Comparing Costs and Healthcare Resource Utilization Between nmHSPC and mHSPC Patients: A Retrospective Claims Analysis

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Abstract

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BACKGROUND: Prostate cancer has a high financial and health burden in the United States, being the most common cancer among American men. The disease typically manifests as localized non-metastatic hormone sensitive prostate cancer (nmHSPC) but can become metastatic and/or castration resistant. Metastatic hormone sensitive prostate cancer (mHSPC) is more difficult to treat than localized disease and requires different treatments than nmHSPC. Advanced disease can result in increased costs and healthcare resource utilization (HCRU), placing additional burden on patients, payers, and the health care system. Although studies have been conducted on the differences in costs and HCRU between non-metastatic castration-resistant prostate cancer and metastatic castration-resistant prostate cancer patients, no studies have been conducted yet in the HSPC setting.

OBJECTIVE: Our objective was to estimate the differences in HCRU and costs for nmHSPC and mHSPC patients and their payers.

METHODS: We conducted a retrospective cohort analysis using claims data from the IBM® MarketScan® Commercial and Medicare Supplemental databases. Our patient population consisted of male adult patients HSPC, split into non-metastatic and metastatic cohorts. HSPC was defined as having at least one inpatient services claim or two outpatient services claims within six months with a prostate cancer diagnosis. Additionally, patients must have had a claim evident of androgen deprivation therapy use within six months of their initial observed diagnosis date. Metastatic patients must have had a secondary diagnosis code of metastasis with their initial claim with prostate cancer as a primary diagnosis. The index date and follow-up period began 12 months after the initial diagnostic date, with 12 months of follow-up. Patients must have been continuously enrolled from their first diagnostic claim until the end of their follow-up period 24 months later. The 12-month follow-up period was used to assess the outcomes of interest, which were the difference between nmHSPC and mHSPC cohorts in terms of mean annual patient out of pocket (OOP) and payer costs, and healthcare resource utilization in terms of mean annual days spent hospitalized, outpatient prescription fills, and unique visits to outpatient services. Linear regression models were used to assess the outcomes during the follow-up period, adjusting for age, geographical region, plan type, and Charlson Comorbidity Index (CCI) score category.

RESULTS: A total of 4,239 patients met the study inclusion and continuous enrollment criteria. On average, the 12-month costs of mHSPC patients were significantly greater than that of nmHSPC patients for both patient OOP ($1,336; 95% CI: $1,064 to $1,608) and payer ($65,368; 95% CI: $57,248 to $73,488) costs. mHSPC patients also had higher mean annual outpatient prescription fills (8.38 fills; 95% CI: 6.03 to 10.72) and unique outpatient services visits (9.81 visits; 95% CI: 7.60 to 12.02). There was no statistically significant difference observed for mean annual days spent in inpatient services between the two cohorts. Subgroup analysis for age indicated that mHSPC patients had greater costs and HCRU than nmHSPC patients, although the under 65 years subgroup observed a significantly greater difference than the 65 years and older subgroup. Geographic region subgroup analysis shows that the mHSPC patients in the South had the greatest incremental cost difference compared to other regions.

CONCLUSIONS: Our analysis suggests that compared to nmHSPC patients, individuals with mHSPC impose a significantly greater financial burden on themselves and payers as well as incur greater healthcare resource utilization. There did not appear to be statistically significant differences in terms of hospitalization costs and inpatient resource utilization. Younger patients, under the age of 65, appear to have higher incremental costs and HCRU compared to those 65 years and older, which may be driven by more aggressive treatment.

ACKNOWLEDGEMENTS

My gratitude goes to Dr. Ryan N. Hansen and Dr. Josh J. Carlson for their guidance and mentorship not just in the completion of this thesis, but also in my development as a health economist during my course of studies this past year. Special thanks to Dr. Hansen for challenging me to think critically while providing the freedom to explore my interests. He has been extremely supportive and patient throughout my entire educational experience, and I have learned so much from him. I would also like to acknowledge the faculty and staff of the CHOICE Institute for the excellent education I have received despite the challenges that arose this past tumultuous year. I would not have given up this experience for anything. I am extremely grateful to my co-fellows for their friendship and rapport, I could not have asked for a better cohort by my side. Lastly, sincere thanks to the Data Generation & Observational Studies team at Bayer Pharmaceuticals for their encouragement throughout this year in my academic endeavors. I look forward to joining the team in the second year of my fellowship.

DEDICATION

I dedicate this thesis to my parents, Ching-Rong Ko (柯青榮) and May-Jun Chao (趙美君). I will forever appreciate the sacrifices you have made and the challenges you surmounted in bringing our family to the United States in order to give us a better life. I would not be half the person I am today without your love and support; my accomplishments are yours.

Additionally, this thesis is dedicated to my paternal grandmother, Tsao-Chih Ko Wang (柯王悉治), who passed away from cancer in 2019. Your unconditional love shone through our language barrier.

May you rest in peace.

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1. BACKGROUND

Prostate cancer is the most commonly diagnosed cancer among men in the United States and is the second leading cause of cancer death in American men.[1] In 2020, it is estimated that there were more than 200,000 new cases of prostate cancer in the United States, with over 30,000 deaths attributed to the disease. [1] Approximately one in nine men will be diagnosed with prostate cancer during his lifetime. About 60% of cases are diagnosed in men who are aged 65 or older, with the disease being rare in men under age 40.[1] The majority of men newly diagnosed with prostate cancer have localized hormone-sensitive disease, which can be complicated by progression to metastatic or castration-resistant disease, or both.[2] The pathophysiology of castration-resistant disease is unclear, although it has been suggested that the development of androgen-independent cells may be a contributing factor.[3] Although prognosis is poor, only 10%-20% of men diagnosed with prostate cancer will develop castration-resistant disease.[3] The majority of the burden of prostate cancer still remains with hormone-sensitive prostate cancer (HSPC). The prevalence of non-metastatic hormone-sensitive prostate cancer (nmHSPC) is estimated at approximately 76%, compared to 6% for metastatic hormone-sensitive prostate cancer (mHSPC).[4] According to Surveillance, Epidemiology, and End Results (SEER) data from 2010 to 2016, nmHSPC has a 5-year relative survival rate of 100% while mHSPC has a dismal 30%.[4] Despite the high relative survival rate of nmHSPC, the long duration of the disease can be a significant burden on patients, payers, and health systems in terms of costs and healthcare resource utilization.

Curative treatment options for localized HSPC generally consists of surgery or radiotherapy.[5] Androgen deprivation therapy (ADT) is the primary systemic therapy for regional or advanced HSPC.[6] ADT consists of orchiectomy, a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist, or an LHRH agonist plus a first-generation antiandrogen. In patients who present with mHSPC, ADT is the gold standard for initial treatment. [6] Docetaxel provides an additional line of treatment, in conjunction with

ADT.[6] Novel hormonal therapies such as apalutamide, abiraterone and enzalutamide are newly indicated treatments for mHSPC, after a spate of recent approvals by the Food and Drug Administration (FDA).[6] Treatment for HSPC has advanced greatly in the past two decades, improving the treatment paradigm for patients. However, the growth of available treatment options has driven an increase in the economic impact of prostate cancer.[7]

The economic burden of prostate cancer is high, with major contributing factors including high prevalence and the long duration of the disease. A 2010 study by the National Cancer Institute estimated the United States costs associated with prostate cancer to be $11.85 billion; the burden of prostate cancer can only have increased in the decade since due to the rising prevalence of the disease.[8] Although a multitude of studies have been published on the economic burden of prostate cancer, there is an evidence gap in terms of recent publications, studies that use real-world data as opposed to predictive modeling, and HSPC specifically.[8,9,10] There is an even greater paucity of research assessing the differences in economic burden between non-metastatic and metastatic HSPC. A better understanding of these differences would aid in optimizing resource allocation, access, and may provide useful data for informing health economic analysis as potential treatments for HSPC are investigated. In this study, we sought to compare the costs and resource utilization among patients with nmHSPC versus mHSPC.

2. OBJECTIVES

The primary objective of this study was to compare the mean annual direct payer and patient out of pocket costs between nmHSPC and mHSPC patients in the commercially insured U.S. population and Medicare supplemental beneficiaries. We also sought to compare healthcare resource utilization between nmHSPC and mHSPC patients, in terms of days spent in inpatient services, unique number of outpatient visits, and prescription drug fills.

3. METHODS

3.1 Study Design and Data Source

The data source for this retrospective cohort study was administrative claims from the IBM®/Watson Marketscan® Research databases between January 1, 2016 through December 31, 2019. We utilized the IBM® Marketscan® Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (MDCR) databases. The IBM® Marketscan® Commercial database consists of medical and drug data from employers and health plans and is representative of commercially insured patients. The IBM® Marketscan® Medicare Supplemental database consists of claims data of retirees with Medicare supplemental insurance paid by employers. The Enrollment (A), Outpatient Services (O), Inpatient Services (S), Inpatient Admissions (I) and Outpatient Pharmaceutical Claims (D) from these two databases were used to gather data on patient and payer 12-month costs and healthcare resource utilization. All patient-level data are de-identified in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

3.2 Sample Selection

Sample enrollment criteria and timeline are shown in Figure 1. The nmHSPC and mHSPC cohorts included male, adult individuals who were at least 18 years old at the index date, with at least one inpatient service or two outpatient services claims within a six-month period that had a primary or secondary diagnosis of prostate cancer. An individual's first inpatient services claim or second outpatient services claim with a primary diagnosis of prostate cancer was defined as the diagnostic claim, while the date of the claim served as the diagnostic date. ICD-10 codes for prostate cancer diagnosis are provided in Appendix 1. We required subjects be continuously enrolled for 24 months starting at their diagnostic date. Additionally, individuals in both cohorts must have had at least one outpatient services or outpatient pharmaceutical claim for androgen deprivation therapy (ADT) within

12 months of their diagnostic date. Individuals in the mHSPC cohort must additionally have had a secondary diagnosis code for metastasis in their initial claim with prostate cancer as a primary diagnosis. A full list of metastatic ICD-10 codes is provided in Appendix 2. Those who were originally non-metastatic but had any metastatic claims between their first prostate cancer claim and end of follow-up were excluded. Lastly, the nmHSPC cohort must not have had any claims for drugs used only in metastatic disease from their diagnosis date until the end of the follow-up period. These drugs included docetaxel, abiraterone, enzalutamide, and apalutamide.

The index date for each individual was defined as 12 months after their diagnostic claim. This 12-month period was chosen to ensure that patients have established disease by the start of the follow-up period and initial diagnostic and treatment costs are not inadvertently captured. Individuals were followed for 12 months starting from the index date. Index dates ranged between January 1, 2017 to December 31, 2018 while follow-up periods ranged between January 1, 2017 to December 31, 2019.

3.3 Study Measures and Outcomes

Baseline demographic characteristics, including age, Charlson Comorbidity Index (CCI), health insurance plan type, and geographic region were assessed during the pre-index enrollment period. The CCI variable excluded any cancer-related measures due to prostate cancer being an inclusion criterion; inclusion of these measures may inadvertently bias the results of the analysis.

The primary outcomes of interest were incremental differences in mean annual payer and patient out-of-pocket (OOP) total costs between the nmHSPC and mHSPC cohorts. Patient OOP costs were defined as the sum of co-insurances, co-pays, and deductibles. Costs for both patient and payers were derived from outpatient drug, outpatient services, and inpatient services claims. Costs were summed at the individual level before analysis was conducted. To quantify the contribution each resource type (inpatient services, outpatient services, outpatient prescription drugs) made to the overall differences in costs, the incremental differences in mean annual cost between the nmHSPC and mHSPC cohorts was also assessed for each separate resource type. All costs were reported in 2020 U.S. dollars using the medical care component of the Consumer Price Index for all urban consumers.

The secondary outcomes of interest were mean annual healthcare resource utilization, which included days spent in inpatient services, unique outpatient services visits, and number of outpatient drug fills. Unique outpatient visits was chosen as the outcome instead of days spent in outpatient services as a patient could have multiple visits for different outpatient services in a single day. Healthcare resource utilization data was sourced from the inpatient services, outpatient services, and outpatient drug claims, respectively. The Marketscan® variable Quantity of Services (QTY) was summed for each individual to obtain number of outpatient drug fills, in order to take into account transaction reversals that are not uncommon in claims data. Selecting claims with only positive QTY and excluding claims with negative QTY would falsely inflate the apparent number of outpatient drug claims for individuals.

Subgroup analysis was conducted for age and geographical region. Age subgroups were under 65 years old and 65 years and greater. Geographical region subgroups were stratified into Northeast, North Central, South, and West. Individuals who had their geographical region categorized as Unknown were omitted from subgroup analysis.

One exploratory outcome was examined a posteriori. The first exploratory outcome investigated if there were any trends in mean annual patient OOP and payer costs in terms of age. Non-metastatic and metastatic costs were assessed separately for this outcome, with age broken down into five-year categories. The purpose of this analysis was to assess if there was a linear relationship between cost and age.

3.4 Statistical Analysis

Baseline demographic characteristics were summarized, using mean and standard deviation (SD) for continuous variables and frequencies and proportions for categorical variables. Chi-square tests were used to assess differences in categorical variables and Student's t-tests were used to compare differences for continuous variables between cohorts.

Differences in the primary and secondary outcomes of interest between nmHSPC and mHSPC patients were estimated from multivariable linear regression models. Cost was the outcome of interest, with metastasis the predictor variable while adjusting for age, CCI, health insurance plan type, and geographic region.

The multivariable linear regression models for the secondary outcomes of interest are similar to that of the primary outcomes of interest, except instead of cost as the outcome variable, it is days spent in inpatient services, unique outpatient visits, or number of outpatient prescription drug fills instead. The nmHSPC cohort was the reference group in the regression analysis.

Four multivariable linear regression models were constructed for the age trend exploratory outcome. For each patient OOP costs and payer costs, two multivariable regression models were used to assess costs for nmHSPC and mHSPC cohorts, separately. The models were similar to that of the primary outcomes, except missing the metastasis predictor variable and with age buckets of five instead of 10 years.

Patient cohorts were identified in SAS version 9.4 (SAS Institute Inc., Cary, NC) while baseline demographics testing and regression analyses were conducted in R studio version 1.4.1106 (Rstudio Inc., Bost, MA). A two-sided alpha with a significance level of 5% was used for all statistical comparisons.

4. RESULTS

4.1 Baseline Characteristics

A total of 4,329 patients were identified from the inpatient services and outpatient services tables of the Marketscan® CCAE and MDCR databases who met the prespecified sample selection criteria and were included in the analysis (Figure 7.2). 3,279 of these patients were in the nmHSPC cohort while 600 were in the mHSPC. Baseline demographics and clinical characteristics of patients are shown in Table 8.1. The average age was similar between the nmHSPC cohort (68.03 years ± 11.23) and the mHSPC cohort (68.49 years ± 11.28). Proportion of patients in each age group was also similar between the two cohorts, with the largest difference being in the 55-64 age group (41.0% for nmHSPC and 37.8% for mHSPC). The nmHSPC cohort had a higher proportion of patients with a CCI score of 0 compared to the mHSPC cohort (47.1% vs 44.0%), while the proportions were fairly similar for CCI scores of 1,2, and 3 or greater. In terms of region, the largest difference in proportions was in the South geographical region, which contained 38.9% of the nmHSPC cohort compared to 30.5% of the mHSPC cohort. None of these differences were statistically significant when evaluated with chi-square tests. However, the South geographical region contained the most patients of each cohort compared to any other regions. In both cohorts, the majority of patients were enrolled in preferred provider organization (PPO) plans, had non-full time employment status and were not in a union, with similar proportions across all categories of these baseline demographics.

4.2 Primary Outcomes

The mean adjusted annual patient OOP costs were significantly greater among patients in the mHSPC cohort ($1,342; 95% CI: $1,072 to $1,612), along with mean annual payer costs ($65,767; 95% CI $57,653 to $73,860).

Separate models were constructed to estimate the contributions of the inpatient, outpatient services, and outpatient prescription claims to the overall differences in overall costs between the nmHSPC and mHSPC cohorts. There did not appear to be statistically significant differences in costs for inpatient services, with a mere $23 difference between the nmHSPC and mHSPC cohorts. Outpatient services and outpatient prescriptions appeared to have roughly equal contribution to overall differences between nmHSPC and mHSPC patient OOP costs (outpatient services: $640; 95% CI $489 to $854; outpatient prescriptions: $687; 95% CI $473 to $703) and payer costs (outpatient services: $31,600; 95% CI $25,771 to $37,429; outpatient prescriptions: $31,010; 95% CI $26,997 to $35,024). Analysis of the 15 most expensive outpatient services was conducted separately for nmHSPC and mHSPC patients to identify key drivers behind the cost differences between the two cohorts. Radiotherapy and sipuleucel-t constituted some of the most expensive services for patients and payers in the mHSPC cohort (Appendix 3 & 4).

Subgroup analysis was conducted on two different variables, age and region. Age was stratified into two groups, under 65 and 65 or greater. Region was split between Northeast, North Central, South, and West geographical regions. In the under 65 years subgroup, the mHSPC cohort observed greater annual patient OOP costs ($2,069; 95% CI: $1,573 to $2,565) and annual payer costs ($106,517; 95% CI: $91,422 to $121,612). The 65 years and older subgroup had similar results to the younger age subgroup, with the mHSPC cohort observing greater mean annual patient OOP costs ($773; 95% CI: $505 to $1485) and mean annual payer costs ($33,680; 95% CI: $26,715 to $40,646). The magnitude of difference in mean annual costs between nmHSPC and mHSPC cohorts appear to be less in the 65 years and older subgroup compared to the under 65 years subgroup. Testing for the significance of interaction between metastasis and age using multiple F-testing showed that age was a significant effect modifier ($p < 0.001$), although both subgroups indicated that metastatic patients had higher mean annual patient OOP and payer costs. In geographic region subgroup analysis, the mHSPC cohort had higher mean annual patient OOP and payer costs in all regions. The South geographical region had the most pronounced differences in costs, for both mean annual patient OOP costs ($1,780; 95% CI $1,297 to $2,263) and mean annual payer costs ($81,190; 95% CI: $65,033 to $97,348). The Northeast geographical region had the smallest difference between the nmHSPC and mHSPC cohorts, for both mean annual patient OOP costs ($772; 95% CI: $266 to $1,278) and mean annual payer costs ($51,797; 95% CI: $38,497 to $65,097). Multiple F-tests for showed that region was a statistically significant effect modifier for both patient OOP and payer costs using an alpha level of 0.05, although the p-value of the patient OOP test (0.048) was fairly close to the alpha level.

4.3 Secondary Outcomes

Results for secondary outcomes are shown in Table 8.3. The difference between the nmHSPC and mHSPC cohorts in terms of mean annual number of days spent in inpatient services, number of unique outpatient services visits, and number of outpatient prescription fills were estimated using multiple linear regression. On average, metastatic patients spent less days annually in inpatient services compared to non-metastatic patients (-0.61 days; 95% CI: -2.73 to 1.50), although this difference was not statistically significant. On the other hand, patients in the mHSPC cohort had a higher mean annual number of outpatient services visits compared to the nmHSPC cohort (9.86 visits; 95% CI: 7.65 to 12.08). Similar to outpatient services visits, metastatic patients had higher mean annual number of outpatient prescription fills compared to non-metastatic patients (8.47 fills; 95% CI: 6.13 to 10.82).

Similar to the primary outcomes, subgroup analysis for age and region was conducted for secondary outcomes. The differences between non-metastatic and metastatic patients for mean annual days spent in inpatient services was not statistically significant for either age subgroups or for any of the region subgroups. Mean annual unique outpatient services visits was greater for patients in the mHSPC cohort compared to the nmHSPC cohort for both the under 65 years subgroup (13.9 visits; 95% CI: 10.03 to 17.77) and 65 years or greater subgroup (6.76 visits; 95% CI: 4.25 to 9.28). Of the various regions, the

South geographical region observed the greatest increase in mean annual unique outpatient services visits for patients in the mHSPC cohort (12.79 visits; 95% CI: 7.98 to 17.61), although multiple F-testing indicated that there was no statistically significant difference between the regions ($p = 0.432$). Patients in the mHSPC cohort observed greater mean annual outpatient prescription fills for both the under 65 years subgroup (13.9 fills; 95% CI: 10.0 to 17.8) and the 65 years and older subgroup (6.8 fills; 95% CI: 4.3 to 9.3). Multiple F-testing for regions showed no statistical significance in differences between non-metastatic and metastatic patients ($p = 0.70$) although similar to unique outpatient services visits, patients in the South geographical region observed the greatest difference in fills between non-metastatic and metastatic patients (10.8 fills; 95% CI: 6.2 to 15.3).

4.4 Exploratory Outcomes

Multivariable linear regression models examining the possibility of age trends in terms of patient OOP and payer costs for the nmHSPC and mHSPC cohorts indicated that there were no linear age trends. Additionally, many of the partial F-test for each age group category was not statistically significant using an alpha level of 0.05, suggesting no relationship between age and cost.

5. DISCUSSION

5.1 Results Summary

We evaluated the annual mean incremental cost of mHSPC patients compared to nmHSPC patients. Multivariable linear regression indicated that patient OOP and payer costs were higher for the mHSPC cohort over a 12-month period. Outpatient services and outpatient prescription claims contributed the most to the cost differences between mHSPC and nmHSPC patients, while we did not find that inpatient services claims were a statistically significant independent contributor. This lack of statistical significance could be due to the much smaller proportion of inpatient services claims that contributed to total annual cost for patients, as only 13.6% of the nmHSPC and mHSPC cohort combined had an inpatient claim. Although there was a higher proportion of mHSPC patients who had an inpatient services claim, 22.5% compared to 12.2% for the nmHSPC cohort, we did not find a significant impact on annual mean costs of hospitalization. Analysis of the 15 most expensive outpatient services separately for nmHSPC and mHSPC patients revealed that the majority of the high-cost services were not cancer related. However, it does appear that there were more cancer-related outpatient services in the mHSPC cohort. Metastatic patients may require more cancer specific interventions compared to non-metastatic patients with less severe disease. Subgroup analysis for age indicated that although mean annual patient and payer costs are higher for mHSPC patients for both under age 65 and 65 and greater, the difference is amplified for those under age 65. Geographic region subgroup analysis found that the patient and payer costs was higher for mHSPC patients in all geographical, with the South observing the greatest difference.

As secondary outcomes, we evaluated the difference in healthcare resource utilization between nmHSPC and mHSPC patients in terms of mean annual days spent in inpatient services, number of outpatient prescription fills, and unique outpatient services visits. No statistically significant differences were found for mean annual days spent in inpatient services, supporting our findings that inpatient costs did not contribute meaningfully to the overall differences in costs between nmHSPC and mHSPC patients. The under age 65 subgroup observed higher inpatient services utilization, although these results were not statistically significant. Mean annual outpatient services, unique visits, and prescription fills were significantly higher for the mHSPC cohort. Similar to the trends observed in costs, the differences were greater in the under 65 years age subgroup. The incremental differences in the under 65 age years subgroup was more than twice as great as the 65 years and older subgroup for both outcomes, highlighting the greater resource utilization of the younger subgroup. In order to identify the drivers behind the differences observed in mHSPC and nmHSPC patients for outpatient prescription fills, we conducted a deeper analysis of the outpatient prescriptions dataset. On average, mHSPC prescription fills consisted of more unique NDCs (13.5 vs 11.6), unique therapeutic classes (8.9 vs 7.9), and lower days supply (45 days vs 51 days). The lower days supply may partially explain the higher number of prescription fills, as metastatic patients fill more often than non-metastatic.

Overall, mHSPC patients appear to incur significantly greater costs and healthcare resources compared to nmHSPC patients. Similar trends were observed in several studies which analyzed differences in costs and healthcare resource utilization, although none focused on HSPC specifically. A retrospective claims analysis that compared differences in costs and HCRU between non-metastatic and metastatic castration-resistant prostate cancer patients, which found an increase of approximately $120,000 in mean per-patient-per-year healthcare costs after patients progressed to metastatic cancer.[11] Healthcare resource utilization in terms of inpatient admissions and emergency department visits was also observed to have increased in metastatic patients. A retrospective cohort study using data from the SEER cancer registry reported monthly total healthcare costs of $2,746 for localized prostate cancer patients and $4,677 for metastatic prostate cancer patients.[12] This difference equates to $23,177 over a 12-month period, which is lower than the differences observed in our analysis. However, this study did not include the cost of outpatient prescription drugs which had contributed to a significant portion of the cost differences in our analysis. Similar to our findings, this study found that health care resource utilization was significantly greater for metastatic patients, although different endpoints were used to assess this outcome.

Interestingly, younger patients under the age of 65 appear to have increased costs and healthcare resource utilization compared to older patients 65 years and older. This could be due to the slower nature of prostate cancer, where intensive interventions may not be cost-effective in older patients. Additionally, commercial payers generally offer higher reimbursement rates than Medicare for the same services, which could also have driven the higher costs observed for patients under Medicare eligibility age.[13] Palliative care, which would be cheaper than curative treatments, may be utilized more commonly in older patients. The South geographical region appeared to have the largest differences in costs and healthcare resource utilization between mHSPC and mHSPC patients, although the estimates were not statistically significant for secondary outcomes.

5.2 Limitations

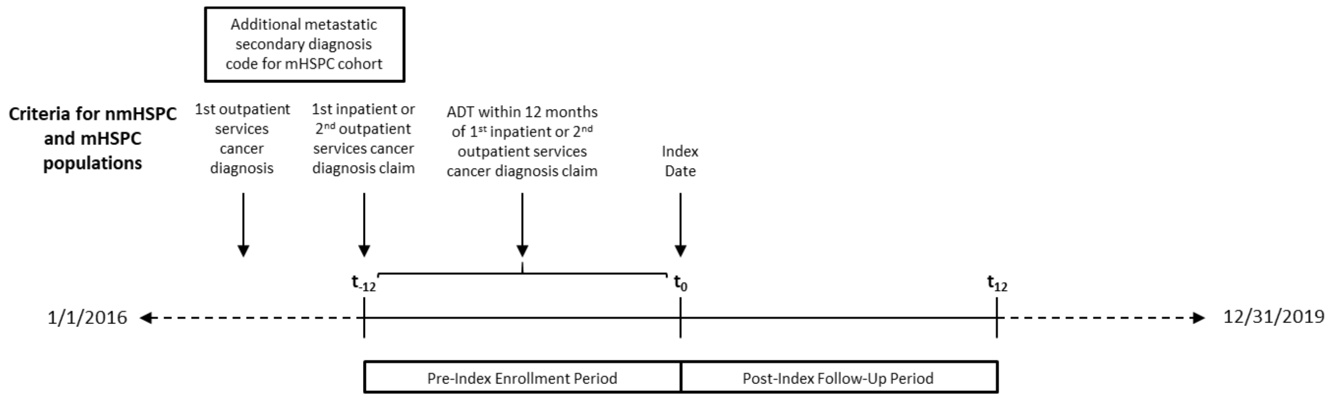
This analysis has several limitations. Firstly, the Marketscan® Medicare Supplemental dataset that contributed to the data used in this analysis is not completely representative of the Medicare population. The Medicare Supplemental dataset is derived from MediGap claims, representing the healthcare experience of retirees with Medicare supplemental insurance paid by employers. All MediGap plans cover Medicare Part A coinsurance and hospital costs, while most cover Part A deductible, Part B copays and coinsurance. The majority of MediGap plans do not cover Part B deductibles, and none cover prescription drugs. This could impact the generalizability of the results for those who are aged 65 years and older. Commercial claims make up the other portion of our dataset, which leaves the Medicaid population unrepresented. A second limitation is the lack of consistency in ICD-10 coding for nmHSPC and mHSPC. Although ICD-10 codes exist for these disease states, in practice patients with these diseases are not coded as such. Despite our best efforts to identify each cohort with the use of prostate cancer ICD-10 codes and history of ADT use, it is possible that patients who truly have the disease will be missed during enrollment or miscoded. A third limitation is the continuous enrollment requirement of our study, which only included patients who had health coverage for the 24 months from their first diagnostic claim until the end of their follow-up period. This requirement excluded approximately 14,000 individuals from our analysis and could have impacts on our results compared to if less stringent enrollment criteria had been utilized. Lastly, Marketscan® data does not contain variables that could be potential confounders such as race and income. Adjusting for these variables may impact our analysis. Subgroup analysis for these variables would have provided further insight on the drivers behind the cost and healthcare resource utilization differences between nmHSPC and mHSPC patients.

6. CONCLUSION

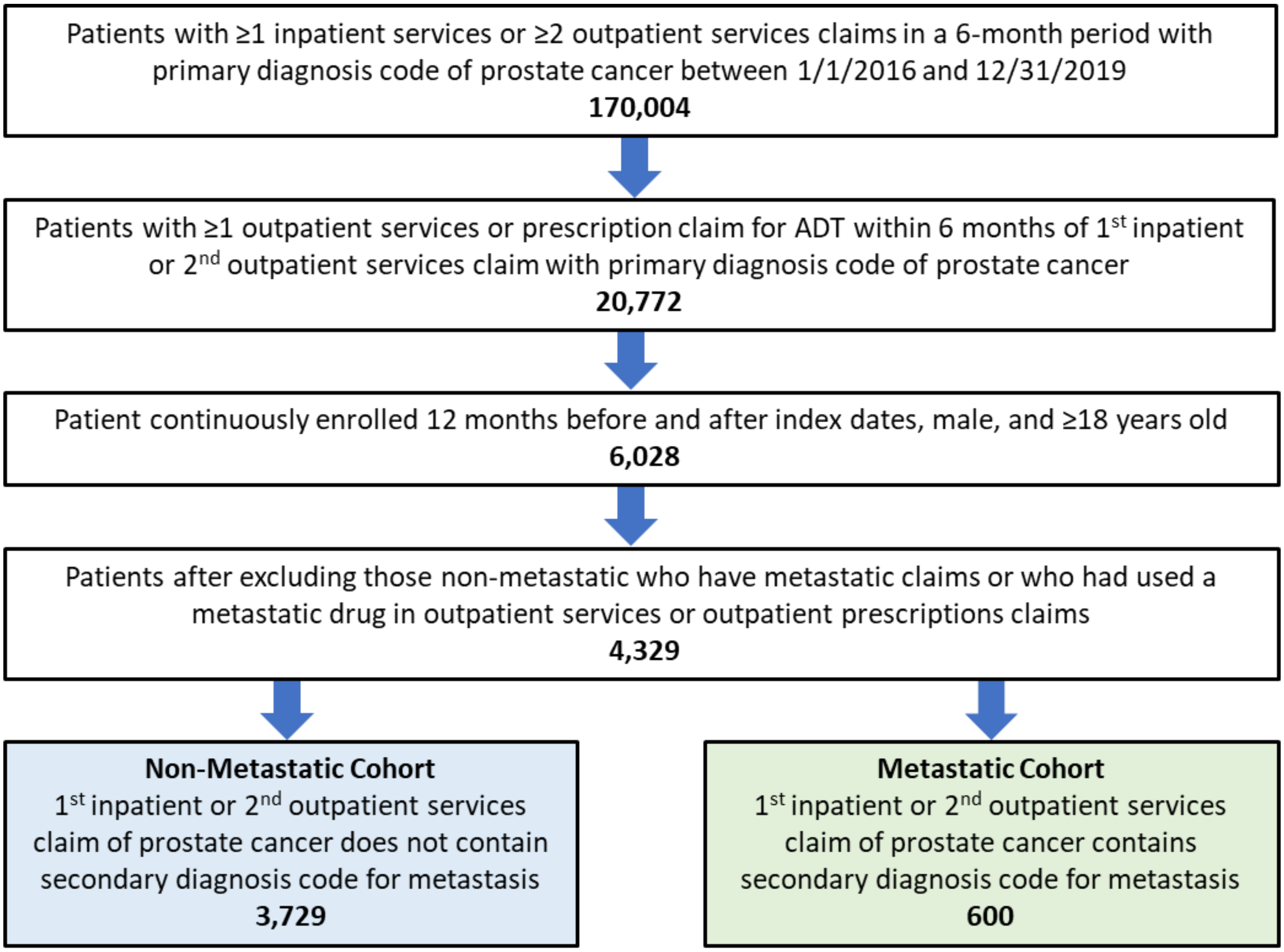
This retrospective claims analysis found that not only do mHSPC patients pay significantly more than nmHSPC patients, but payers are also impacted. Metastatic patients utilize more healthcare resources than non-metastatic in terms of outpatient prescription fills and unique outpatient services visits. The cost and healthcare resource utilization differences between nmHSPC and mHSPC patients were greater in magnitude for patients under 65 years old compared to those who are Medicare-eligible. New agents approved in this space may offer opportunities to delay the development of metastatic disease and resultant increase in HCRU and costs to both patients and payers. To date, this is the first population-level analysis of the incremental costs and healthcare resource utilization of mHSPC patients compared to nmHSPC. The results of this research could help in informing health economic models in the HSPC space to ascertain the value of novel treatments. Future research may provide additional insight into benefits of delaying metastatic disease progression by utilizing datasets more inclusive of Medicare and Medicaid populations.

7. LIST OF FIGURES

7.1 [Figure 1] Study Enrollment Criteria



7.2 [Figure 2] Sample Attrition Figure



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8.1 [Table 1] Baseline Demographics and Clinical Characteristics of Study Participants

Characteristic	Non-metastatic	Metastatic	p-value	SMD
n	3729	600		
AGE (mean (SD))	68.03 (11.23)	68.49 (11.28)	0.349	0.041
Index Year (mean (SD))	2017.28 (0.45)	2017.20 (0.4)	<0.001	0.177
Age Group			0.611	0.082
<45	11 (0.3)	3 (0.5)		
45-54	296 (7.9)	46 (7.7)		
55-64	1530 (41.0)	227 (37.8)		
65-74	723 (19.4)	130 (22.8)		
75-84	817 (21.9)	137 (22.8)		
85+	352 (9.4)	57 (9.5)		
Region			0.001	0.185
Northeast	1045 (28.0)	186 (31.0)		
North Central	737 (19.8)	135 (22.5)		
South	1451 (38.9)	183 (30.5)		
West	486 (13.0)	92 (15.3)		
Unknown	10 (0.3)	4 (0.7)		
CCI Category			0.380	0.076
0	1758 (47.1)	264 (44.0)		
1	932 (25.0)	160 (26.7)		
2	350 (9.4)	57 (9.5)		
3	689 (18.5)	110 (18.3)		
Plan Type			0.081	0.166
Comprehensive	557 (15.2)	105 (18.0)		
EPO	36 (1.0)	7 (1.2)		
HMO	502 (13.7)	95 (16.3)		
POS	86 (2.4)	20 (3.4)		
PPO	2008 (54.9)	304 (52.1)		
POS with capitation	135 (3.7)	8 (1.4)		
CDHP	207 (5.7)	31 (5.3)		
HDHP	128 (3.5)	13 (2.2)		
Union Status			0.415	0.058
Non-Union	1798 (48.2)	306 (51.0)		
Union	771 (20.7)	121 (20.2)		
Other/Unknown	1160 (31.1)	173 (28.8)		
Employment Status			0.354	0.043
Full Time	1275 (34.2)	193 (32.2)		
Non-Full Time	2454 (65.8)	407 (67.8)		
Commercial/Medicare			0.114	0.072
Commercial	1836 (49.2)	274 (45.7)		
Medicare	1893 (50.8)	326 (54.3)		

*p-value <0.001

8.2 [Table 2] Primary Outcomes

Primary Outcomes		
	mHSPC Incremental Mean Patient OOP Costs (95% CI)	**mHSPC Incremental Mean Payer Costs (95% CI)**
Base Case Model	$1,342 ($1,072 to $1,612)***	$65,757 ($57,653 to $73,860)***
Inpatient Services	$24 (-$15 to $62)	$3,511 ($1,268 to $5,754)**
Outpatient Services	$640 ($489 to $791)***	$31,600 ($25,771 to $37,429)***
Outpatient Prescriptions	$687 ($473 to $901)***	$31,010 ($26,997 to $35,024)***
Age Subgroup Model‡		
<65 Years	$2,067 ($1,572 to $2,565)***	$106,517 ($91,422 to $121,612)***
≥65 Years	$773 ($509 to $1,036)***	$33,680 ($26,715 to $40,646)***
Region Subgroup Model‡‡		
Northeast	$772 ($266 to $1,278)*	$51,797 ($38,497 to $65,097)*
North Central	$1,485 ($957 to $2,012)*	$70,716 ($55,146 to $86,285)*
South	$1,780 ($1,297 to $2,263)*	$81,190 ($65,032 to $97,348)*
West	$1,394 ($754 to $2,034)*	$53,841 ($32,519 to $75,165)*

*p<0.05, **p<0.01, ***p<0.001
Payer costs were identified using the net payment variable
Patient costs were calculated as the sum of each individual's copay, coinsurance, and deductible
Models were adjusted for age, CCI score, region and insurance plan type unless otherwise noted
‡Adjusted for CCI score, region, and insurance plan type
‡‡Adjusted for age, CCI score, insurance plan type

8.3 [Table 3] Secondary Outcomes

Secondary Outcomes				
		Days Spent in Inpatient Services (95% CI)	**Number of Prescription Fills (95% CI)**	**Unique Outpatient Services Visits (95% CI)**
Base Case		-0.62 (-2.73 to 1.50)	8.47 (6.13 to 10.82) ***	9.86 (7.65 to 12.08) ***
65 Subgroup‡				
	<65 Years	2.50 (-1.42 to 6.42)[b]	12.66 (8.93 to 16.39) **	13.9 (10.03 to 17.78) **
	≥65 Years	-2.08 (-4.64 to 0.48)[b]	5.36 (2.40 to 8.32) **	6.76 (4.25 to 9.28) **
Region Subgroup[a‡‡]				
	Northeast	-1.89 (-5.07 to 1.73)	7.56 (3.99 to 11.13)	8.81 (5.31 to 12.32)
	North Central	1.53 (-2.08 to 5.13)	7.06 (1.86 to 12.27)	8.01 (4.15 to 11.88)
	South	-1.55 (-7.10 to 4.00)	10.75 (6.16 to 15.34)	12.79 (7.98 to 17.61)
	West	0.904 (-2.62 to 4.43)	7.07 1.62 to 12.51)	8.18 (2.86 to 13.51)

[a]Multiple F-test for effect modification resulted in non-statistical significant p-value for all secondary outcomes

[b]Multiple F-test for effect modification resulted in non-statistical significant p-value for days spent in inpatient services outcome

*p<0.05, **p<0.01, ***p<0.001

Models were adjusted for age, CCI score, region and insurance plan type unless otherwise noted

‡Adjusted for CCI score, region, and insurance plan type

‡‡Adjusted for age, CCI score, insurance plan type

9. APPENDIX

9.1 [Appendix 1] Procedure Codes and Their Descriptions for Primary Diagnosis of Prostate Cancer and Hormone Sensitive Malignancy

ICD-10 Code	Description
C61	Malignant neoplasm of prostate
C19.1	Hormone sensitive malignancy status

9.2 [Appendix 2] Procedure Codes and Their Descriptions for Secondary Diagnosis of Metastasis

ICD-10 Code	Description
C770	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C771	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
C772	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
C773	Secondary and unspecified malignant neoplasm of axilla and upper limb lymph nodes
C774	Secondary and unspecified malignant neoplasm of inguinal and lower limb lymph nodes
C775	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
C778	Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions
C779	Secondary and unspecified malignant neoplasm of lymph node, unspecified
C7800	Secondary malignant neoplasm of unspecified lung
C7801	Secondary malignant neoplasm of right lung
C7802	Secondary malignant neoplasm of left lung
C781	Secondary malignant neoplasm of mediastinum
C782	Secondary malignant neoplasm of pleura
C7830	Secondary malignant neoplasm of unspecified respiratory organ
C7839	Secondary malignant neoplasm of other respiratory organs
C784	Secondary malignant neoplasm of small intestine
C785	Secondary malignant neoplasm of large intestine and rectum
C786	Secondary malignant neoplasm of retroperitoneum and peritoneum
C787	Secondary malignant neoplasm of liver and intrahepatic bile duct
C7880	Secondary malignant neoplasm of unspecified digestive organ
C7889	Secondary malignant neoplasm of other digestive organs
C7900	Secondary malignant neoplasm of unspecified kidney and renal pelvis
C7901	Secondary malignant neoplasm of right kidney and renal pelvis
C7902	Secondary malignant neoplasm of left kidney and renal pelvis
C7910	Secondary malignant neoplasm of unspecified urinary organs
C7911	Secondary malignant neoplasm of bladder
C7919	Secondary malignant neoplasm of other urinary organs
C792	Secondary malignant neoplasm of skin
C7931	Secondary malignant neoplasm of brain
C7932	Secondary malignant neoplasm of cerebral meninges
C7940	Secondary malignant neoplasm of unspecified part of nervous system
C79.49	Secondary malignant neoplasm of other parts of nervous system
C7951	Secondary malignant neoplasm of bone
C7952	Secondary malignant neoplasm of bone marrow
C7970	Secondary malignant neoplasm of unspecified adrenal gland
C7971	Secondary malignant neoplasm of right adrenal gland
C7972	Secondary malignant neoplasm of left adrenal gland
C7981	Secondary malignant neoplasm of breast
C7982	Secondary malignant neoplasm of genital organs
C7989	Secondary malignant neoplasm of other specified sites
C799	Secondary malignant neoplasm of unspecified site
C800	Disseminated malignant neoplasm, unspecified

9.3 [Appendix 3] Top 15 Most Expensive Outpatient Services for nmHSPC Patients

Patient Costs		**Payer Costs**	
Service Description	**Average Cost ($)**	**Service Description**	**Average Cost ($)**
Ambulance service, conventional air services, transport	$3,955	Sipuleucel-t	$40,380
Injection, rituximab 10 mg and hyaluronidase	$3,930	Revision or removal of implanted spinal neurostimulator	$28,268
Cochlear implant, external speech processor and controller	$2,805	Image-guided robotic linear accelerator-based sterotactic	$233,589
Nasal/sinus endoscopy, surgical	$2,224	Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral	$19,978
Injection, rasburicase, 0.5 mg	$2,071	Addition to lower extremity prosthesis	$16,646
Repair, revision, and/or reconstruction procedures on hands and fingers	$1,961	Injection, plerixafor, 1 mg	$14,778
Under percutaneous transcatheter closure procedures	$1,739	Revascularization, endovascular, open or percutaneous, iliac artery	$14,571
Hearing aid, digital, bunaural, ite	$1,731	Injection, siltuximab, 10 mg	$13,700
Injection, rituximab, 10 mg	$1,726	Injection, c-1 esterase inhibitor, cinryze, 10 u	$13,370
Arthroplasty, knee, condyle and plateau	$1,573	Percutaneous transluminal revascularization	$13,340
Hearing aid, digital, binaural, itc	$1,288	Revascularization, endovascular, open or percutaneous	$13,340
Hearing aid, digitally programmable, binaural, btw	$1,175	Injection, cabazitaxel, 1 mg	$11,201
Repair procedures on the penis	$1,155	Prothesis, penile, inflatable	$10,561
Fracture nasal inferior turbinates, therapeutic	$1,143	Injection, c-1 esterase inhibitor, berinert	$10,033
Nasal/sinus endoscopy, surgical	$1,143	Fracture and/or dislocation procedures on the leg (tibia and fibula) and ankle joint	$9,625

9.4 [Appendix 4] Top 15 Most Expensive Outpatient Services for mHSPC Patients

Patient		**Payer**	
Service Description	**Average Cost ($)**	**Service Description**	**Average Cost ($)**
Bronchoscopy, rigid or flexible	$5,355	Samarium sm-153 lexidronam	$76,490
Stereotactic radiosurgery	$1,980	Treatment of atrial fibrillation by ablation	$53,791
Injection procedure for Peyronie disease	$1,682	Injection ocrelizumab 1 mg	$35,401
Bronchoscopy, rigid or flexible	$1,516	Sipuleucel-t	$32,023
Targeted genomic sequence analysis panel, solid organ neoplasm	$1,409	Prosthesis, urinary sphincter	$26,941
Treatment of atrial fibrillation by ablation	$1,364	Radiopharmaceutical	$24,651
Laryngoscopy direct, with or without tracheoscopy	$1,165	Injection, octreotide	$20,548
Retinal tamponade device, silicone oil	$1,143	Radium ra-223 dichloride	$17,407
Injection of corpora cavernosa with pharmacologic agents	$865	Total knee arthroplasty	$14,542
Targeted genomic sequence analysis panel, solid organ neoplasm	$783	Repair of retinal detachment with vitrectomy	$8,003
Level 4 hospital ED visit	$746	Repair of detached retina and drainage of eye fluid between lens and retina	$6,102
Chemical cauterizaton of granulation tissue	$715	Insertion of replacement of permanent implantable defibrillator	$5,912
Intermittent limb compression device	$690	Convert nephrostomy catheter to nephroureteral catheter, percutaneous	$5,507
Injection, phenylephrine	$677	Stereotactic radiosurgery	$5,439
Removal of single or dual chamber pacing cardioverter-defibrillator electrode(s)	$649	Choline c-11, diagnostic	$5,425

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