.001	-0.15	0.01	<0.001

Variables	No Interaction			With interaction		
	Fully adjusted analysis [‡]					
	Beta	SE	Prob	Beta	SE	Prob
Time	0.49	0.04	<0.001	0.50	0.04	<0.001
ICI use				N/A		
Yes	0.91	0.07	<0.001			
No	(ref)					
Multimorbidity				N/A		
Yes	0.72	0.07	<0.001			
No	(ref)					
ICI-Multimorbidity Interaction	N/A					
Yes ICI and Yes Multimorbidity				0.02	0.16	0.90
Yes ICI and No Multimorbidity				((ref)		
No ICI and Yes Multimorbidity				-0.73	0.14	<0.001
No ICI and No Multimorbidity				-1.51	0.15	<0.001
Time squared	-0.12	0.01	<0.001	-0.12	0.01	<0.001

Note: Based on 6 repeated observation of 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.

[‡]Fully adjusted model also included year of diagnosis, age, sex, race, marital status, dual eligibility, oncologist visit, and primary care physician visits.

Probability p<0.05 was considered significant

Abbreviations: GLMM, Generalized linear mixed model; ICI, Immune checkpoint inhibitors; N/A, Not applicable; Prob, Probability; ref, Reference; SE, Standard error

CHAPTER 5

5. SUMMARY AND CONCLUSION

5.1. Summary of Findings and Discussion

Pre-existing multimorbidity is prevalent among the elderly yet remains understudied among older patients with melanoma. Patients with cancer often present with multiple chronic conditions, i.e. multimorbidity.^{65,66} Cancer is usually a manifestation of adverse lifestyles, such as smoking, obesity, and alcohol use, which are also the underlying causes of other chronic conditions.⁷⁷ Therefore, as a person ages, they accumulate chronic conditions, thereby increasing the prevalence of multimorbidity in older ages, especially among the elderly (>65 years) patients with cancer.¹⁴⁸ Despite being rampant in patients with cancer, multimorbidity is not included in cancer care. This is because patients with multimorbidity are often excluded from randomized clinical trials (RCTs).⁷² Moreover, guidelines often adopt a “single-disease” approach, thereby posing a problem to oncologists on treating such patients.⁷² Information on prevalence of pre-existing multimorbidity may shed light on the need to update guidelines to include multimorbidity in cancer care.

While prevalence of multimorbidity in other cancers has been studied in detail, late-stage melanoma has not received wide attention. This may be because late-stage melanoma is the deadliest form of skin cancer with a high mortality rate.²⁴ However, this was also the first cancer for which immune checkpoint inhibitors (ICI) were approved for treatment.⁹² The clinical trials of ICIs reported a significant improvement in the mean overall survival of patients with late-stage melanoma, increasing from six to eight months to up to five years.^{93,149,150} As survivors of late-stage melanoma may increase, knowledge on the prevalence of pre-existing multimorbidity

will assist healthcare providers personalize care for their older patients by creating guidelines with chronic conditions in mind.

Prevalence of pre-existing multimorbidity among older adults with late-stage melanoma is high. This is the first study to explore the prevalence and factors associated with the presence and type of multimorbidity among older adults with late-stage melanoma in the US. This study found that pre-existing multimorbidity is highly prevalent among older adults with four out of five patients having two or more chronic conditions. This study also notes that the most common comorbid conditions were cardiovascular, endocrine, and musculoskeletal diseases or a combination of the three in dyads and triads. Cardiovascular, endocrine, and musculoskeletal diseases are highly prevalent in older adults.^{75,76} As these diseases and cancer share modifiable risk factors, with some studies stating a bidirectional relationship between them, our findings were not surprising.⁷⁷⁻⁷⁹ These findings point to the fact that healthcare providers managing patients with late-stage melanoma may need to routinely monitor for the presence of these conditions and coordinate their care with the primary care physicians.

Various types of multimorbidity (any, physical health conditions [PHC], autoimmune diseases [AD], and mental health conditions [MHC] multimorbidity) and the risk factors associated with those multimorbidity were also explored. This study confirms findings from previous studies that age is a risk-factor for any multimorbidity.^{29,33} The region of residence was also associated with multimorbidity; however, studies on regional variations are lacking for us to adequately explain these results. The PHC multimorbidity shared risk-factors with any multimorbidity, perhaps because PHC contributed to the bulk of multimorbidity. Pre-existing AD was one of the PHC focused on, because of its complicated relationship with ICIs and the surge of interest in this condition among the oncology community. This study found that

although prevalence of pre-existing AD was not high, one in 10 older patients with late-stage melanoma will present with multimorbidity. Moreover, sex, region, and social support as a risk factor for AD multimorbidity also mimicked the findings of a previous studies.^{36,82,83}

Oncologists should consider these risk factors when deciding if a drug acting via the immune system (such as ICI) is the best course of treatment for older patients. About 30% of older adults with late-stage melanoma in this study were diagnosed with any MHC, consistent with literature.^{84,85} The risk factors associated with MHC were sex, social support, and dual Medicare/Medicaid eligibility, which was consistent with previous studies.⁸⁶⁻⁹⁰ These risk factors with MHC should be assessed in order to reduce further psychological distress and appropriate follow-up interventions.

The treatment landscape of late-stage melanoma has changed since the approval of ICIs in 2011. However, it is unknown if these changes have been implemented to real-world clinical settings. Despite the poor prognosis for survival, an overwhelming majority (82%) of older patients in this study did not receive any treatment for their late-stage melanoma, which was consistent with a previous study on chemotherapy for late-stage melanoma treatment.¹⁰¹ In addition, the rates of treatment with ICI in the study was very low (6%) and lower than that reported in recent studies.^{25,102,103} The reason speculated was due to the differences in the population studied. The study also 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,¹⁰⁴ oncologists may be cautious in using ICI among older patients with late-stage melanoma.

The factors associated with use of ICI among older patients with late-stage melanoma were determined to be lower age range, presence of social support in the form of a spouse,

having dual Medicare/Medicaid eligibility, residing in Northeast region, and recent years of diagnosis. However, multimorbidity was not significantly associated with receipt of ICI suggesting that multimorbidity was not a barrier in the receipt of ICI. Since guidelines on cancer care do not take multimorbidity into consideration, these results entail that those lack of guidelines may force oncologists to use newer therapies despite concerns regarding additional conditions.

Healthcare expenditures in the United States are increasing. However, healthcare expenditures associated with ICI use and multimorbidity among older-adults with late-stage melanoma remain unknown. This study reports that healthcare expenditures significantly increased after a terminal cancer, such as late-stage melanoma, diagnosis, which is in line with published studies.^{50–52,127} Older patients who had multimorbidity and those who had used ICI had significantly higher healthcare expenditures compared to those who did not have multimorbidity and had not use ICIs. Moreover, among ICI users, outpatient expenditures were the driving force behind total expenditures, accounting for 83% of the total expenditures. This confirmed findings from previous studies that late-stage melanoma care have shifted from inpatient to outpatient settings.^{54,147} In addition, the administration costs associated with ICIs are higher compared to other therapies.¹³⁰ The ICI-multimorbidity interaction revealed that irrespective of the multimorbidity status, ICI was the driving force behind the total healthcare expenditures. This finding shows that expenditures associated with ICI use were higher than those accrued by multimorbidity. Taken together, the use of ICI is significantly associated with higher total healthcare expenditures.

5.2. Implications and suggestions for future research

The findings of this study suggest that oncologists will encounter four in five older late-stage melanoma patients with multimorbidity. With lack of late-stage melanoma treatment guidelines for older patients with multimorbidity, clinicians and other stakeholders should consider updating guidelines to better guide healthcare workers on treatment of such patients. The lack of clear evidence from clinical trials and guidelines may, therefore, leave oncologists guessing on treating older patients with newer therapies. With an already poor prognosis associated with late-stage melanoma, ICIs may be used regardless of multimorbidity.

Future studies exploring the outcomes, such as . overall survival, associated with ICI use for late-stage melanoma in older adults with multimorbidity may shed light on the effectiveness of ICI in this subpopulation. Further, exploring the effect of various dyad and triad clusters of chronic conditions on survival after ICI use may provide useful information on conditions highly susceptible to adverse outcomes after ICI use. For example, patients with pre-existing autoimmune diseases and cardiovascular diseases may not be good candidates for receiving ICI compared to patients with osteoporosis and depression. This is because conditions like cardiovascular diseases have intersecting pathways with cancer, as explained above, and therefore, are adversely affected by ICI further exacerbating these conditions. Health-related quality of life among ICI users and nonusers was not explored in this study. Future studies can explore the humanistic burden of ICI use among older adults with or without multimorbidity.

Healthcare expenditures were higher among ICI users, regardless of multimorbidity. The newer payment models like Oncology Care Models are needed now more than ever to reduce healthcare expenditures. This study provides policymakers, healthcare workers, and other

stakeholders with a starting point for curbing the high expenditures among older patients with late-stage melanoma.

Future studies can further explore the healthcare utilization among these patients and the difference in healthcare expenditures between ICI users and non-users. Moreover, future studies can also include Part D expenditures. Prescription drug expenditures may be higher among patients with multimorbidity compared to those without multimorbidity. Therefore, the healthcare expenditures of older patients with multimorbidity may be even higher. These studies will strengthen the need for preventative measures to avoid multimorbidity among the elderly.

5.3. Strengths and Limitations

The present study has several limitations. First, SEER does not contain information on individual behavior such as smoking status, alcohol consumption, or functional status, all of which can further affect the risk of having multimorbidity. Second, individual-level socioeconomic factors, such as education and income were not available. 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. Fourth, the reasons for not receiving any treatment in older patients was unknown. Though disparities in ICI use were observed, the reason for these disparities, whether due to patient preferences or shared decision-making of providers and patients, could not be evaluated. Such information could direct healthcare providers on measures that can be taken to enhance the adoption of ICIs. Fifth, the database did not have detailed information on tumor characteristics or genetic markers such as BRAF status. Information on these could provide further insights into use of ICIs. Sixth, Part D medications were unavailable to us and therefore, prescription expenditure was not included. However, the current therapies for melanoma are covered under

Part B. Therefore, melanoma-related treatment costs were adequately captured in this study. Seventh, a 12-month follow-up period may not be adequately assessing the impact of various factors on healthcare expenditures. However, the mean overall survival for late-stage melanoma is approximately a year. Therefore, a 12-month follow-up period was chosen.

Despite these limitations, this study has several strengths. Although few studies on comorbid conditions in individuals with melanoma exist, they did not focus on late-stage melanoma, perhaps because the prognosis was poor with low chances of survival.⁹¹ Therefore, prognostic burden of multimorbidity in such individuals was deemed less important.⁹¹ However, newer therapies such as ICIs will improve survivorship of patients with late-stage melanoma. Therefore, information on the prevalence and type of multimorbidity in such individuals can help both physicians and patients in choice of cancer treatment, survivorship plans, and quality of life care. An exhaustive list of PHC and MHC, including pre-existing AD was included. Moreover, 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 study on healthcare expenditure adopted a longitudinal design and compared expenditures over time. The longitudinal design allowed us to minutely look at the various time points pre- and post- cancer diagnosis and evaluated the reasons for changing expenditures in during each time point. This

study provides payers with strong evidence on the influences of various factors on healthcare expenditures.

5.4. Conclusion

This dissertation concludes that prevalence of multimorbidity among older adults with late-stage melanoma is high. However, multimorbidity is not a barrier to access to ICIs. Multimorbidity is associated with higher expenditures compared to no multimorbidity. However, when the patients were treated with ICI, the healthcare expenditures increased significantly and the presence or absence of multimorbidity did not change the results. Clinical trials have shown that the ICIs have drastically improved survival of patients with late-stage melanoma; however, they come with a hefty price tag. Future studies are needed to examine overall survival among older patients with multimorbidity treated with ICIs to assess the risk-benefit of these newer therapies for late-stage melanoma.

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7. APPENDIX

Appendix 7.1: List of autoimmune diseases

S.No.	Autoimmune disease
1	Achalasia
2	Addison's disease
3	Adult Still's disease
4	Agammaglobulinemia
5	Alopecia areata
6	Amyloidosis
7	Ankylosing spondylitis
8	Anti-GBM/Anti-TBM nephritis
9	Antiphospholipid syndrome
10	Autoimmune angioedema
11	Autoimmune dysautonomia
12	Autoimmune encephalomyelitis
13	Autoimmune hepatitis
14	Autoimmune inner ear disease (AIED)
15	Autoimmune myocarditis
16	Autoimmune oophoritis
17	Autoimmune orchitis
18	Autoimmune pancreatitis
19	Autoimmune retinopathy
20	Autoimmune urticaria
21	Axonal & neuronal neuropathy (AMAN)
22	Balo disease
23	Benign mucosal pemphigoid
24	Castleman disease
25	Celiac disease
27	Chagas disease
27	Chronic inflammatory demyelinating polyneuropathy (CIDP)
28	Chronic recurrent multifocal osteomyelitis (CRMO)
29	Cicatricial pemphigoid
30	Cogan's syndrome
31	Cold agglutinin disease
32	Congenital heart block
33	Coxsackie myocarditis
34	CREST syndrome
35	Crohn's disease
36	Dermatitis herpetiformis
37	Dermatomyositis
38	Devic's disease (neuromyelitis optica)

S.No.	Autoimmune disease
39	Discoid lupus
40	Dressler's syndrome
41	Endometriosis
42	Eosinophilic esophagitis (EoE)
43	Eosinophilic fascitis
44	Erythema nodosum
45	Evan syndrome
46	Fibromyalgia
47	Fibrosing alveolitis
48	Giant cell myocarditis
49	Glomerulonephritis
50	Goodpasture's syndrome
51	Grave's disease
52	Guillain-Barre syndrome
53	Hashimoto's thyroiditis
54	Hemolytic anemia
55	Herpes gestationis or pemphigoid gestationis (PG)
56	Hiradenitis Suppurativa (HS) (Acne inversa)
57	Hypogammaglobulinemia
58	IgA Nephropathy
59	IgG4-related sclerosing disease
60	Immune thrombocytopenic purpura (ITP)
61	Inclusion body myositis (IBM)
62	Interstitial cystitis
63	Kawasaki disease
64	Lambert-eaton syndrome
65	Leukocytoclastic vasculitis
66	Lichen planus
67	Ligenous conjunctivitis
68	Linear IgA disease (LAD)
69	Lupus
70	Lyme disease chronic
71	Meniere's disease
72	Mixed connective tissue disease
73	Mooren's ulcer
74	Mucha-Habermann disease
75	Multifocal motor neuropathy
76	Multiple sclerosis
77	Myasthenia gravis
78	Myositis

S.No.	Autoimmune disease
79	Narcolepsy
80	Neuromyelitis optica
81	Neutropenia
82	Ocular cicatricial pemphigoid
83	Optic neuritis
84	Palindromic rheumatism
85	Paraneoplastic cerebellar degeneration
86	Paroxysmal nocturnal hemoglobinuria
87	Parry Romberg syndrome
88	Pars planitis (peripheral uveitis)
89	Parsonage-Turner syndrome
90	Pemphigus
91	Peripheral neuropathy
92	Perivenous encephalomyelitis
93	Pernicious anemia
94	Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS syndrome)
95	Polyglandular syndromes type I, II, III
96	Polymyositis
97	Postmyocardial infarction syndrome
98	Postpericardiotomy syndrome
99	Primary biliary cirrhosis
100	Primary sclerosing cholangitis
101	Progesterone dermatitis
102	Psoriasis
103	Psoriatic arthritis
104	Pure red cell aplasia
105	Pyoderma gangrenosum
106	Raynaud's phenomenon
107	Reactive arthritis
108	Reflex sympathetic dystrophy
109	Relapsing polychondritis
110	Restless legs syndrome
111	Retroperitoneal fibrosis
112	Rheumatic fever
113	Rheumatic arthritis
114	Sarcoidosis
115	Schmidt syndrome
116	Scleritis
117	Sjogren's syndrome
118	Stiff person syndrome

S.No.	Autoimmune disease
119	Subacute bacterial endocarditis
120	Susac's syndrome
121	Sympathetic ophthalmia
122	Takayasu's arteritis
123	Thrombocytopenic purpura
124	Tolosa-Hunt syndrome
125	Transverse myelitis
126	Ulcerative colitis
127	Undifferentiated connective tissue disease
128	Uveitis, Panuveitis
129	Vasculitis
130	Vitiligo
131	Vogt-Koyanagi-Harada disease

Appendix 7.2: Codes for identification of chemotherapy and radiation for the treatment of late-stage melanoma

	Chemotherapy	HCPCS Codes	CPT Codes
factor	Amifostine	'J0207'	'96374'
	Bacillus Calmette-Guérin	'90585', '90586', 'J9031'	'90471', '90472'
	Bleomycin	'J9040'	'96401', '96409'
	Carboplatin	'J9045'	'96409', '96413*', '96415**
	Cisplatin	'J9060'	'96409', '96413*', '96415**
	Carmustine	'J9050'	'96413', '96415**
	Dacarbazine	'J9130'	'96409', '96413**
	Docetaxel	'J9171 '	'96413**
	Granulocyte-macrophage colony-stimulating	'J2820'	'96365', '96366', '96372'
	IL-2- aldesleukin	'J9015'	'96409'
	Interferon alfa-2b	'C9399',* 'J9999**	'96372', '96401'
	Lomustine	'J8999*', 'S0178'	-
	Megestrol acetate	'J8999*', 'S0179'	-
	Melphalan	'J9245'	'96409', '96413**
	Nab-paclitaxel	'J9264'	-
	Paclitaxel	'J9265'	'96413**', '96415**
	Temozolomide	'J8700'	-
	Vincristine	'J9370'	'96409'
	Vinblastine	'J9360'	'96409'
	Radiation	HCPCS Codes	CPT Codes
	Intensity Modulated Radiation Therapy	-	'77301', '77338'
	Stereotactic Body Radiation Therapy	'G0339', 'G0340'	'77373', '77435'
	2D and 3D Conformal	'G6003', 'G6004', 'G6005', 'G6006', 'G6007', 'G6008', 'G6009', 'G6010', 'G6011', 'G6012', 'G6013', 'G6014'	'77280', '77285', '77290', '77295', '77402', '77407', '77412'
	Stereotactic Radiosurgery	'G0339', 'G0340'	'77371', '77372', '77432'
	Brachytherapy		'67218', '77316', '77317', '77318', '77778'

* Unclassified drugs/biologics; Not otherwise classified, antineoplastics; * Not included for identification of chemotherapy

Appendix 7.3
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
Linked Surveillance, Epidemiology, and End Results and Medicare Claims Database

Characteristics	ALL %	ICI %	No ICI %	p-value	Significance
ALL	100	5.6	94.4		
Year of diagnosis					
2012	24.2	3.2	96.8	0.0008	***
2013	24.1	5.8	94.2		
2014	25.8	6.4	93.6		
2015	25.9	6.8	93.2		
Multimorbidity					
Yes	84.8	5.5	94.5	0.62	
No	15.2	6.0	94.0		
Age (in years)					
65 to 69	20.2	6.8	93.2	0.0004	***
70 to 74	22.2	7.6	92.4		
75 to 79	20	5.0	95.0		
80 and older	37.5	4.1	95.9		
Sex					
Females	35.8	4.5	95.5	0.014	*
Males	64.2	6.2	93.8		
Race					
Whites	96.1	5.5	94.5	0.29	
Non-Whites	3.9	7.3	92.7		
Marital status					
Unmarried	50.9	7.3	92.7	<0.0001	***
Married	49.1	3.9	96.1		
Dual Medicare/Medicaid eligibility					
Yes	3.8	10.0	90.0	0.0104	*
No	96.2	5.4	94.6		
Oncologist visits					
Yes	20.0	12.5	87.5	<0.0001	***
No	80.0	3.8	96.2		
Primary care physicians					
Yes	62.0	6.2	93.8	<0.0001	***
No	38.0	4.6	95.4		

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.

Appendix 7.4: Parameter estimates of select variables of GLMM on average outpatient expenditures

Variables	No Interaction			With interaction		
	Unadjusted analysis					
	Beta	SE	Prob	Beta	SE	Prob
Time	0.40	0.04	<0.001	0.41	0.04	<0.001
ICI use				N/A		
Yes	1.66	0.05	<0.001			
No	(ref)					
Multimorbidity				N/A		
Yes	0.93	0.07	<0.001			
No	(ref)					
ICI-Multimorbidity Interaction	N/A					
Yes ICI and Yes Multimorbidity				0.25	0.09	0.005
Yes ICI and No Multimorbidity				(ref)		
No ICI and Yes Multimorbidity				-1.26	0.08	<0.001
No ICI and No Multimorbidity				-2.24	0.11	<0.001
Time squared	-0.07	0.01	<0.001	-0.07	0.01	<0.001

Variables	No Interaction			With interaction		
	Fully adjusted analysis [‡]					
	Beta	SE	Prob	Beta	SE	Prob
Time	0.17	0.03	<0.001	0.18	0.03	<0.001
ICI use				N/A		
Yes	1.18	0.07	<0.001			
No	(ref)					
Multimorbidity				N/A		
Yes	0.77	0.07	<0.001			
No	(ref)					
ICI-Multimorbidity Interaction	N/A					
Yes ICI and Yes Multimorbidity				0.05	0.17	0.77
Yes ICI and No Multimorbidity				(ref)		
No ICI and Yes Multimorbidity				-0.97	0.16	<0.001
No ICI and No Multimorbidity				-1.79	0.17	<0.001
Time squared	-0.06	0.01	<0.001	-0.06	0.01	<0.001

Note: Based on 6 repeated observations of 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.

[‡]Fully adjusted model also included year of diagnosis, age, sex, race, marital status, dual eligibility, oncologist visit, and primary care physician visits.

Probability p<0.05 was considered significant

Abbreviations: GLMM, Generalized linear mixed model; ICI, Immune checkpoint inhibitors; N/A, Not applicable; Prob, Probability; ref, Reference; SE, Standard error

Appendix 7.5: Parameter estimates of select variables of GLMM on average home healthcare expenditures

Variables	No Interaction			With interaction		
	Unadjusted analysis					
	Beta	SE	Prob	Beta	SE	Prob
Time	0.33	0.06	<0.001	0.33	0.06	<0.001
ICI use				N/A		
Yes	0.23	0.13	0.820			
No	(ref)					
Multimorbidity				N/A		
Yes	1.64	0.16	<0.001			
No	(ref)					
ICI-Multimorbidity Interaction	N/A					
Yes ICI and Yes Multimorbidity				0.81	0.31	0.009
Yes ICI and No Multimorbidity				(ref)		
No ICI and Yes Multimorbidity				0.79	0.30	0.008
No ICI and No Multimorbidity				-0.93	0.34	0.006
Time squared	-0.05	0.01	<0.001	-0.06	0.01	<0.001
Variables	Fully adjusted analysis [‡]					
	Beta	SE	Prob	Beta	SE	Prob
	Beta	SE	Prob	Beta	SE	Prob
Time	0.19	0.06	0.002	0.20	0.07	0.002
ICI use				N/A		
Yes	0.12	0.25	0.622			
No	(ref)					
Multimorbidity				N/A		
Yes	1.21	0.19	<0.001			
No	(ref)					
ICI-Multimorbidity Interaction	N/A					
Yes ICI and Yes Multimorbidity				0.06	0.62	0.928
Yes ICI and No Multimorbidity				(ref)		
No ICI and Yes Multimorbidity				0.24	0.61	0.696
No ICI and No Multimorbidity				-1.07	0.63	0.092
Time squared	-0.05	0.01	<0.001	-0.05	0.01	<0.001

Note: Based on 6 repeated observations of 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.

[‡]Fully adjusted model also included year of diagnosis, age, sex, race, marital status, dual eligibility, oncologist visit, and primary care physician visits.
Probability p<0.05 was considered significant

Abbreviations: GLMM, Generalized linear mixed model; ICI, Immune checkpoint inhibitors; N/A, Not applicable; Prob, Probability; ref, Reference; SE, Standard error

Appendix 7.6: Parameter estimates of select variables of GLMM on average inpatient expenditures

Variables	No Interaction			With interaction		
	Unadjusted analysis					
	Beta	SE	Prob	Beta	SE	Prob
Time	1.94	0.17	<0.001	1.93	0.17	<0.001
ICI use				N/A		
Yes	0.68	0.17	<0.001			
No	(ref)					
Multimorbidity				N/A		
Yes	1.05	0.15	<0.001			
No	(ref)					
ICI-Multimorbidity Interaction	N/A					
Yes ICI and Yes Multimorbidity				0.20	0.34	0.551
Yes ICI and No Multimorbidity				(ref)		
No ICI and Yes Multimorbidity				-0.27	0.29	0.342
No ICI and No Multimorbidity				-1.40	0.32	<0.001
Time squared	-0.34	0.03	<0.001	-0.33	0.03	<0.001
Variables	No Interaction			With interaction		
	Fully adjusted analysis [‡]					
	Beta	SE	Prob	Beta	SE	Prob
Time	1.56	0.22	<0.001	1.56	0.22	<0.001
ICI use				N/A		
Yes	-0.07	0.16	0.676			
No	(ref)					
Multimorbidity				N/A		
Yes	0.63	0.25	0.011			
No	(ref)					
ICI-Multimorbidity Interaction	N/A					
Yes ICI and Yes Multimorbidity				0.02	0.31	0.961
Yes ICI and No Multimorbidity				(ref)		
No ICI and Yes Multimorbidity				0.21	0.29	0.463
No ICI and No Multimorbidity				-0.46	0.35	0.179
Time squared	-0.30	0.04	<0.001	-0.30	0.04	<0.001

Note: Based on 6 repeated observation of 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.

[‡]Fully adjusted model also included year of diagnosis, age, sex, race, marital status, dual eligibility, oncologist visit, and primary care physician visits.

Probability p<0.05 was considered significant

Abbreviations: GLMM, Generalized linear mixed model; ICI, Immune checkpoint inhibitors; N/A, Not applicable; Prob, Probability; ref, Reference; SE, Standard error