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End Of Life Costs In Medicare Beneficiaries With Parkinson'S Disease

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END OF LIFE COSTS IN MEDICARE BENEFICIARIES WITH PARKINSON'S DISEASE

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Abstract

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder which is characterized by motor and non-motor disorders. The prevalence of PD is high among elderly patients. Due to the chronic nature of PD, increasing prevalence and ageing population, it is important to understand the burden of PD at various stages of patient's life so that value of PD therapies can be assessed. While direct healthcare costs during the life time of PD were assessed in previous studies, there is lack of information about end of life costs in PD patients. This dissertation aimed at filling the gap in literature by assessing end of life (EOL) costs in PD patients.

First, the duration of EOL period in PD patients was identified through a data-driven approach using Joinpoint regression (piece-wise linear regression). We determined the EOL period in PD patients to be the 9-mon period prior to death. Second, we assessed the direct healthcare cost burden of PD patients during the 9-mon EOL period. Further, a cohort of non-PD patients with comparable demographics and baseline comorbidity burden was identified. Based on the results from generalized linear models, we found that EOL costs were significantly higher in PD patients when compared to non-PD patients. Last, we assessed the EOL costs among patients who died at hospice facilities and non-hospice facilities. In order to compare EOL costs among patients who died at hospice facilities and non-hospice facilities, we used ordinary least squares (OLS) regression and an instrumental variable regression in order to minimize the bias due to lack of randomization. While results from OLS regression indicated that patients in hospice cohort had significantly higher costs when compared to non-hospice cohort, results from

IV regression indicated that costs are not significantly different in both the cohorts. Overall, our study helps understand the EOL cost burden of PD patients enrolled in Medicare so that treatment priorities can be set and value of PD therapies can be assessed.

Dedication

This dissertation is dedicated to my family for their love and support.

List of Abbreviations

2SLS	Two stage least squares regression
ADL	Activities of daily living
CCHS	Canadian Community Health Survey (CCHS)
CCI	Charlson comorbidity index
CHF	Congestive heart failure
CMS	Center for Medicare and Medicaid services
CPT	Current Procedural Terminology
DBS	Deep brain simulation
ED	Emergency department
EOL	End of life
ESRD	End stage renal disease
HHA	Home Health Agency
HR	Hazards ratio
HRQoL	Health related quality of life
HSA	Health services area
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
IRB	Institutional Review Board
IV Regression	Instrumental variable regression
KPMCP	Kaiser Permanente Medical Care Program
LTC	Long term care
MPC	Monthly percentage change
NCI	National Cancer Institute
NINDS	National Institute of Neurological Disorders and Stroke

OLS Regression	Ordinary Least Squares regression
PD	Parkinson’s disease
PDE	Part D Drug Event
PPPM	Per patient per month
PPV	Positive predictive value
RIF	Research identifiable files
SAS	Statistical analysis software
SD	Standard deviation
SNF	Skilled nursing facility
SPECT	Single photon emission CT (SPECT)
QoL	Quality of life

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CHAPTER 1

INTRODUCTION

Parkinson's disease

Overview of Parkinson's disease

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder which affects a person's ability to control their movements, body and emotions. It belongs to a group of conditions which are referred to as motor system disorders. Although the exact cause of PD is unknown it is attributed to the loss of neurons in the substantia nigra region of brain which leads to reduced dopamine production (Samii, Nutt, & Ransom). PD is also characterized by the accumulation of a protein, alpha-synuclein, also called Lewy Bodies in the brain stem, spinal cord and cortical regions (Lees, Hardy, & Revesz). Genetic mutations are likely to account for 10% of the cases while the majority (90%) of the cases are considered sporadic (De Lau & Breteler, 2006). The primary motor symptoms of PD include tremor, bradykinesia, rigidity and postural instability. Depression, apathy, sleep disorders and erectile dysfunction are some of the non-motor symptoms of PD (Chaudhuri & Schapira, 2009; Jankovic, 2008). The course of PD usually starts with a diagnosis and a maintenance phase where complete symptom relief can be achieved with pharmacological treatment. It is followed by a complex phase where motor complications and neuropsychiatric complications occur. The disease course ends with a palliative phase where advanced PD is treated followed by the end of life care (Clarke, Sullivan, & Mason, 2006; Lokk & Delbari, 2012).

Diagnosis

Currently, there are no reliable diagnostic tests or markers to diagnose PD. Hence, physicians rely on the presence of cardinal symptoms which include tremor, bradykinesia, rigidity and asymmetric onset for the clinical diagnosis of PD (Jankovic, 2008). Although functional neuroimaging techniques such as single photon emission CT (SPECT) or positron emission tomography (PET) are increasingly used in the early diagnosis of PD(Niethammer, Feigin, & Eidelberg, 2012), the adoption of these techniques is still low due to factors such as high cost and limited accessibility (Gelb, Oliver, & Gilman, 1999; Massano & Bhatia, 2012). Since the motor symptoms of PD can occur in other disorders as well physicians need to rule out symptoms including, but not limited to, dementia preceding motor symptoms, hallucinations unrelated to medications, freezing, supranuclear gaze palsy, severe symptomatic dysautonomia, prominent postural instability, unusual features early in the clinical course and other documented conditions known to produce parkinsonism such as focal brain lesions. Also, responsiveness to treatment with levodopa or a dopamine agonist is another indicator for PD diagnosis. Previous studies have indicated that around 94% to 100% of patients whose PD diagnosis was confirmed by autopsy have responded to levodopa therapy (Hughes, Daniel, & Lees, 1993; Louis, Klatka, Liu, & Fahn, 1997).

The National Institute of Neurological Disorders and Stroke (NINDS) outlined a diagnostic criteria for PD diagnosis. Diagnosis of PD is considered as probable if any three of the four cardinal symptoms are present, no symptoms of competitive diagnoses were present for a duration of more than three years and the patients shows a substantial and sustained response to levodopa or a dopamine agonist. The diagnosis is considered as possible if only two of the cardinal symptoms were present, no symptoms of competitive diagnoses were present for less than three years and the

patient has either substantial and sustained response to levodopa or a dopamine agonist or have not adequately been treated with them (Gelb et al., 1999).

Epidemiology

PD is the second most common neurodegenerative disorder in the US after Alzheimer's disease (De Lau & Breteler, 2006). It is also the second most common movement disorder after essential tremor (Alves, Forsaa, Pedersen, Gjerstad, & Larsen, 2008; Tanner & Aston, 2000). The incidence of PD is low before 50 years of age and increases with age up to 80. The median age-standardized incidence rate of PD in the US was estimated to be 14 per 100,000 people among the overall population and 160 per 100,000 in individuals aged 65 years and above (Hirtz et al., 2007). The prevalence of PD is more common in men when compared to women with the lifetime risk of developing PD being 2.0% in men and 1.3% in women (Elbaz et al., 2002). This study estimated that the total number of PD patients in the US was around 349,000 in the year 2005. Another study using the Medical Expenditure Panel Survey (MEPS) data estimated the prevalence rate of PD in population aged 45 and below to be 0.01% and in population over age 65 the prevalence rate was 1.2%. This study estimated that the total no of PD patients in 2010 were 630,000 which is projected to reach 819,000 by 2020, 1.06 million by 2030, 1.24 million by 2040 and 1.34 million by 2050 (Kowal, Dall, Chakrabarti, Storm, & Jain, 2013).

Previous epidemiological studies have reported inconsistent results about the distribution of PD by race in the US. Some studies have indicated that the prevalence of PD is higher in whites compared to non-whites (Kurtzke & Goldberg, 1988; Lanska, 1997; Lilienfeld et al., 1990; Wooten, Currie, Bovbjerg, Lee, & Patrie, 2004) while one study conducted in Northern Manhattan found a higher incidence in African Americans compared to Hispanics and whites (Mayeux et al., 1995). Another study using Kaiser Permanente Medical Care Program (KPMCP) database found

that the incidence of PD is highest in Hispanics followed by Asians, non-Hispanic whites and African Americans (Van Den Eeden et al., 2003).

The prevalence of PD is very high among Medicare beneficiaries. A retrospective observational study by Willis et al. found that the mean annual incidence from 2002 to 2005 was 445.9 per 100,000 population and the mean prevalence was 1,588.43 per 100,000 Medicare population. This study also found that the incidence of PD is higher in non-Hispanic whites when compared to other racial groups in the US. In terms of geographic region, Midwest and Northeast regions were found to have higher incidence and prevalence of PD (Wright Willis, Evanoff, Lian, Criswell, & Racette, 2010).

Treatment

There are no available therapies that can alter the underlying neurodegenerative process involved in PD (AlDakheel, Kalia, & Lang, 2014). Due to the lack of such therapies, symptomatic treatment is provided to patients to improve their physical, physiological morbidity and quality of life. The current interventions for PD management include pharmaceutical products, surgery and physical therapy (Lang & Lees, 2002). Pharmacological treatment is initiated in patients who begin to experience functional impairment and social embarrassment due to symptoms and the choice of therapy depends on age of onset and specific symptoms (Connolly & Lang, 2014). In patients with mild motor symptoms, treatment can be initiated with a monoamine oxidase type B inhibitor (MAOBI). In patients with impairment in activities of daily living, treatment is usually started with levodopa or a dopamine agonist. Although clinical trials have shown that levodopa has greater symptomatic benefit and lesser side effects when compared to dopamine agonists (Ferreira et al., 2013) there is growing evidence of better efficacy and lesser incidence of motor complications of dopamine agonists in early PD patients (Holloway et al., 2004; Rascol et al., 2000). Other drugs

like anticholinergics, amantadine and beta blockers are also used to initiate treatment in PD patients to avoid levodopa-related motor complications.

Surgical treatment options of PD include deep brain simulation (DBS) or neural transplantation. Currently three areas in the brain are usually targeted by surgery: globus pallidus interna (Gpi), the subthalamic nucleus (STN), and ventralis intermedius nucleus of the thalamus. While Gpi and STN are used to improve overall PD symptoms, a surgery in the ventralis intermedius area of brain is used in the treatment of tremor (Eskandar, Cosgrove, & Shinobu, 2001; Walter & Vitek, 2004).

Physical therapy and psychosocial counseling is provided to PD patients to improve their overall quality of life and reduce their dependency on care givers. Physical therapy in PD patients aims to prevent physical inactivity and falls (Lang & Lees, 2002).

Comorbidities

PD is usually associated with several comorbid conditions since the typical onset of PD is usually between 60 to 70 years of age and the prevalence of age-related comorbid conditions is very high in the population after 60 years of age. Some of the common comorbid disorders of PD include anxiety, depression and sleep disorders (Bergamasco, 2003; Martignoni et al., 2004). A Canadian study using data from the Canadian Community Health Survey (CCHS) found that urinary incontinence and arthritis were most frequent comorbidities which resulted in an incremental burden on PD patients. The study had shown that comorbidities of PD affected the health status of PD patients in terms of ambulation, dexterity and cognition (Pohar & Jones, 2009). A hospital based longitudinal study found that the most frequent comorbid events in PD patients

were trauma (30.5%) which is mostly due to falls and vascular disorders (29.3%) (Martignoni et al., 2004).

Burden associated with PD

Economic burden

The high prevalence of PD along with the ageing population is expected to impose an increasing social and economic burden on the patients, caregivers and the overall US healthcare and social support systems (De Lau & Breteler, 2006; Mateus & Coloma, 2013). Previous research has indicated that the burden of illness increases with PD disease severity along with a decrease in productivity (Chrischilles, Rubenstein, Voelker, Wallace, & Rodnitzky, 1998). In 2010, the direct cost to the US healthcare system incurred by PD patients was estimated to be $14 billion. The average per patient burden of PD care was estimated to be $22,800 annually. The total indirect costs due to PD were estimated at $6.3 billion which translates to approximately $10,000 per person. The study also found that the direct economic burden of PD is $8 billion higher than patients without PD (Kowal et al., 2013). Other studies have estimated that the total cost of PD to the US healthcare system ranged from $24 billion to $35 billion (Huse et al., 2005; Whetten-Goldstein, Sloan, Kulas, Cutson, & Schenkman, 1997).

Noyes et al. (2006) used the 1992–2000 Medicare Current Beneficiary Survey to evaluate the economic burden of PD among Medicare beneficiaries. The study found that Medicare beneficiaries with PD have a significantly higher healthcare costs when compared to beneficiaries without PD ($18,528 vs. $10,818). The likelihood of using medical care was 277% higher in PD patients and the likelihood of using long term care and Home Health care was 280% and 108% higher respectively (Noyes, Liu, Li, Holloway, & Dick, 2006). The direct costs and survival in

Medicare beneficiaries with early PD were previously studied. This study estimated that early PD patients have an excess cost of $2,399 in the one year period following diagnosis (Kaltenboeck et al., 2012). A retrospective database study in Medicare beneficiaries also showed that PD patients were more likely to have inpatient stays, skilled nursing facility (SNF) visits, Hospice visits and part D pharmacy visits when compared to non PD patients indicating higher healthcare resource use in PD patients in Medicare (Xie et al., 2015).

Patients with PD were estimated to have incurred $8.1 billion excess healthcare costs when compared to patients without PD. Of the $8.1 billion excess healthcare costs in PD patients, Medicare paid for approximately 24% ($1.9 billion). The excess healthcare costs in PD patients pose a significant burden to Medicare due to the high prevalence of PD in Medicare beneficiaries (Kowal et al., 2013).

Quality of life and mortality

PD has a significant negative impact on patient's quality of life (QoL). The impact of PD on patient's Health Related Quality of Life (HRQoL) begins with the onset of motor symptoms which reduce the patient's ability in performing activities of daily living (ADL) (Dodel, Berger, & Oertel, 2001). Depression and cognitive impairment are the main predictors of QoL in PD patients while physical, medication-related, and cognitive/psychiatric symptoms can also be significant predictors of QoL in PD patients as well (Rahman, Griffin, Quinn, & Jahanshahi, 2008).

Data from the National Vital Statistic Report indicate that PD was the 14th leading cause of death in the United States in 2013. The unadjusted death rate was 8.0 per 100,000 population and the overall age-adjusted death rate due to PD was 7.3 per 100,000 population. The death rate due to PD increases exponentially after age 65. The unadjusted death rate in population aged 65 to

74 was 12.7 per 100,000 and increased to 78.5 per 100,000 in the population of 75 to 84 years. In age groups 85 and over, the death rate due to PD was 231.6 per 100,000 population (Murphy, Xu, Kochanek, & Bastian, 2016).

Results from previous studies indicate that people who die with PD were older and also had higher comorbidities. Lethbridge et al. conducted a study using the death certificate database in Canada. They found that the most frequent comorbidities leading to death among PD patients were Alzheimer's disease/dementia (26.2%), pneumonia (22.3%), stroke (14.2%), ischemic heart disease (13.4%) and cancer (11.1%). The higher likelihood of having dementia or pneumonia in PD patients who died also has implications on the end of life (EOL) care for PD patients (Lethbridge, Johnston, & Turnbull, 2013).

The rate of mortality among elderly PD patients is also significantly higher when compared to Medicare beneficiaries without PD. The hazard ratio (HR) for early PD patients, PD patients with ambulatory assistance device, PD patients in skilled nursing facilities was 1.43 ($p < 0.001$), 2.37 ($p < 0.001$) and 3.34 ($p < 0.001$) respectively which indicates the higher risk of death in PD patients when compared to patients without PD (Kaltenboeck et al., 2012).

End of life care in PD

Palliative care is usually provided to patients during the end of life period. However, in the case of PD treatment, palliative care need not to be considered as terminal care, since palliative care usually starts before the terminal or end of life phase in patients who no longer respond to treatments. Palliative care is initiated when patients are unable to tolerate dopaminergic therapy, unsuitable for surgery or when advanced comorbidities are present (Clarke et al., 2006; MacMahon & Thomas, 1998). The mean duration of PD was estimated to be 14.6 years of which palliative

care is usually provided for 2.2 years (MacMahon, Thomas, & Campbell, 1999). Advanced PD patients are treated with interventions such as DBS surgery, intraduodenal levodopa infusion or apomorphine infusion. But these therapies are not indicated for end-stage PD patients since they can no longer tolerate the treatment (Thomas & MacMahon, 2004b). While early palliative care aims at minimizing dyskinesia and improving motor function of the patient, end-stage palliative care is focused on treating predominant non-motor symptoms and improving patient's quality of life. The common non-motor symptoms in end-stage PD patients include psychosis, depression, cognitive complications, sleep disturbance, apathy, autonomic dysfunction, orthostatic hypotension, gastrointestinal disorders, urologic dysfunction, pain, dysphagia and pressure ulcers (Lokk & Delbari, 2012).

In the initial stages of PD treatment, patients are usually supported by family caregivers. However, as the disease progresses patient's disability increases which leads to more dependency, and symptoms such as depression, hallucinations and falls get worse and thereby leading to increased caregiver burden. Such symptoms often lead the PD patients to seek institutional care (Lökk, 2008). Institutional care usually aims to prevent further complications and provide symptom relief. The focus of institutional care gradually changes from life prolonging therapy to palliative care (Thomas & MacMahon, 2004a).

End of life costs in PD

End of life costs in PD have been understudied. There were no studies in the US which looked at the end of life costs in PD patients. However, previous research has shown that nearly 30% of Medicare spending is spent on the 5% to 6% of patients who die in that year (Emanuel & Emanuel, 1994). Another study found that the average medical expenditure in the one year prior to death is $37,581 when compared to an average cost of $7,365 during the prior years (Hoover,

Crystal, Kumar, Sambamoorthi, & Cantor, 2002). Around 38% of Medicare beneficiaries had nursing home stay and 19% of Medicare beneficiaries used Hospice in the last year of their life (Hogan, Lunney, Gabel, & Lynn, 2001). These studies indicate that there is an excessive burden of end of life costs on Medicare, in general.

Need for the Study

Due to the increasing prevalence of PD there is a significant burden on the US healthcare system. Coupled with the ageing population, chronic nature of PD, the burden of PD on US healthcare and social support system is projected to be significantly higher in the future. Hence it is important to understand the burden of PD throughout the disease course so that treatment priorities can be appropriately set and the value of PD therapies can be measured (Kaltenboeck et al., 2012). While previous studies have assessed the costs of PD during the early course of disease such as the diagnosis and maintenance phase, no studies have assessed the costs of PD patients during the palliative phase and the end of life period.

Since palliative phase in PD starts with the worsening of symptoms when patients do not respond to any of the treatment interventions, palliative phase does not imply end of life period in PD patients. However, end-stage palliative care is usually provided during the end of life period. While previous studies have indicated that the average duration of palliative phase is 2.2 years, there is limited information in the literature regarding the average duration of end of life care provided to terminal PD patients. Also, there is a further need to understand the demographic and health related predictors of end of life costs such as age, race, and comorbidities in order to understand the drivers of end of life costs in the PD patients.

In addition, the impact of place at death on the end of life costs in PD patients is unknown. Considering the high spending of Medicare (30%) on 5% to 6% of patients who die in that year (Marshall, McGarry, & Skinner, 2011), it is essential to understand the drivers of end of life costs along with the impact of place at death on end of life costs in PD patients to develop strategies to reduce end of life costs without compromising on quality of care.

Specific Aims and Objectives

1. Use Joinpoint regression (piecewise regression) to identify the duration of the end of life phase in elderly Medicare patients with Parkinson's disease
2. To assess the end of life costs in Parkinson's disease patients enrolled in Medicare
    a. To assess the healthcare costs during the end of life phase in patients with Parkinson's disease who were enrolled in Medicare
    b. To assess the demographic and health related predictors including age, gender, race, comorbidities of end of life costs in Medicare patients with Parkinson's disease
    c. To assess the incremental end of life costs in Medicare patients with Parkinson's disease as compared to those without Parkinson's disease
3. To evaluate the relationship between place at death and end of life costs in Parkinson's disease patients enrolled in Medicare

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CHAPTER 2: PAPER 1

Using Joinpoint Regression to Identify the Duration of End of Life Phase in Patients with Parkinson's Disease

Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder which affects a person's ability to control their movements, body and emotions. It belongs to a group of conditions which are referred to as motor system disorders. Although the exact cause of PD is unknown it is often attributed to the loss of neurons in the substantia nigra region of brain which leads to reduced dopamine production (Samii, Nutt, & Ransom). PD is also characterized by the accumulation of a protein, alpha-synuclein, also called Lewy bodies in the brain stem, spinal cord and cortical regions (Lees, Hardy, & Revesz). Genetic mutations are likely to account for 10% of the cases while the majority (90%) of the PD is considered sporadic (De Lau & Breteler, 2006). The primary motor symptoms of PD include tremor, bradykinesia, rigidity and postural instability. Depression, apathy, sleep disorders and erectile dysfunction are some of the non-motor symptoms of PD (Chaudhuri & Schapira, 2009; Jankovic, 2008). The progression of PD is generally measured using a rating scale known as Hoehn and Yahr scale (Hoehn & Yahr, 1967). Based on this scale, PD progression is classified into five stages. Stages one and two represent the early stage where initial diagnosis of PD is made and patients experience mild symptoms. Stage three represents the mid stage where PD symptoms start affecting activities of daily living. Stages four and five represent the advanced stage of PD where patients experience severe symptoms such as

falling, poor balance, speech and swallowing problems and cannot perform activities of daily living (Clarke, Sullivan, & Mason, 2006; Müller et al., 2000).

Palliative care usually refers to care provided to patients with terminal illnesses who no longer respond to the available treatment options. Palliative care focuses on providing relief from pain and suffering along with improving the patient's overall quality of life (Cassel & Field, 1997; Lo, Quill, & Tulsky, 1999). Palliative care is usually initiated in PD patients who are unable to tolerate dopaminergic therapy, unsuitable for surgery or when advanced comorbidities are present (MacMahon & Thomas, 1998). End of life (EOL) is the final stage of life and care provided during EOL is focused on providing comfort to the patient (Curtis, 2008; Lunney, Lynn, Foley, Lipson, & Guralnik, 2003; Murray, Kendall, Boyd, & Sheikh, 2005). For terminal diseases such as cancer, palliative care is usually provided during the EOL phase. In case of PD patients, palliative care may not be considered as EOL care since it is initiated well before the EOL phase when PD treatments no longer provide benefits to the patients (Clarke et al., 2006). The diminished benefit of anti-Parkinson's medications and other treatments is usually evident during the mid-stage of the disease. During advanced stage of the disease, non-motor complications such as cognitive difficulty and dementia become more prevalent and patients may have physical disability, cognitive decline and other comorbid disorders (Bunting-Perry, 2006; Diamond & Jankovic, 2006). The higher likelihood of dementia and decline in cognitive function among end-stage PD patients were found to be the primary contributors of increased caregiver burden. The increase in caregiver burden along with the worsening of symptoms lead PD patients to seek institutional palliative care (Lökk, 2008).

The mean duration of PD was estimated to be 14.6 years, of which palliative care is usually provided for 2.2 years (MacMahon, Thomas, & Campbell, 1999). However, the duration of EOL

in PD patients is less than the 2.2 years since palliative care is initiated prior to the EOL phase. The duration of EOL depends on the illness trajectory of the disease. While diseases like terminal cancer often have a short EOL phase where the decline of patient's health is clearly evident, diseases such as Alzheimer's disease and PD have a prolonged time of receding health status therefore the duration of EOL care in PD patients is not clearly defined (Murray et al., 2005). Clinical decision aids are used by doctors to identify patients who are nearing the EOL and might benefit more from EOL care when compared to hospitalization or other treatments such as surgery or pharmacological treatment. These clinical aids are based on the factors which predicted short term and medium term death and are used to initiate EOL conversations with the patients. Having age ≥ 65, having emergency department visits, ICU admissions, hospitalization in the past year, cognitive impairment, evidence of frailty, evidence of active disease are some of the prominent factors which indicate that the patient is nearing the EOL phase (Cardona-Morrell & Hillman, 2015; Glare et al., 2008; Levine, Sachs, Jin, & Meltzer, 2007). These factors also indicate that healthcare costs will start to increase significantly once the patient approaches the EOL phase. Joinpoint regression is a piece-wise linear regression used in healthcare research to identify the best-fitting points where statistically significant changes in the trend of disease prevalence, mortality or costs occur. Also referred to as segmented regression, broken line regression or multiphase regression with continuity constraint (Kim, Fay, Feuer, & Midthune, 2000), Joinpoint regression has been used in to identify significant change in the trend of prevalence or mortality , as well as to identify the points where statistically significant changes in healthcare cost occur among patients with cancer, atrial fibrillation and COPD (Govindan et al., 2006; López-Campos, Ruiz-Ramos, & Soriano, 2014). Identifying the point before death where healthcare costs increase significantly enables clinicians, patients and their family to identify the EOL phase in PD patients

(Brown, Riley, Schussler, & Etzioni, 2002b). Hence, the objective of the current study was to identify the duration of the EOL phase in elderly PD patients enrolled in Medicare through a data-driven approach where healthcare costs are modeled to identify the time point prior to death where EOL care is initiated.

Methods

Data Source and Study Design

A retrospective study was conducted using 5% random national sample of Medicare administrative claims data from January 1, 2014 – December 31, 2016 which is available through the Centers for Medicare and Medicaid services (CMS) for research purposes. The Medicare claims database contains the claims of healthcare services offered to Medicare beneficiaries including inpatient, outpatient, long-term care, skilled nursing facility (SNF) and prescription drugs. The Medicare Beneficiary Summary file contains information related to the patients' demographics and enrollment status. The Medicare Carrier file contains claims related to the services provided by non-institutional providers such as physicians, nurse practitioners and physician assistants. Outpatient file contains the claims related to the services performed by institutional outpatient providers like hospitals, renal dialysis facilities and community mental health centers etc. Inpatient and SNF services claims were provided in the MedPAR files. These files contain procedure codes of services which were classified using the Current Procedural Terminology (CPT) along with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 or ICD-10 diagnosis codes and the amount reimbursed for the services. Records for prescription drugs dispensed under Medicare part D were included in the Part D Drug Event (PDE) file. An encrypted beneficiary identification number was used to link the claims from

all files. The study was approved by the Institutional Review Board (IRB) of the University of Mississippi.

Patient selection

The sample for this study contained Medicare beneficiaries who: (1) were ≥ 65 years of age as of January 1, 2014 (2) who died during the one year period between January 1, 2016 to December 31, 2016 (3) who had continuous enrollment in Medicare Parts A, B, & D from January 1, 2014 until death. Patients with PD were identified from administrative claims databases using ICD-9-CM/ICD-10-CM diagnosis codes from 2014 to 2016. Previously published approaches to identify PD relied on ICD-9 diagnosis codes 332.0, 332.1, 333.0, 333.1 in medical claims and the use of levodopa from pharmacy claims. However, the sensitivity of these approaches was less than ideal varying from 66.0% to 89.2% (Butt et al., 2014; Noyes, Liu, Holloway, & Dick, 2007; Szumski & Cheng, 2009). In the current study, the identification of Medicare beneficiaries with PD was based on the approach outlined by Szumski et al. (2009). Patients with at least two medical claims with ICD-9 diagnosis code of 332.0 or ICD-10 diagnosis code of G20 in the one-year period prior to index date were identified as PD patients. This approach of identifying patients with PD was found to have a sensitivity of 89.2% and a positive predictive value (PPV) of 79.4% (Szumski & Cheng, 2009). Patients who were enrolled in managed care plans, patients with dual eligibility and patients with end stage renal disease (ESRD) (ICD-9-CM code 585.6, ICD-10 code N18.6) or cancer (ICD-9-CM/ICD-10-CM codes presented in Table 1) were excluded from the study. The date of death was identified from the Medicare Beneficiary Summary file and was considered as the index date. A diagrammatic representation of patient selection was provided in Figure 1.

Analysis

The baseline descriptive characteristics for all subjects were reported using means and standard deviations for continuous variables, and number and percentages for categorical variables. Joinpoint regression analysis was performed using Joinpoint regression software, a software program developed by the Surveillance Research Program of the National Cancer Institute (NCI) (Joinpoint regression program, NCI, Bethesda, MD). All-cause healthcare costs were calculated as the sum of costs incurred towards inpatient visits, outpatient visits, emergency department (ED) visits, home health visits, hospice visits and pharmacy prescriptions. Average monthly all-cause costs was aggregated and modeled backwards from the date of death to the previous 24 months. The model selection for Joinpoint regression analysis was informed by the Cook-Weisberg test for heteroscedasticity and the Breusch-Godfrey LM test for autocorrelation. A Joinpoint is a point of inflection where statistically significant change in the trend of monthly costs occurs. The study used a minimum of 1 joinpoints to a maximum of 4 joinpoints to identify the best fit of data (Kim et al., 2000). The joinpoints prior to death was used to identify the duration of EOL phase in PD patients. In order to identify the best fit of the data, a sequential algorithm-based method called grid search method was used. Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc., Cary, NC) was used for data management in the study.

Results

A total of 1,178 PD patients who died during the study index period met the study inclusion criteria (Figure 1). Mean age of these patients was 83.6 (± 7.3) years with a high proportion of patients in the age group 86 years and older (43.1%). The percentage of men (52.6%) is slightly higher than women and majority of the patients were non-Hispanic white (94.3%). Average comorbidity burden, as measured by Charlson comorbidity index score (CCI) was 3.8 (± 2.2) and more than half of the patients had at least 4 or more CCI score indicating high comorbidity burden

in these patients. The most frequent baseline comorbidities were dementia (77.3%), stroke (59.6%) and congestive heart failure (46.1%). The description of baseline demographic and clinical characteristics of study sample was presented in Table 2.

Average all-cause monthly costs were lowest during the 24th month prior to death ($4,661 ± $13,706) and increased as the patient neared end of life with highest average monthly costs during the 1-month period prior to death ($28,487 ± $54,097). Average costs by month was found to have serial correlation based on results from Bresuch-Godfrey LM test and was also found to have heteroskedasticity.

Results from the Joinpoint regression model indicate that there is a statistically significant inflection point in the trend of monthly costs at month 3 (monthly percent change [MPC]: 30.86%; confidence interval [CI]: 51.1% to 21.5%) and month 9 (MPC: 10.78%; CI: 14.9% to 6.5%) prior to death (Figure 2). Based on these results and clinical judgement, the duration of end of life period in PD patients was identified as the 9-month period prior to death. In addition, all-cause costs during the 3-mon EOL period were assessed as sensitivity analysis.

All-cause healthcare costs along with the components of costs were assessed during the 3-month and 9-month period prior to death and the results are presented in Table 3. Mean (SD) all-cause healthcare costs during the 3-month period prior to death was estimated to be $20,576 (20,474). Average costs were driven by inpatient costs [Mean (SD): $11,810 (20,474)] followed by costs in a palliative care setting [Mean (SD): $4,815 (1,502)]. All-cause healthcare costs during the 9-month period prior to death were estimated to be $46,339 (37,863) and were driven by inpatient costs [Mean (SD): $21,252 (30,845)] followed by costs in palliative care setting [Mean (SD): $11,810 (20,474)].

Discussion

Using a data-driven Joinpoint regression approach, we found that there is a significant change in the trend of all-cause healthcare costs at the 3-and 9-month time points prior to death among Medicare beneficiaries with PD which indicates a possible shift in the focus of patient and family from active treatment to palliative care. Considering the high Medicare spending in the final year of patient's lives (one-fourth of overall Medicare expenditures) there is increased focus in understanding costs in Medicare patients during their EOL period (Duncan, Ahmed, Dove, & Maxwell, 2019). There is no consistent basis to define EOL phase and prior studies defined EOL phases arbitrarily or based on clinical judgement (Brown, Riley, Schussler, & Etzioni, 2002a). Hence, our study used a data-driven approach using Joinpoint regression which can provide a basis for identification of phases of care in PD patients. Our study identified that there is significant change in trend of costs during months 3 and 9 prior to death. Based on clinical judgement, our study will consider the 9-month period prior to death as EOL phase in PD patients. The 9-month EOL phase in PD patients is longer than the 3-mon or 5-mon period prior to death used as EOL period using a data-driven approach in patients with metastatic breast cancer and metastatic melanoma respectively (Atkins, Coutinho, Nunna, Gupte-Singh, & Eaddy, 2018; Brown et al., 2002a).

To our knowledge, our study is the first study to use a data-driven approach with Joinpoint regression to estimate the duration of EOL phase in progressive neurodegenerative diseases such as PD.

Our study estimated that the average 3-month end of life costs for elderly PD patients was $20,576. The EOL costs were lower than EOL costs in cancer patients which ranged from $24,073 during the 3-month period prior to death in ovarian cancer patients to around $32,000 during the

3-month period prior to death in metastatic breast cancer patients (Bramley, Antao, Lunacsek, Hennenfent, & Masaquel, 2016; Urban, He, Alfonso, Hardesty, & Goff, 2018). The 9-month EOL costs in our study were estimated to be $46,339, which were significantly lower than the 6-month EOL costs estimated in a sample of patients with malignant cancers to be $74,212 possibly due to the high costs associated with cancer treatments such as chemotherapy, immuno-oncology treatments which require hospitalizations along with supportive care therapies in cancer patients (Chastek et al., 2012). While EOL costs in PD patients were lower than cancer patients, costs were higher when compared to a general sample of Medicare patients in the US. All-cause costs in 6-month EOL period in general sample of Medicare patients was estimated to be $18,500 which is lower than both the 3-mon EOL period and 9-month EOL period costs in PD patients. These results indicate that EOL costs are higher in PD patients when compared to a general sample of Medicare population even after adjusting for inflation which is possibly due to the lower use of acute care or SNF services in EOL period in this sample of general Medicare patients (Bekelman et al., 2016).

This study has several strengths. First, the current study used a data-driven approach using Joinpoint regression to model healthcare costs during the months prior to death and identify the points of inflection where there is a significant change in trend of costs. We used clinical judgement along with the data-driven approach to identify the EOL period in PD patients in contrast with previous studies which used clinical judgement only. Second, the study used Medicare administrative claims data to assess healthcare costs in PD patients. Since the prevalence of PD is significantly higher in patients aged 65 or more, the use of a Medicare sample provides the opportunity to assess the real-world costs among a general sample of elderly PD patients receiving care in real world clinical settings in the US. Third, the availability of reliable death information of patients in Medicare administrative claims data through the social security

administration provides a better estimate of EOL costs when compared to commonly used proxy algorithms for death (Bert Kestenbaum, 1992; Bertram Kestenbaum & Reneé Ferguson, 2002). Death is identified in the proxy algorithms using hospitalization and ED visits for a life threatening event followed by loss of enrollment for insurance benefits. This approach may overinflate costs in the EOL period as patients have significant costs associated with the life threatening event (Atkins et al., 2018; Joyce et al., 2004). However, results from this study also should be interpreted in light of certain limitations. Current Medicare administrative claims data does not include any information about patients enrolled in Medicare advantage or supplemental Medicare plans and thus may not be representative of non-FFS Medicare patients. It should be noted that although the current study used a data driven approach to identify the EOL phase among elderly patients with PD, clinical judgement should be used in conjunction with the data-driven approach to determine the duration of EOL phase in PD patients. Also, the current study did not assess costs in PD patients after their initial diagnosis and thus may not support estimation of initial phase of care in PD patients.

Conclusion

This study also forms a basis to identify phases of PD which can help build phase-based costing models. Phase-based costing is a novel approach where the duration of disease is divided into several phases such as initial, interim and end of life phase and average costs are estimated during each phase and the mean lifetime costs of disease are calculated (Wijeysundera, Wang, Tomlinson, Ko, & Krahn, 2012). In the current literature, while phase-based costing has been widely used to assess lifetime costs of oncology conditions (Aly, Clancy, Ung, Agarwal, & Shah, 2018; Atkins et al., 2018; Liu et al., 2016). the use of phase-based costing approaches in non-oncology conditions is limited since the overall duration of some of these conditions may span

over several years (Tawfik et al., 2016). PD, being a progressive neurodegenerative disorder with a mean duration of PD to be 14.6 years (MacMahon et al., 1999), may be required to be divided into more than three phases. Further studies with longer follow-up periods are required to identify phases of care during early stages of PD, assess the costs during these phases so that phase-based costing models are developed to estimate life time costs of PD.

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APPENDIX A

Table 1.1: ICD-9-CM and ICD-10 codes for identification of cancer	
ICD-9-CM code	**Description**
140.xx - 149.xx	Malignant Neoplasm Of Lip, Oral Cavity, And Pharynx
150.xx - 159.xx	Malignant Neoplasm Of Digestive Organs And Peritoneum
160.xx - 165.xx	Malignant Neoplasm Of Respiratory And Intrathoracic Organs
170.xx - 176.xx	Malignant Neoplasm Of Bone, Connective Tissue, Skin, And Breast
179.xx - 189.xx	Malignant Neoplasm Of Genitourinary Organs
190.xx - 199.xx	Malignant Neoplasm Of Other And Unspecified Sites
200.xx - 209.xx	Malignant Neoplasm Of Lymphatic And Hematopoietic Tissue
230.xx - 234.xx	Carcinoma In Situ
235.xx - 238.xx	Neoplasms Of Uncertain Behavior
239.xx	Neoplasms Of Unspecified Nature

Table 1.2. Characteristics of Parkinson's disease (PD) patients who died during the study index period

Demographic and clinical characteristics	All Parkinson' disease patients (N = 1,178)	
Age in years, Mean (SD)	83.6	(7.3)
Age Group (N, %)		
65-70	67	(5.7%)
71-75	114	(9.7%)
76-80	185	(15.7%)
81-85	304	(25.8%)
>85 years	508	(43.1%)
Gender (N, %)		
Male	620	(52.6%)
Female	558	(47.4%)
Ethnicity (N, %)		
Caucasian	1111	(94.3%)
African American	37	(3.1%)
Other	30	(2.5%)
Region (N, %)		
Northeast	213	(18.1%)
South	445	(37.8%)
Midwest	311	(26.4%)
West	207	(17.6%)
Other	2	(0.2%)
CCI (Mean, SD)	3.79	(2.2)
CCI category		
0	71	(6.0%)
1	121	(10.3%)
2	165	(14.0%)
3	206	(17.5%)
4+	615	(52.2%)
Comorbidities of interest		
AZ	331	(28.1%)
Dementia	911	(77.3%)
Pneumonia	267	(22.7%)
Stroke	702	(59.6%)
CHF	543	(46.1%)

Table 1.3. All-Cause healthcare costs during the 3-month and 9-month period prior to death in patients with PD

	All PD Patients N = 1,176	
Direct Healthcare Costs		
All-cause Costs During 3-mon EOL		
Total costs	$20,576	($20,474)
Inpatient costs	$11,810	($18,518)
Outpatient costs	$3,065	($3,511)
Pharmacy costs	$886	($2,116)
Palliative care costs	$4,815	($1,502)
All-cause Costs During 9-mon EOL		
Total costs	$46,339	($37,863)
Inpatient costs	$21,252	($30,845)
Outpatient costs	$6,355	($5,974)
Pharmacy costs	$2,950	($6,270)
Palliative care costs	$10,396	($12,065)

APPENDIX B

Figure 1.1: Patient selection

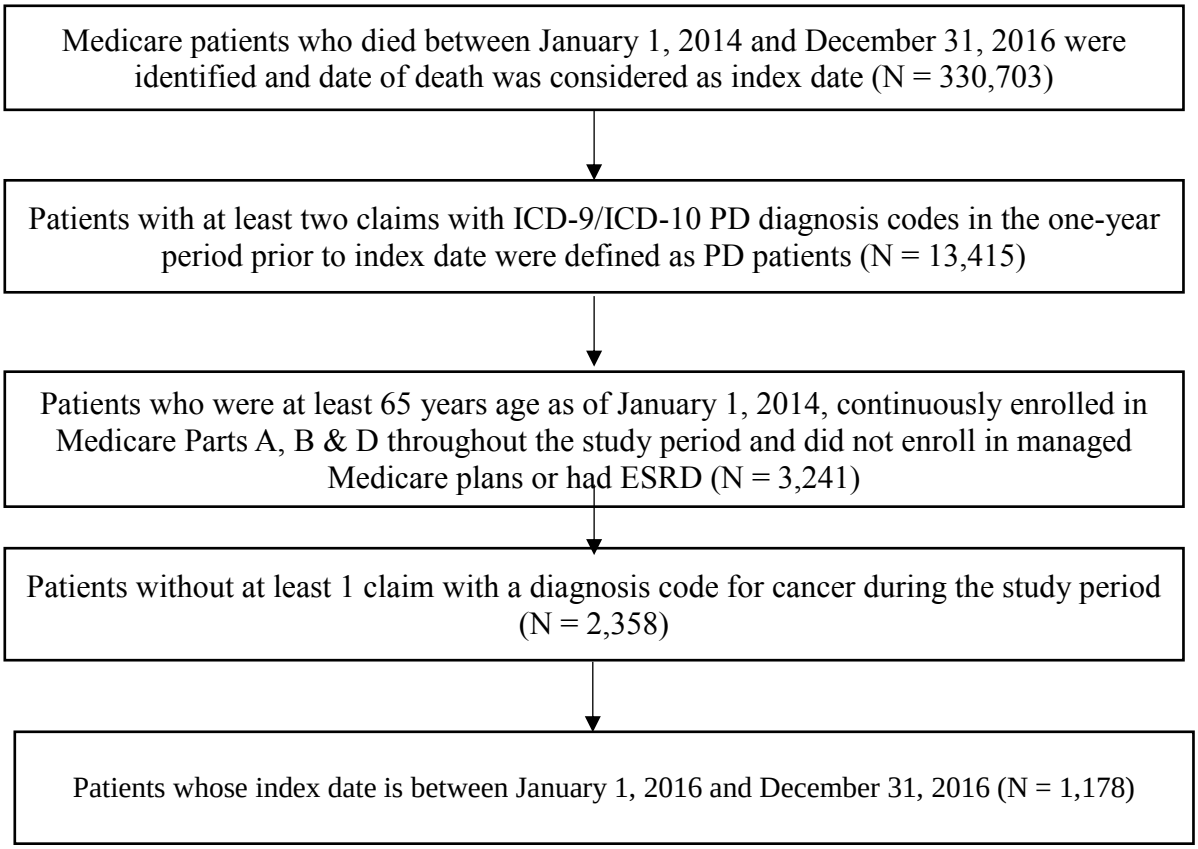

Figure 1.2: Duration of EOL phase in PD patients

CHAPTER 3: PAPER 2

Predictors of End of Life Healthcare Costs in Medicare Beneficiaries with Parkinson's Disease

Introduction

Parkinson's disease (PD) is a progressive neurological disorder which is characterized by various motor and non-motor symptoms which can impact the patient's functional status. It belongs to a group of conditions which are referred to as motor system disorders. The exact cause of PD is unknown, but the reduced dopamine production due to degeneration of dopamine-producing cells in the sustantia nigra region of brain is believed to be the main cause of PD (Samii, Nutt, & Ransom). PD is usually diagnosed by the asymmetric occurrence of cardinal symptoms which include tremor, bradykinesia, rigidity (Jankovic, 2008). There are no available therapies that can alter the underlying neurodegenerative process involved in PD (AlDakheel, Kalia, & Lang, 2014). Due to the lack of curative therapies, symptomatic treatment is provided to PD patients to manage symptoms and improve quality of life. The current interventions for PD include pharmaceutical treatment, surgery and physical therapy (Lang & Lees, 2002). The course of PD usually starts with a diagnosis and maintenance phase where complete symptom relief is obtained by pharmacological treatment. It is followed by a complex phase where motor complications and neuropsychiatric complications occur. The disease course ends with a palliative phase where end of life (EOL) care is provided (Clarke, Sullivan, & Mason, 2006; Lokk & Delbari, 2012).

Medicare beneficiaries with PD were found to have incurred significantly higher costs ($18,528 vs. $10,818) when compared to Medicare beneficiaries without PD. The likelihood of using medical care services was 277% higher in PD patients and particularly the likelihood of using long-term care (LTC) services and Home Health care was 280% and 108% higher, respectively when compared to patients without PD (Noyes, Liu, Li, Holloway, & Dick, 2006). Also, PD patients were more than two times likely (OR: 2.12, 95% CI: 1.99 to 2.25) to use Home Health services when compared to patients without PD (Bhattacharjee et al., 2015). A study in Medicare patients has shown that 73.5% of PD patients were hospitalized, 69.8% used Hospice services and 44% used skilled nursing facility (SNF) services during the last year of life (Willis et al., 2012). These studies have shown that the incremental healthcare resource use and costs in Medicare patients with PD are significant.

PD is usually associated with several comorbid conditions since the typical onset of PD is between 60 to 70 years of age and the prevalence of age-related comorbid conditions is high in this population. Some of the common comorbid disorders of PD include anxiety, depression and sleep disorders (Bergamasco, 2003; Martignoni et al., 2004). A hospital based longitudinal study reported that the most frequent comorbid events in PD patients were trauma (30.5%) which is mostly due to falls and vascular disorders (29.3%) (Martignoni et al., 2004). Another study looked at the prevalence of neurological, cardiovascular and other comorbidities in PD patients who died (Lethbridge, Johnston, & Turnbull, 2013) and found that PD patients had higher comorbidities compared to the general population. Alzheimer's disease (26%), pneumonia (22%), stroke (14%), chronic ischemic heart disease (13%) and cancer (11%) were found to be the most prevalent comorbidities in PD patients. While the proportion of patients with comorbidities such as Alzheimer's disease, pneumonia and stroke is higher in PD patients when compared to age and

sex matched sample of non-PD patients, the proportion of patients with ischemic heart disease and cancer is lower when compared to non-PD patients.

Studies have shown that the use of medical services such as hospital, Home Health, SNF, LTC or Hospice services in PD patients during the EOL period is generally due to complications and comorbidities associated with PD rather than PD itself. Terminal PD patients often have cognitive decline, motor and neuropsychiatric complications therefore resulting in higher healthcare costs during the EOL period. For example, one study shows that terminal PD patients were hospitalized for cardiovascular diseases (15%), infections (29.5%) and were rarely hospitalized for PD itself (4.2%) (Willis et al., 2012). Another study reports that hip fracture and dementia were significant predictors of using LTC services during the last year of life (Safarpour et al., 2015).

Previous research has shown that nearly 30% of Medicare annual spending is spent on the 5 to 6% of patients who die in that year (Emanuel & Emanuel, 1994). Another study found that the average medical expenditure for Medicare patients in the one year prior to death is $37,581 when compared to an average cost of $7,365 during the prior years (Hoover, Crystal, Kumar, Sambamoorthi, & Cantor, 2002). Elderly Medicare beneficiaries with PD have higher comorbidity and economic burden when compared to patients without PD (Lethbridge et al., 2013; Martignoni et al., 2004; Noyes et al., 2006; Safarpour et al., 2015). However, there is a lack of information about the EOL costs in these patients. Considering the high use of Hospice, SNF/ LTC and Home Health services during the last year of life of PD patients, we hypothesized that EOL costs in PD patients will be significantly higher when compared to patients without PD. The current study aims to assess the healthcare costs of PD patients during the EOL period and estimate the incremental costs as compared to patients without PD. Furthermore, understanding the drivers of costs during

the EOL period can assist in the planning of EOL care for PD patients. Hence, the study also aims to assess the predictors of EOL costs in PD patients enrolled in Medicare.

Methods

Data Source and Study Design

A retrospective matched cohort study was conducted using data from the 5% random national sample of Medicare administrative claims from January 1, 2014 – December 31, 2016. The data is made available through the Centers for Medicare and Medicaid services (CMS) for research purposes. This database contains the claims of healthcare services offered to Medicare beneficiaries including inpatient, outpatient, long-term care, skilled nursing facility (SNF), Home Health, Hospice and prescription drugs. The Medicare Beneficiary Summary file contains information related to patients' demographics and enrollment status. The Medicare Carrier file contains claims related to services provided by non-institutional providers such as physicians, nurse practitioners and physician assistants. Outpatient file contains the claims related to the services performed by institutional outpatient providers like hospitals, renal dialysis facilities and community mental health centers. Inpatient, SNF and LTC services claims were provided in the MedPAR files. These files contain procedure codes of services which were classified using the Current Procedural Terminology (CPT) along with ICD-9/ICD-10 diagnosis codes and the amount reimbursed for the services. Records for prescription drugs dispensed under Medicare part D were included in the Part D Drug Event (PDE) file. An encrypted beneficiary identification number is used to link the claims. This study obtained approval from the Institutional Review Board (IRB) of the University of Mississippi.

Patient Selection

The sample for this study contained Medicare beneficiaries who: (1) were ≥ 65 years of age as of January 1, 2014 (2) who died during the index period between April 1, 2015 to December 31, 2016 (3) who had continuous enrollment in Medicare Parts A, B, & D from January 1, 2014 until death. Previously published approaches to identify PD relied on ICD-9 diagnosis codes 332.0, 332.1, 333.0, 333.1 in medical claims and the use of levodopa from pharmacy claims. In the current study, the identification of Medicare beneficiaries with PD will be based on the approach outlined by Szumski et al. (2007) where patients with at least two medical claims with ICD-9 diagnosis code 332.0 or ICD-10 diagnosis code G20 in the one-year period prior to index date were identified as PD patients. This approach was found to have a sensitivity of 89.2% and a positive predictive value (PPV) of 79.4% (Szumski & Cheng, 2009). In the current study, date of death was identified from the Medicare Beneficiary Summary file and was considered as the index date. The duration of EOL period was determined as the 9-month period prior to death using results from the Joinpoint regression analysis reported in the previous study and the six month period prior to EOL period was considered as the baseline period. Sensitivity analysis was performed by defining the EOL period as 3 months prior to death. Patients who were enrolled in managed care plans, patients with dual eligibility and patients with end stage renal disease (ESRD) or cancer (ICD-9-CM/ICD-10-CM codes presented in Table 1) from January 1, 2014 until index date) were excluded. A diagrammatic representation of patient selection is provided in Figure 1.

Matched Cohorts

PD patients who died between April 1, 2015 and December 31, 2016 were matched on a 1:4 ratio to non-PD patients who died during the same period. Deyo adaptation of Charlson Comorbidity Index (CCI) was modified by excluding diagnosis codes for cancer and metastases. Modified CCI was calculated during the baseline period using ICD-9/ICD-10 diagnosis codes from

MedPAR, Carrier and Outpatient files (Deyo, Cherkin, & Ciol, 1992). PD and non-PD cohorts were matched using a greedy match algorithm on modified CCI along with age at death (±3 years) and gender to obtain a comparable comorbidity profile in both cohorts. This approach allowed the assessment of incremental cost due to PD during the EOL period.

Measures

Outcome Variable

The outcome variables assessed in the study were all-cause healthcare costs. Costs were measured during the EOL period from the Medicare perspective and hence payments made by patients such as co-payments and deductibles were not included. All-cause healthcare costs include payments made for outpatient services, emergency department (ED) visits, inpatient services, SNF/LTC services, Home Health services, Hospice services and prescription drug costs. Office visits were defined as claims with place of service codes 11 (office), 22 (outpatient hospital), 71 (state or public health clinic), or 72 (rural health clinic) or procedure codes 99201-99215, 99241-99245, 99354-99355, 99381-99429 in the Carrier file and Outpatient file.

Predictors of EOL Costs

The key predictors of EOL costs were the severity of PD and comorbidities. Severity of PD was assessed in the baseline period through a proxy measure based on the mean daily tablet load of PD medication approach proposed by Fargel et al. (see Table 2 for the list of PD medications used). Fargel et al, reported that the mean daily tablet load of early stage PD patients was 3.2 tablets of PD-related medications. In advanced PD patients the mean daily tablet load ranged from 8.4 to 9.9 tablets of PD-related medications (Fargel, Grobe, Oesterle, Hastedt, & Rupp, 2007). In the current study, patients with a mean daily PD-related tablet load of more than

8, 4 to 7, 3 and less were categorized as advanced PD patients, mid stage PD patients and early stage PD patients, respectively. The mean daily PD-related tablet load was calculated during the baseline period as well. Comorbidities include Alzheimer's disease, dementia, pneumonia, stroke, ischemic heart disease and congestive heart failure (CHF) were included in the model as predictors. Demographic predictors included in the study were age, gender, race and geographic region. Age was calculated at death and was used as a continuous variable. Gender was measured as male or female. Race was used as a categorical variable and was categorized as non-Hispanic white, African American and other racial group (including Asian, Hispanic, Native Hawaiian, Pacific Islander, American Indian or Alaskan Native, or unknown race). Geographic region was categorized as Northeast, South, Midwest and West.

For the matched cohort analysis comparing EOL costs in the PD and non-PD cohort, the diagnosis of PD was the primary independent variable of interest. Race, geographic region and comorbid conditions of interest were controlled for in the model.

Statistical Analysis

All statistical analyses were conducted using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC). Descriptive characteristics for the PD cohort and non-PD cohort were reported using means and standard deviations (SD) for continuous variables and frequencies and percentages were reported for categorical variables. Generalized linear models were used to identify the predictors of EOL costs and calculate the incremental all-cause cost burden of PD patients. Due to the presence of zero values for some patients for inpatient costs, outpatient costs, pharmacy and palliative care costs, two-part models were used to estimate adjusted costs for these cost components. The first part of the model used a logistic regression to predict the probability of observing non-zero costs and the second part of the model was a generalized linear model with

gamma distribution and log link for recipients with non-zero costs. Final costs estimates were estimated by multiplying probability of non-zero costs estimated in part one and estimated costs from part two. Adjusted costs were calculated using LSMEANS option in SAS in both generalized linear models and two-part models. Pregibon goodness-of-link test was used to examine adequacy of hypothesized link for the data and Modified Park Test (MPT) was used to identify the appropriate family of the generalized model. Informed by Pregibon goodness-of-link test and modified Park's test, a generalized model with log link and gamma distribution was used to identify significant predictors of EOL costs in PD patients when compared to age-, sex- and CCI-matched non-PD cohort with race, geographic region, Alzheimer's disease, dementia, pneumonia, stroke, ischemic heart disease and congestive heart failure as predictors. Costs were adjusted to 2016 USD using the medical component of consumer price index (CPI).

For the matched sample, unadjusted costs were compared using Wilcoxon signed-rank test. EOL costs between PD cohort and non-PD cohort were compared using generalized linear models. Adjusted mean all-cause healthcare costs were obtained from the generalized model after controlling for race, geographic region and comorbidities of interest.

Results

A total of 11,130 patients who died during the index period (Apr 1, 2015 to Dec 31, 2018) were included in our study. Of these, 2,226 were PD patients and 8,904 patients were non-PD patients matched on age, gender, and CCI with the PD cohort. The demographic and clinical characteristics of PD cohort and non-PD were presented in Table 3. The matched PD and non-PD cohorts were similar in terms of age, gender and comorbidity burden as assessed by CCI. While non-Hispanic whites comprised on more than 90% of both cohorts, the percentage was higher in

PD cohort when compared to non-PD cohort (94.4% in PD cohort vs. 91.9% in non-PD cohort, p <0.0001).

Regarding the comorbidities of interest, prevalence of comorbidities is significantly higher in PD cohort when compared to non-PD cohort with the exception of CHF. CHF was the most frequently found comorbidity in the overall cohort and the prevalence of CHF was significantly higher in the non-PD cohort when compared to PD cohort (52.6% vs. 44.3%, $p < 0.0001$). The prevalence of dementia and stroke was significantly higher in the PD cohort when compared to non-PD cohort. Dementia was present in 75.1% in PD cohort vs 42.8% in non-PD cohort ($p < 0.0001$) whereas 55.8% in PD cohort vs. 44.6% in non-PD cohort ($p < 0.0001$) had stroke. The prevalence of another progressive neurological disorder, Alzheimer's disease, was significantly higher in PD cohort when compared to non-PD cohort (16.4% in PD cohort vs. 9.6% in non-PD cohort, $p < 0.0001$).

The 9-month EOL costs were significantly higher in PD cohort (unadjusted costs: $45,701 vs. $39,775, $p < 0.001$; adjusted costs: $48,429 vs. $43,054, $p = 0.0324$). 9-mon EOL costs were driven by hospitalization costs in both cohorts (46% in PD cohort and 66% in non-PD cohort). The percentage of 9-mon EOL costs incurred towards palliative care (home health and hospice) were significantly higher in PD cohort when compared to non-PD cohort (21% in PD cohort vs. 14% in non-PD cohort) indicating the higher use and costs incurred towards EOL services in PD patients when compared to patients with similar age, sex and comorbidity burden. The 9-mon EOL costs were significantly higher in PD cohort when compared to non-PD patients ($\beta = 0.12$, 95% CI: 0.07 to 0.16, $p = < 0.0001$). While no racial differences were found to be significant, 9-mon EOL costs were higher in Midwest and Western regions of US when compared to the Northeastern US.

In terms of comorbidities, Alzheimer's disease, dementia, pneumonia, stroke and CHF were found to be significant predictors of 9-month EOL costs. Congestive heart failure is the strongest predictor of EOL costs with β = 0.47 (95% CI: 0.43 to 0.50, p < 0.0001) followed by pneumonia (β = 0.30; 95% CI: 0.26 to 0.33, p < 0.0001) and stroke (β = 0.30; 95% CI: 0.26 to 0.33, p < 0.001). Neurological comorbidities such as dementia (β = 0.12, 95% CI: 0.08 to 0.16, p < 0.0001) and Alzheimer's disease (β = 0.06, 95% CI: 0.01 to 0.12, p = 0.033) were found to be significant predictors of EOL costs. These results also indicate that patients with multiple neurological conditions have significantly higher EOL costs when compared to patients without.

In contrast, results of the sensitivity analysis show that the mean unadjusted all-cause costs during the 3-month EOL period were significantly lower in PD cohort when compared to non-PD cohort ($20,769 vs. $21,237, p = 0.0006). However, after adjustment for baseline covariates, mean all-cause costs were higher in PD cohort when compared to non-PD cohort ($24,248 vs. $23,978, p = 0.7539), but the difference was not statistically significant.

Results from the generalized model indicate that the 3-mon EOL costs are not significantly different in PD cohort and non-PD cohort (β = 0.008, 95% CI: -0.04 to 0.06, p = 0.7539). African Americans were found to have significantly higher EOL costs when compared to non-Hispanic whites (β = 0.16, 95% CI: 0.07 to 0.25, p = 0.0005). Results from the model also indicate that patients in Midwest and Western regions of the US have significantly lower 3-mon EOL costs when compared to patients residing in the Northeast US (β for MW = - 0.11, 95% CI: -0.16 to -0.05, p = 0.0002, β for W: -0.10, p = 0.001).

Discussion

Results from our study indicate the costs in PD patients were significantly higher when compared to non-PD patients of comparable demographics and baseline comorbidity burden during the 9-month EOL period before death. In sensitivity analysis, while the results were not statistically significant, adjusted 3-month EOL costs were also higher in PD patients when compared to non-PD patients. Our results indicate that EOL costs in PD patients are driven by hospitalization costs and palliative care costs where as EOL costs in non-PD cohort are driven by hospitalizations costs and outpatient visit costs. Due to the nature of PD progression, the intent of treatment during the EOL period in PD patients shifts to palliative care. As a result, PD-specific treatments are discontinued in some patients and the focus of treatment shifts to treating predominant non-motor symptoms of PD (Richfield, Jones, & Alty, 2013). The shift in focus of treatment to palliative care may have led to lower treatment intensities in advanced PD patients leading to similar costs of hospitalizations between PD and non-PD cohorts during the EOL period. This shift in treatment intent also may have led to higher palliative care costs and lower pharmacy costs in PD patients when compared to non-PD patients. To our knowledge, ours is the first study to estimate EOL cost burden in PD patients. Our study also reported costs associated with home health and hospice services along with inpatient, outpatient and pharmacy services among elderly PD patients. These results indicated the higher cost burden associated with home health and hospice services in PD patients when compared to non-PD patients.

Annual direct costs in patients with PD during their lifetime was estimated to be between $10,043 and $12,491 (Huse et al., 2005; O'Brien, Ward, Michels, Tzivelekis, & Brandt, 2009). Cost estimates during the 9-month EOL period from our study results are $45,701. Considering that the 9-mon EOL costs are around four times of annual costs during PD patients' lifetime, we conservatively estimate that there is more than four-fold increase in the costs during the EOL

period prior to death when compared with annual costs during the overall course of PD. Also, results from our study indicate that African Americans had higher EOL costs when compared to non-Hispanic whites. These racial differences in higher EOL costs are consistent with other studies which had similar findings about higher EOL costs in African Americans even though per patient healthcare spending in African Americans enrolled in Medicare is lower than other racial groups (Hogan, Lunney, Gabel, & Lynn, 2001). In terms of regional disparities, EOL costs in Midwest and Western regions of the US have significantly lower EOL costs when compared to Northeastern US. These results are consistent with prior studies which indicated that racial and geographic disparities influence the treatment choices and access to care during the EOL period (Baicker, Chandra, & Skinner, 2005; Baicker, Chandra, Skinner, & Wennberg, 2004; Cooper, Rivara, Wang, MacKenzie, & Jurkovich, 2012).

Informed by literature, our study assessed the association between comorbidities of interest such as Alzheimer's disease, pneumonia, stroke, chronic ischemic heart disease and EOL costs (Lethbridge et al., 2013; Martignoni et al., 2004). While previous literature indicated that cancer is a highly prevalent comorbidity in PD patients, our study excluded patients with cancer since EOL costs in cancer patients were studied extensively and including cancer patients can bias the cost estimates in the sample due to the expensive treatment options for cancer (Kovačević et al., 2015). PD cohort in our study had prevalent dementia in ~75% of the patients which is consistent with the literature (Hely, Reid, Adena, Halliday, & Morris, 2008). The high prevalence of dementia in our study sample also indicates that majority of PD patients in our sample are in advanced stage of PD since Parkinson's dementia is a sign of disease progression in PD patients (Dubois et al., 2007). Results from our study indicate that dementia is associated with significant EOL cost burden. While the prevalence of neurological comorbidities is in our study sample is in line with

current literature, the prevalence of cardiovascular comorbid conditions such as CHF, ischemic stroke was higher in PD patients in our study sample when compared to other studies in PD patients possibly due to the restriction of sample to patients aged at least 65 years in our study (Lethbridge et al., 2013).

Our study has several strengths. First, our study was conducted using the 5% Medicare sample which has the advantage of being representative of Medicare patients from most of the states in the US. Also, the use of Medicare 5% sample also provides a better tool to understand the EOL costs in PD patients since the prevalence of PD is highest in older patients aged 65 or older. In addition, Medicare data contains information on date of death through social security administration and the availability of accurate information of patient's death in Medicare database enables better estimation of EOL costs when compared to studies which use proxy algorithms based on occurrence of life threatening events and loss of eligibility for benefits to identify date of death (Atkins, Coutinho, Nunna, Gupte-Singh, & Eaddy, 2018; Joyce et al., 2004; Bert Kestenbaum, 1992; Bertram Kestenbaum & Reneé Ferguson, 2002). Second, this study excluded patients with malignant tumors since the EOL costs in cancer patients were significantly higher than non-cancer patients and were upwards of $70,000 during the 6 months prior to death (Atkins et al., 2018; Kovačević et al., 2015; Sheffield et al., 2011). However, due to this exclusion criteria, the study results must be interpreted among PD patients without comorbid cancer. Third, the availability of hospice and home health services data in Medicare administrative claims enable us to better understand PD patients' burden of home health and hospice services when compared to non-PD cohort.

Our study also has a fair share of limitations. First, our study excluded Medicare patients with Medicare advantage, supplemental Medicare or dual eligibility due to the non-availability of

complete data for these patients. Prior studies found that the presence of chronic conditions was slightly lower in patients enrolled in Medicare advantage plans when compared to Medicare fee-for-service plans (Miller, Decker, & Parker, 2016). Hence, our study results may not be generalizable to all Medicare patients. Also, our study is restricted to patient population 65 years or older. While the prevalence of PD in patients aged less than 65 years, nevertheless, previous studies have shown that early onset PD significantly reduces life expectancy (Ishihara, Cheesbrough, Brayne, & Schrag, 2007) and thus results from our study may not be representative of PD patients who died before attaining 65 years of age.

Conclusion

In summary, EOL costs among PD patients were significantly higher when compared to non-PD patients of similar age, gender and CCI. Results from the multivariable analysis also indicate that the presence of comorbidities during the baseline period significantly affect the costs during EOL period. Also, results from this study indicate significant racial and geographic disparities in costs and healthcare utilization provided to the PD patients.

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APPENDIX A

Table 2.1: ICD-9-CM codes for identification of cancer

ICD-9-CM code	Description
140.xx - 149.xx	Malignant Neoplasm Of Lip, Oral Cavity, And Pharynx
150.xx - 159.xx	Malignant Neoplasm Of Digestive Organs And Peritoneum
160.xx - 165.xx	Malignant Neoplasm Of Respiratory And Intrathoracic Organs
170.xx - 176.xx	Malignant Neoplasm Of Bone, Connective Tissue, Skin, And Breast
179.xx - 189.xx	Malignant Neoplasm Of Genitourinary Organs
190.xx - 199.xx	Malignant Neoplasm Of Other And Unspecified Sites
200.xx - 209.xx	Malignant Neoplasm Of Lymphatic And Hematopoietic Tissue
230.xx - 234.xx	Carcinoma In Situ
235.xx - 238.xx	Neoplasms Of Uncertain Behavior
239.xx	Neoplasms Of Unspecified Nature

Table 2.2: List of anti-Parkinson's drugs	
Anti-Parkinson's drug class	**Drug name**
Anticholinergic agents	Benztropine
	Biperiden
	Diphenhydramine
	Procyclidine
	Trihexyphenidyl
Carbidopa/levodopa therapy agents	Carbidopa
	Carbidopa-Levodopa
	Carbidopa/Entacapone/Levodopa
	Levodopa
COMT inhibitors	Entacapone
	Tolcapone
Dopamine agonists	Apomorphine
	Bromocriptine
	Cabergoline
	Pergolide
	Pramipexole
	Ropinirole
	Rotigotine
MAO-B inhibitors	Rasagiline
	Selegiline
Other parkinson's medications	Amantadine
	Droxidopa
	Pimavanersin
	Rivastigmine Tartrate

Table 2.3. Characteristics of PD cohort and non-PD cohort

Demographic and clinical characteristics	All Subjects (N = 11,130)		PD Cohort (N = 2,226)		Non-PD Cohort (N = 8,904)	
Age in years, Mean (SD)	83.4	(7.3)	83.4	(7.3)	83.4	(7.3)
Age Group (N, %)						
65-70	590	(5.3%)	118	(5.3%)	472	(5.3%)
71-75	1,198	(10.8%)	240	(10.8%)	958	(10.8%)
76-80	1,939	(17.4%)	387	(17.4%)	1,552	(17.4%)
81-85	2,648	(23.8%)	530	(23.8%)	2,118	(23.8%)
>85 years	4,755	(42.7%)	951	(42.7%)	3,804	(42.7%)
Gender (N, %)						
Male	5,855	(52.6%)	1,171	(52.6%)	4,684	(52.6%)
Female	5,275	(47.4%)	1,055	(47.4%)	4,220	(47.4%)
Ethnicity (N, %)						
Caucasian	10,288	(92.4%)	2,102	(94.4%)	8,186	(91.9%)
African American	540	(4.9%)	67	(3.0%)	473	(5.3%)
Other	302	(2.7%)	57	(2.6%)	245	(2.8%)
Region (N, %)						
Northeast	1,973	(17.7%)	430	(19.3%)	1,543	(17.3%)
South	4,491	(40.4%)	846	(38.0%)	3,645	(40.9%)
Midwest	2,878	(25.9%)	586	(26.3%)	2,292	(25.7%)
West	1,755	(15.8%)	359	(16.1%)	1,396	(15.7%)
Other	33	(0.3%)	5	(0.2%)	28	(0.3%)

Table 2.3 (Contd.). Characteristics of PD cohort and non-PD cohort

Demographic and clinical characteristics	All Subjects (N = 11,130)		PD Cohort (N = 2,226)		Non-PD Cohort (N = 8,904)	
CCI (Mean, SD)	3.4	(2.2)	3.4	(2.2)	3.4	(2.2)
CCI category						
0	1,030	(9.3%)	206	(9.3%)	824	(9.3%)
1	1,445	(13.0%)	289	(13.0%)	1,156	(13.0%)
2	1,630	(14.6%)	326	(14.6%)	1,304	(14.6%)
3	1,845	(16.6%)	369	(16.6%)	1,476	(16.6%)
4+	5,180	(46.5%)	1,036	(46.5%)	4,144	(46.5%)
Comorbidities of interest						
AZ	1,220	(11.0%)	364	(16.4%)	856	(9.6%)
Dementia	5,485	(49.3%)	1,672	(75.1%)	3,813	(42.8%)
Pneumonia	3,170	(28.5%)	695	(31.2%)	2,475	(27.8%)
Stroke	5,213	(46.8%)	1,243	(55.8%)	3,970	(44.6%)
CHF	5,674	(51.0%)	987	(44.3%)	4,687	(52.6%)

Table 2.4. Comparison of 3-mon EOL All-Cause Healthcare Costs Between PD Cohort and non-PD Cohort

	Unadjusted cost, mean (SD)				Adjusted cost[3], mean (SE)		
	All	PD Cohort	Non-PD Cohort		PD Cohort	Non-PD Cohort	
Direct Healthcare Costs[1]	**N = 11,130**	**N = 2,226**	**N = 8,904**	**P-value[2]**	**N = 2,226**	**N = 8,904**	**P-value[3]**
All-cause Costs							
Total costs	$21,144 ($24,066)	$20,769 ($20,555)	$21,237 ($24,866)	0.0006 *	$24,248 ($885)	$23,978 ($727)	0.7539
Inpatient costs	$13,753 ($21,507)	$12,206 ($18,671)	$14,139 ($22,143)	0.0003 *	$15,826 ($570)	$17,109 ($503)	0.6137
Outpatient costs	$3,321 ($3,978)	$3,131 ($3,494)	$3,369 ($4,089)	0.6884	$3,677 ($141)	$3,722 ($120)	0.5126
Pharmacy costs	$808 ($2,158)	$886 ($1,850)	$788 ($2,229)	<.0001 *	$893 ($41)	$718 ($28)	<.0001 *
Palliative care costs	$3,262 ($4,515)	$4,546 ($4,977)	$2,941 ($4,333)	<.0001 *	$3,892 ($153)	$2,859 ($97)	<.0001 *

* P-value < 0.05

Table 2.5. Comparison of 9-mon EOL All-Cause Healthcare Costs Between PD Cohort and non-PD Cohort

	Unadjusted cost, mean (SD)				Adjusted cost[3], mean (SE)		
	All	PD Cohort	Non-PD Cohort		PD Cohort	Non-PD Cohort	
Direct Healthcare Costs[1]	**N = 10,880**	**N = 2,226**	**N = 8,904**	**P-value[2]**	**N = 2,226**	**N = 8,904**	**P-value[3]**
All-cause Costs							
Total costs	$40,960 ($38,137)	$45,701 ($36,434)	$39,775 ($38,461)	<.0001 *	$48,429 ($1,369)	$43,054 ($1,090)	0.0324 *
Inpatient costs	$21,259 ($30,619)	$21,434 ($29,719)	$21,215 ($30,841)	0.8746	$26,125 ($913)	$25,684 ($745)	0.0483 *
Outpatient costs	$6,351 ($6,989)	$6,554 ($6,176)	$6,301 ($7,177)	<.0001 *	$7,019 ($232)	$6,471 ($179)	0.0009 *
Pharmacy costs	$2,625 ($6,305)	$2,951 ($5,296)	$2,544 ($6,531)	<.0001 *	$3,108 ($129)	$2,444 ($86)	<.0001 *
Palliative care costs	$6,785 ($10,523)	$9,583 ($11,499)	$6,085 ($10,146)	<.0001 *	$8,296 ($358)	$5,980 ($223)	<.0001 *

* P-value < 0.05

Healthcare costs were measured during the EOL period, defined as the 3-month period or 9-mon period prior to the index date

P-values were estimated from Wilcoxon rank-sum tests for comparison of unadjusted healthcare costs.

Table 2.6. Generalized model assessing the relationship between PD and All-cause health care costs during the 3 mon EOL period

	Beta Coefficient (95% CI, p)				
Characteristic	**All cause costs**			**P-value**	
Parkinson's Disease	0.01	-0.04	0.06	0.7539	
Race					
African American	0.16	0.07	0.26	0.0005	*
Other	0.12	-0.01	0.24	0.0693	
Non-Hispanic White (Ref)					
Region					
MW	-0.11	-0.16	-0.05	0.0002	*
W	-0.10	-0.16	-0.04	0.001	*
S	-0.02	-0.09	0.05	0.5617	
NE (Ref)					
Comorbidities					
Alzheimer's Disease	0.06	-0.01	0.13	0.0732	
Dementia	-0.07	-0.12	-0.03	0.001	*
Pneumonia	0.26	0.22	0.30	<.0001	*
Stroke	0.33	0.29	0.37	<.0001	*
Congestive Heart Failure	0.52	0.48	0.56	<.0001	*

* P-value < 0.05

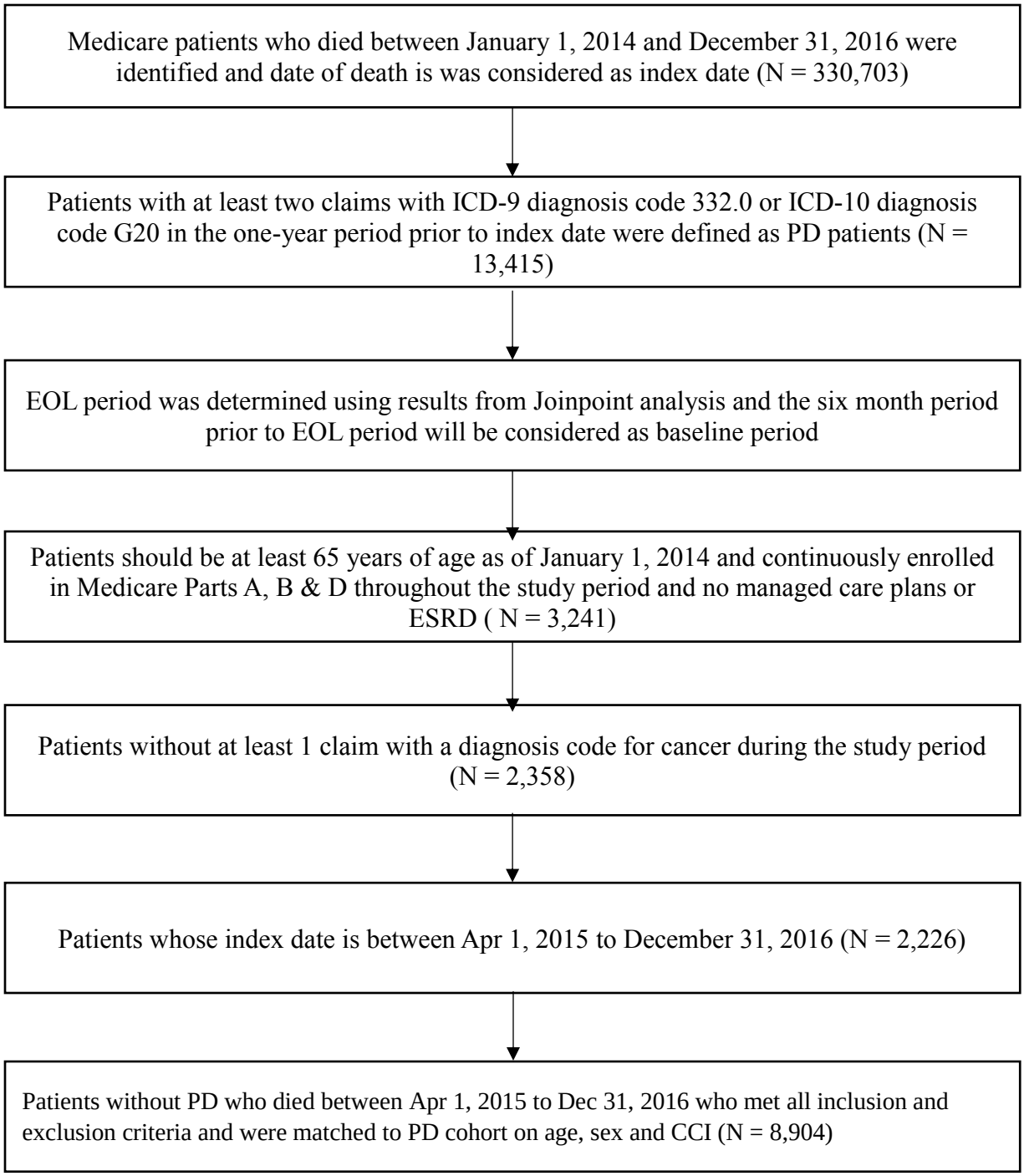
Table 7. Generalized model assessing the relationship between PD and All-cause health care costs during the 9 mon EOL period

	Beta Coefficient (95% CI, p)				
Characteristic	**All cause costs**			**P-value**	
Parkinson's Disease	0.12	0.07	0.16	<.0001	*
Race					
African American	0.0661	-0.01	0.15	0.1032	
Other	0.0054	-0.10	0.11	0.9206	
Non-Hispanic White (Ref)					
Region					
MW	-0.05	-0.10	0.00	0.0319	*
W	-0.06	-0.11	-0.01	0.0174	*
S	0.03	-0.03	0.09	0.2672	
NE (Ref)					
Comorbidities					
Alzheimer's Disease	0.06	0.01	0.12	0.033	*
Dementia	0.12	0.08	0.16	<.0001	*
Pneumonia	0.30	0.26	0.33	<.0001	*
Stroke	0.30	0.26	0.33	<.0001	*
Congestive Heart Failure	0.47	0.43	0.50	<.0001	*

* P-value < 0.05

APPENDIX B

Figure 2.1: Patient selection



CHAPTER 4: PAPER 3

End of Life Costs by Place at Death in Medicare Beneficiaries with Parkinson's Disease: An Instrumental Variable Approach

Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder belonging to a group of conditions referred to as motor system disorders. The exact cause of PD is unknown, but is attributed to the loss of neurons in the substantia nigra region of brain which leads to reduced dopamine production (Samii, Nutt, & Ransom). As PD progresses, it affects a person's ability to control their movements and the overall body. Tremor, bradykinesia, rigidity and postural instability are the primary motor symptoms of PD. Some of the non-motor symptoms of PD include depression, apathy, sleep disorders and erectile dysfunction (Chaudhuri & Schapira, 2009; Jankovic, 2008). The course of PD usually starts with a diagnosis and maintenance phase where complete symptom relief can be achieved with pharmacological treatment. It is followed by a complex phase where motor complications and neuropsychiatric complications occur. This phase is followed by a palliative phase where advanced PD is treated followed by the end of life (EOL) care (Clarke, Sullivan, & Mason, 2006; Lokk & Delbari, 2012).

Palliative care is usually provided to patients during the EOL period. However, in the case of PD treatment, palliative care is not necessarily equal to EOL care, since palliative care usually starts before the EOL phase in patients who no longer respond to treatments. Palliative care is initiated when patients are unable to tolerate dopaminergic therapy, unsuitable for surgery or when

advanced comorbidities are present (Clarke et al., 2006; MacMahon & Thomas, 1998). The mean duration of PD was estimated to be 14.6 years of which palliative care is usually provided for 2.2 years (MacMahon, Thomas, & Campbell, 1999). In the initial phases of PD such as diagnosis and maintenance phase, PD symptoms improve with the use of medication. As the disease progresses, PD symptoms do not improve with medication therapy and a high percentage of patients (~30%) experience symptoms such as depression, hallucinations and falls. These symptoms often lead the PD patients to seek institutional palliative care (Lökk, 2008). Institutional palliative care is provided in long term care (LTC) facilities, skilled nursing facilities (SNF) or freestanding Hospice facilities. Institutional palliative care usually aims to prevent further complications and provide symptom relief (Thomas & MacMahon, 2004).

While institutional palliative care is frequently used during the EOL period with around 60% of deaths happening in hospital, some patients prefer to die at home (Gallup, 1997; Hays, Galanos, Palmer, McQuoid, & Flint, 2001; Weitzen, Teno, Fennell, & Mor, 2003). Such patients are provided care through Home Health agencies and home-based Hospice services. While hospital-based EOL care has shown to improve some aspects of quality of life in patients during the EOL period, there is evidence of favorable dying experience at home when compared to an institutional setting (Higginson et al., 2002; Teno et al., 2004). Previous studies have shown that the use of home-based care with a multidisciplinary approach consisting of symptom control, pain relief, emotional and spiritual support and patient education resulted in a significantly lower healthcare resource use, costs and better quality of life when compared to other home-based care services such as home health care, home-based hospice care or institutional palliative care services such as hospice care during the EOL period (R. Brumley et al., 2007; R. D. Brumley, Enguidanos, & Cherin, 2003; Lustbader et al., 2017). For example, in a randomized trial conducted in terminally

ill patients, Brumley et al., (2007) found that when compared to patients receiving usual care such as Home Health services, acute care services, primary care services, and Hospice care, patients enrolled in an interdisciplinary home-based care program during the EOL period had higher patient satisfaction and lower healthcare resource use. EOL costs place a disproportionate burden on Medicare with around 30% of yearly spending on 5% to 6% patients that die in that year (Emanuel & Emanuel, 1994). EOL costs calculated in previous studies may not be representative of the EOL costs in PD patients since a significant percentage of patients receiving EOL care are cancer patients (Duncan, Ahmed, Dove, & Maxwell, 2019; Hogan, Lunney, Gabel, & Lynn, 2001). Considering the high burden of EOL costs on Medicare, it is essential to understand the EOL costs in PD patients enrolled in Medicare and to assess the impact of place at death on EOL costs. Results from such a study will complement studies on quality of life improvement and dying experience during the EOL period to aid discussions regarding patient's choice of EOL care. In this study, we aim to understand the association between place at death and EOL costs among older Medicare beneficiaries with PD. An instrumental variable (IV) was used to control for confounding and measurement error in this study.

In retrospective observational studies using claims database, patients cannot be randomly allocated to interventions such as use of Home-based palliative care or institutional palliative care. The choice of place of palliative care during the EOL period depends on a number of factors such as the severity of patient's disease and patient's preference for palliative care. The availability of palliative care services in the patient's region may also play an important role in patient's choice of the place of palliative care. In addition, physician recommendations may also influence patient's choice. Lack of randomization can lead to treatment selection bias in a study. Use of multivariable models can control for observed differences between patients in treatment groups but are unable

to minimize the unmeasured confounding due to strong selection bias (Stukel et al., 2007). IV analysis is an econometric method which can be used to control for confounding in observational studies when randomization is not feasible. An IV can be considered as a variable which can introduce variation in the exposure (place at death) variable like a randomized assignment. An IV can adjust for both observed and unobserved confounding and should have two key characteristics 1) it is highly associated with the patient's choice of place of receiving EOL care and 2) the instrument does not independently affect the outcome, which is EOL costs in the study (Brookhart, Rassen, & Schneeweiss, 2010; Newhouse & McClellan, 1998). Since the IV is highly associated with intervention, the variation in IV induces a variation called exogenous variation in the intervention variable which mimics randomization. While ordinary least squares (OLS) regression measures the effect of intervention on the outcome, IV regression measures the effect of exogenous variation in the intervention on the outcome. Thus, the use of IV regression can lead to unbiased estimation of the relationship between intervention (place at death) and the outcome (EOL cost) (Earle et al., 2001; Newhouse & McClellan, 1998; Penrod, Goldstein, & Deb, 2009; Stukel et al., 2007).

Methods

Data Source and Study Design

A retrospective observational cohort study was conducted using data from Medicare 5% random national sample claims from January 1, 2014 – December 31, 2016 which is made available through the Centers for Medicare and Medicaid services (CMS) for research purposes. This database contains the claims of healthcare services offered to Medicare beneficiaries including inpatient, outpatient, long-term care, skilled nursing facility (SNF), Hospice, Home Health and prescription drugs. The Medicare Beneficiary Summary file contains information related to

patients' demographics, enrollment status and mortality information. The Medicare Carrier file contained claims related to services provided by non-institutional providers such as physicians, nurse practitioners and physician assistants. Outpatient file contained claims related to services performed by institutional outpatient providers like hospitals, renal dialysis facilities and community mental health centers etc. Inpatient and SNF services claims were provided in the MedPAR files. Services provided through Home Health agencies were provided in the Home Health Agency (HHA) research identifiable files (RIF). Hospice RIF contained the fee for service and managed care claims submitted by Hospice providers once the beneficiaries have opted for Hospice services. These files contain procedure codes of services which were classified using the Current Procedural Terminology (CPT) along with ICD-9/ ICD-10 diagnosis codes and the amount reimbursed for the services. Records for prescription drugs dispensed under Medicare part D were included in the Part D Drug Event (PDE) file. An encrypted beneficiary identification number is used to link the claims. This study was approved by the Institutional Review Board (IRB) of the University of Mississippi.

Patient Selection

The sample for this study contained Medicare beneficiaries who: (1) were ≥ 65 years of age as of January 1, 2014 (2) who died during the period between April 1, 2015 to December 31, 2016 (3) who had continuous enrollment in Medicare Parts A, B, & D from January 1, 2014 to index date. Only Patients who received home-based palliative care and died at home or patients who received institutional palliative care and died at a medical facility were included in the study. In the current study, the identification of Medicare beneficiaries with PD was based on the approach outlined by Szumski et al. (2009). Patients with at least two medical claims containing ICD-9 diagnosis code 332.0 or ICD-10 diagnosis code G20 in the one-year period prior to index

date will be defined as PD patients. This approach to identify PD was found to have a sensitivity of 89.2% and a positive predictive value (PPV) of 79.4% (Szumski & Cheng, 2009). The date of death was identified from the Medicare Beneficiary Summary file and was considered as the index date. The duration of EOL period was determined as the 9-mon period prior to death using results from the Joinpoint analysis. Sensitivity analysis was performed by varying the definition of EOL period as 3 months prior to death. The six month period prior to EOL period was considered as baseline period. Dual eligible beneficiaries, patients enrolled in managed care, patients with unknown location of death (identified using patient discharge status code 42 from Hospice RIF or MedPAR RIF), patients with end stage renal disease (ESRD) or cancer (ICD-9-CM/ICD-10 codes presented in Table 1) during the study period were excluded. A diagrammatic representation of patient selection is provided in Figure 1.

Measures

Outcome Variable

The outcome measured in the study was all-cause healthcare costs. Costs were measured during the EOL period and were adjusted to 2016 USD using the medical component of consumer price index (CPI). This study was conducted from Medicare's perspective therefore payments made by patients such as co-payments and deductibles were not included in the cost calculation. All-cause healthcare costs included payments made for outpatient services, office visits, emergency department (ED) visits, inpatient services, SNF/LTC services, Home Health services, Hospice services and prescription drug costs.

Exposure Variable

The key exposure variable of interest was the place at death. PD patients were categorized as "died at institutional hospice" or "died at non-institutional hospice". Place at death was identified using the patient discharge status variable "PTNT_DSCHRG_STUS_TB" in Hospice RIF and "STUS_CD" in Home Health RIF. Patients with discharge status "41" and who had at least one claim for hospice during the 90-day period prior to death were included in hospice cohort. Patients with discharge status "40" who did not have at least one hospice claim were included in non-hospice cohort.

Covariates

Covariates in the study included age, gender, race, modified Charlson Comorbidity Index (CCI), geographic region and PD severity. Age was calculated at index date and was used as a continuous variable. Gender was measured as male or female. Race was categorized as non-Hispanic white, African American, Hispanics and other racial group (including Asian, Native Hawaiian, Pacific Islander, American Indian or Alaskan Native, or unknown race). Geographic region was categorized as Northeast, South, Midwest and West. Deyo adaptation of CCI was modified by excluding diagnosis codes for cancer and metastases. Modified CCI was calculated during the baseline period using ICD-9/ICD-10 diagnosis codes from MedPAR, Carrier and Outpatient files (Deyo, Cherkin, & Ciol, 1992). The mean daily load of PD medication was used as a proxy measure for PD severity. A previous study found that the mean daily tablet load of early PD patients is 3.2 tablets of PD-related medications. In advanced PD patients the mean daily tablet load ranged from 8.4 to 9.9 tablets of PD-related medications (Fargel, Grobe, Oesterle, Hastedt, & Rupp, 2007). Hence patients with a mean daily PD-related tablet load of more than 8, 4 to 7, 3 and less were categorized as advanced PD patients, mid stage PD patients and early PD patients respectively. The mean daily PD-related tablet load was calculated during the baseline period. In

addition, a number of comorbidities of interest, including Alzheimer's disease, dementia, pneumonia, stroke and congestive heart failure (CHF) during the baseline period were included as covariates.

Instrumental Variables (IV)

Due to the observational nature of the study design it is not feasible to randomly assign patients to home-based palliative care or institutional palliative care. To minimize the bias due to lack of randomization, an instrumental variable (IV) approach was used to account for observed and unobserved confounding biases. (Carlsen & Grytten, 1998; D'Agostino, 2007; Newhouse & McClellan, 1998; Stukel et al., 2007).

The instruments used in this study were identified in calendar year 2016. Three instruments were used in the study: the first instrument (IV1) was based on the regional variation at the Health Service Area (HSA) level in the use of EOL care among all PD patients. It is the ratio of the number PD patient's receiving EOL care at home to the number of PD patient's receiving EOL care at an institutional facility. The rationale for using an instrument based on regional variation in the use of EOL care is that a patient's preference for EOL care is more likely to be influenced by the wide spread use of a particular EOL service in that geographic unit (Basu, Heckman, Navarro-Lozano, & Urzua, 2007; Stukel et al., 2007). The second instrument (IV2) was based on physician preference of home-based palliative care versus institutional palliative care in PD patients. The rationale for using this instrument is that physician recommendations play an important role in patient's choice of EOL care (Brookhart et al., 2010; Brookhart, Wang, Solomon, & Schneeweiss, 2006; Wang et al., 2005). All PD patients who met study inclusion and exclusion criteria were assigned a primary physician, defined as the physician who wrote the highest number of PD prescriptions during the EOL period or the physician who had the highest number of

outpatient/office visits for the treatment of PD during the EOL period. The ratio of patients who used home-based palliative care to total number of patients was calculated for each of these designated primary physicians during 2016 and used as an IV for physician preference in the study. The third instrument (IV3) was based on the availability of home-based palliative care providers such as Home Health agencies and institutional palliative care providers such as freestanding Hospice agencies in the patient's HSA. The ratio of the number of Home Health agencies to the total number of Home Health agencies and free standing Hospice agencies was used as the third IV. The rationale for using this instrument is that patients are likely to choose the type of EOL care based on the availability of the services. Also, the availability of EOL care in a particular region can also lead to physician enthusiasm or supplier induced demand (Carlsen & Grytten, 1998; Pritchard et al., 1998).

Statistical Analysis

Descriptive characteristics for the non-hospice cohort and hospice cohort were reported using means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables. T-tests and chi-squared tests were used to compare continuous variables and categorical variables respectively. In the IV analysis, relevance of instruments was tested using first-stage regressions and Durbin-Wu-Hausman test was used to test the endogeneity in IV estimation. The impact of place at death on EOL costs was assessed using a two stage least squares regression (2SLS) controlling for baseline characteristics including age, gender, race, modified CCI, geographic region and PD severity. Costs were log-transformed and a two stage least squares regression using the PROC SYSLIN procedure in SAS (SAS Institute Inc., Cary, NC) was used to conduct the IV analysis.

Results

A total of 1,354 older PD patients who died during the index period (Apr 1, 2015 to Dec 31, 2016) met our inclusion criteria. Of these, 749 patients used home-based palliative care services during the 90-day period prior to death and died at home were included in the non-hospice cohort. A total of 605 patients who used institutional palliative care during the 90-day period prior to death and died at an institutional facility providing palliative care were included in the hospice cohort. Demographic and clinical characteristics of patients in both cohorts were presented in Table 2. The mean age of patients in the overall study sample was 83.9 (±7.1) with around 45% of patients in the age group > 85 years. Patients in non-hospice cohort were slightly older when compared to the hospice cohort (mean age of 84.6 in non-hospice cohort vs 83.4 in hospice cohort, $p = 0.006$). Around 94% of patients in overall study sample were non-Hispanic whites. Average comorbidity burden, as measured by CCI, was significantly higher in patients who used institutional palliative care (3.1 in non-hospice cohort vs. 3.5 in hospice cohort, $p = 0.0002$). Around 40.9% of patients in the non-hospice cohort had CCI score ≥ 4 when compared to 47.9% in hospice cohort ($p = 0.002$). Also, the prevalence of comorbidities of interest, such as Alzheimer's disease, dementia, pneumonia, stroke and CHF during the baseline period was significantly higher in the hospice cohort when compared to the non-hospice cohort.

Mean unadjusted all-cause costs during the 9-month EOL period were significantly lower in non-hospice cohort when compared to the hospice cohort [$47,316 (± 32,095) vs. $53,581 (± $35,128), $p = 0.0001$]. EOL costs were largely driven by hospitalization costs in both cohorts with inpatient services contributing to more than 35% EOL costs. Mean costs incurred towards inpatient, outpatient/office visits, pharmacy costs were higher in hospice cohort when compared to non-hospice cohort. However, the average costs incurred towards palliative care services were higher in non-hospice cohort [$15,105 (± $12,902) vs. $11,526 (± $11,439) in hospice cohort, $p <$

0.0001]. The distribution of components of all-cause costs 9-month EOL period were provided in Table 4. In the sensitivity analysis using 3 months prior to death as EOL, similar trends were observed (Table 3). During the 3-month EOL period, all-cause costs in non-hospice cohort were significantly lower than hospice cohort [$18,530 (± $ 16,457) vs. $21,912 (± 18,675), $p < 0.0001$].

The effect of the choice of EOL care and EOL costs were examined using a conventional OLS model controlling for observed confounding, and an IV model controlling for observed and unobserved confounding. IVs under consideration were tested for exogeneity to ensure that they explain the variation in the exposure variable. First the correlation between all the three IVs and the exposure variable (choice of EOL care) was assessed (Table 5). IV2 (physician preference) and IV3 (availability of EOL care) were significantly correlated with choice of EOL care, but IV1 (patient preference) was not significantly correlated with the choice of EOL care. While IV1 was not significantly correlated with choice of EOL care, it was still included in the model since IV1 may be able to explain the variation in choice of EOL care given other covariates in the model and there is strong theoretical basis that patient preferences are significantly related to EOL decisions. Hausman test for endogeneity was found to be significant at an alpha level of 0.05 when IVs 1 and 3 were used together ($t=2.47$; $p=0.014$), which provides evidence to suggest that the IVs are exogenous and the IV model is more efficient than the conventional OLS model (Tables 6 and 7).

A comparison of results for the association between 3-mon and 9-mon EOL costs and choice of EOL care from the OLS model and IV model were presented in Tables 8 and 9 respectively. Based on the conventional OLS model, after controlling for all covariates, patients using home-based palliative care were found to be associated with significantly lower EOL costs when compared to patients using institutional palliative care ($\beta = -0.07$, $p = 0.036$). In contrast, IV model has shown that patients using home-based palliative care were associated with higher costs

when compared to patients using institutional palliative care. However, this relationship in IV model was not statistically significant ($\beta = 0.24$, $p = 0.431$).

Discussion

In this study, we assessed the impact of the choice of EOL care and all-cause healthcare costs during EOL period among older Medicare patients with PD using an IV approach. While previous studies found that patients with non-cancer conditions and patients in general are more likely to use hospice care during EOL period (Duncan et al., 2019; Stevenson, Huskamp, Grabowski, & Keating, 2007), results from our study suggest that the use of non-hospice care is higher in PD patients when compared to hospice care. These results also indicate that patients with higher comorbidity burden were more likely to choose hospice care during EOL period. We also found that unadjusted all-cause costs were significantly higher in patients who used hospice care cohort when compared to patients who were in non-hospice cohort. A previous study by Duncan et al. (2019) in a general sample of Medicare patients estimated per patient per month (PPPM) palliative care costs to be $2,336 in patients who died in Hospice and $1,104 in patients who died in Home Health setting (Duncan et al., 2019). These results are in contrast with our study which found that palliative care costs in PD patients is higher among patients in non-hospice cohort when compared to patients in hospice cohort. The lower costs in non-hospice cohort in Duncan et al. (2009) study could be due to the lower sample size of patients who died while using home health services or could be due to inclusion of patients with primary cancers who were more likely to use institutional care during EOL periods (Addington-Hall, Altmann, & McCarthy, 1998). Change in intent of treatment to non-curative treatment during the last few months before death is associated with less aggressive treatments in PD patients (Gozalo, Plotzke, Mor, Miller, & Teno, 2015). While this change in treatment approach may reduce the cost of treatment, these reduced costs due

to less aggressive treatments were offset by higher costs incurred towards EOL care leading to higher EOL costs in PD patients when compared to patients without PD.

Our study used both conventional OLS regression and IV regression to assess the relationship between choice of EOL care and EOL costs. Results from conventional OLS regression indicate that all-cause costs in the non-hospice cohort were significantly lower than hospice cohort. However, there are several unobserved confounders which might influence the patient's choice of EOL care. Factors such as desire to stay in the proximity of family, having care givers, ability to perform activities of daily living, patient's quality of life all play an important role in patient's EOL care decisions. While randomization can be a way to minimize such unobserved confounding, it is not feasible in observational studies using retrospective claims databases. Hence, our study used an instrumental variable approach which can theoretically account for both observed and unobserved confounding due to the choice of end of life care to provide a better estimate of the impact of choice of EOL care and EOL costs. Results from IV model suggest that EOL costs were higher in the non-hospice cohort but the results did not reach statistical significance. These findings have practical significance for several reasons. First, the type of care desired by the patients may be associated with lower costs, thus health care systems should focus on providing better access to home-based EOL care. While institutional care in general is associated with higher Medicare expenditures (Gozalo et al., 2015), our findings indicate that EOL costs are not significantly different between home-based versus institutional care among older PD patients once we account for both the observed and unobserved confounding.

Our choices of the three IVs needs further discussion. The first IV was patient's preference of EOL care in a geographic region. While this patient preference IV was not significantly correlated with the choice of EOL care, we nevertheless included it as an IV due to the strong

theoretical basis for patient preference in choosing EOL care (Barnato et al., 2007; Gramelspacher, Zhou, Hanna, & Tierney, 1997; Hofmann et al., 1997). Also, the use of patient preferences, physician preferences along with availability of EOL care services at a HSA level can minimize the possibility of instrument-outcome confounding (Garabedian, Chu, Toh, Zaslavsky, & Soumerai, 2014).

The second IV was physician's choice in EOL care. We first identified the physician associated with PD treatment as patient's primary prescriber of the patient. We then assessed the percentage of patients treated by the prescriber who are using home-based care to all patients using home-based or institutional palliative care as an IV. However, considering the stage of PD, some patients may not be prescribed any PD-related medications but we assigned the physician associated with most PD diagnoses as the patient's primary prescriber. This physician preference IV was significantly correlated with EOL care choice. However, inconsistent with previous studies, based on Hausman test for endogeneity, we found that it was not a significant IV. This inconsistency could be due to the nature of our research question in answering which we used physician preference as an IV for patient's choice in EOL care locations while previous studies used physician preference as IVs for actual treatment selection (Brookhart et al., 2006; Rassen, Brookhart, Glynn, Mittleman, & Schneeweiss, 2009). While physicians are often the one to initiate EOL conversations with patients, it is unclear whether the patient's EOL care decisions were more influenced by the physician treating PD or their primary care physicians (PCP) (Ionescu-Ittu, Abrahamowicz, & Pilote, 2012; Markson et al., 1997; Ramanayake, Dilanka, & Premasiri, 2016; Sachs, Shega, & Cox-Hayley, 2004). Further research is necessary into determining the role played by PCP's and specialists on EOL care decisions of patients.

In order to assess the third IV, the availability of EOL care in the patient's geographic location (HSA), our study used the list of providers who were registered with CMS for providing home-based and institutional EOL care to Medicare patients. EOL care availability was significantly correlated with patients' EOL choice and this IV was also found to be valid based on Hausman test. While there is a chance of Medicare patients using non-registered EOL care providers, there is less likelihood since the requirements to register with CMS are not stringent Also, our study did not account for the newer programs instituted by CMS such as Medicare Care Choices Model which is designed to increase access to hospice care and could be associated with better payments based on quality of care (Medicare & Services, 2016). However, considering that this program was started towards the end of 2015 in very few centers, the impact of these programs on patient's EOL care choice during our study period could be minimal.

Our study results must be interpreted in light of certain limitations. Patients who died at home and did not use hospice services in the 90-day period were included in the non-hospice cohort and a similar approach was used to identify patients in the hospice cohort. However, we cannot establish with certainty that the patient truly used only hospice services or non-hospice services. Our study did not include patients who used hospice or home health services and died at an inpatient setting. In order to minimize the possible misclassification, we categorized patients into hospice and non-hospice cohorts based on use of the EOL services during the 90-day period prior to death along with the discharge code indicating the place of death. While the impact of place of death on EOL costs was assessed in our study, we did not assess the impact of type of EOL care used on costs during EOL period. Also, intent of treatment can be a significant predictor of EOL costs (Näppä, Lindqvist, Rasmussen, & Axelsson, 2011; Zdenkowski, Cavenagh, Ku,

Bisquera, & Bonaventura, 2013). However, we cannot accurately ascertain intent of treatment from Medicare claims data.

Our study has several strengths. First, we used retrospective data from the 5% national Medicare sample which contains administrative claims for patients from all the states in the US. In addition to the data's geographic representation, considering that PD is more prevalent in patients more than 65 years of age, Medicare database is the most appropriate database to assess the impact of home-based versus institution care and EOL care cost in older PD patients. Second, Medicare data contains patient's death information through social security administration which is accurate and thus enables better estimation of EOL costs when compared to the use of proxy algorithms. For example, due to patient privacy issues, commercial claims databases do not provide information on death and studies using these databases rely on proxy algorithms which consider loss of enrollment for pharmacy and medical benefits shortly after a life threatening event to identify death (Joyce et al., 2004). In addition, patients in Medicare FFS or Medicare advantage plans have coverage for palliative care services provided by Home Health or Hospice agencies, patients in commercial insurance plans have limited coverage (Chung, Jahng, Petrosyan, Kim, & Yim, 2015; Jackson, Gibson, & Staeheli, 2000). Moreover, the use of Medicare data also provides an opportunity to estimate the real-world costs associated with EOL care in PD patients managed in real-world care settings.

Conclusion

In summary, among older Medicare PD patients who died, all-cause EOL costs were significantly lower in the non-hospice cohort as compared to those in the institutional care cohort using conventional OLS model controlling for the effects of observed confounding only. After controlling for the effect of unobserved confounders with an IV approach, we found that all-cause

EOL costs among patients in the non-hospice cohort were not significantly different from patients in the hospice cohort. However, choice of EOL care among PD patients should be a joint decision between patients and healthcare providers; patient preferences and patient quality of life during EOL period should be considered to design novel EOL care programs which can reduce costs and improve patient's EOL care experience.

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APPENDIX A

Table 3.1: ICD-9-CM codes for identification of cancer	
ICD-9-CM code	**Description**
140.xx - 149.xx	Malignant Neoplasm Of Lip, Oral Cavity, And Pharynx
150.xx - 159.xx	Malignant Neoplasm Of Digestive Organs And Peritoneum
160.xx - 165.xx	Malignant Neoplasm Of Respiratory And Intrathoracic Organs
170.xx - 176.xx	Malignant Neoplasm Of Bone, Connective Tissue, Skin, And Breast
179.xx - 189.xx	Malignant Neoplasm Of Genitourinary Organs
190.xx - 199.xx	Malignant Neoplasm Of Other And Unspecified Sites
200.xx - 209.xx	Malignant Neoplasm Of Lymphatic And Hematopoietic Tissue
230.xx - 234.xx	Carcinoma In Situ
235.xx - 238.xx	Neoplasms Of Uncertain Behavior
239.xx	Neoplasms Of Unspecified Nature

Table 3.2. Characteristics of patients in the non-Hospice Cohort and Hospice Cohort

Demographic and clinical characteristics	All Patients (N = 1,354)		Non- hospice cohort patients (N = 749)		Institutional hospice cohort patients (N = 605)		P-value	
Age in years, Mean (SD)	83.9	(7.1)	84.6	(6.9)	83.4	(7.2)	0.006	*
Age Group (N, %)								
65-70	50	(3.7%)	38	(5.1%)	12	(2.0%)	0.001	*
71-75	146	(10.8%)	85	(11.3%)	61	(10.1%)	0.053	
76-80	214	(15.8%)	119	(15.9%)	95	(15.7%)	0.060	
81-85	334	(24.7%)	187	(25.0%)	147	(24.3%)	0.049	*
>85 years	610	(45.1%)	320	(42.7%)	290	(47.9%)	0.007	*
Gender (N, %)								
Male	692	(51.1%)	381	(50.9%)	311	(51.4%)	0.043	*
Female	662	(48.9%)	368	(49.1%)	294	(48.6%)		
Ethnicity (N, %)								
Caucasian	1,281	(94.6%)	702	(93.7%)	579	(95.7%)	0.027	*
African American	36	(2.7%)	22	(2.9%)	14	(2.3%)	0.106	
Other	37	(2.7%)	25	(3.3%)	12	(2.0%)	0.043	*
Region (N, %)								
Northeast	218	(16.1%)	111	(14.8%)	107	(17.7%)	<.0001	*
South	545	(40.3%)	315	(42.1%)	230	(38.0%)	<.0001	*
Midwest	356	(26.3%)	167	(22.3%)	189	(31.2%)	0.014	*
West	234	(17.3%)	155	(20.7%)	79	(13.1%)	0.021	*
Other	1	(0.1%)	1	(0.1%)	-	(0.0%)		

Table 3.2 (cont.) Characteristics of patients in the non-Hospice Cohort and Hospice Cohort

Demographic and clinical characteristics	All Patients (N = 1,354)		Non-hospice cohort patients (N = 749)		Institutional hospice cohort patients (N = 605)		P-value	
CCI (Mean, SD)	3.3	(2.2)	3.1	(2.2)	3.5	(2.1)	0.0002	*
CCI category								
0	138	(10.2%)	92	(12.3%)	46	(7.6%)	0.001	*
1	190	(14.0%)	123	(16.4%)	67	(11.1%)	0.001	*
2	197	(14.5%)	112	(15.0%)	85	(14.0%)	0.056	
3	233	(17.2%)	116	(15.5%)	117	(19.3%)	0.010	*
4+	596	(44.0%)	306	(40.9%)	290	(47.9%)	0.002	*
Comorbidities of interest								
AZ	238	(17.6%)	121	(16.2%)	117	(19.3%)	0.018	*
Dementia	1,088	(80.4%)	582	(77.7%)	506	(83.6%)	0.001	*
Pneumonia	390	(28.8%)	186	(24.8%)	204	(33.7%)	<.0001	*
Stroke	751	(55.5%)	395	(52.7%)	356	(58.8%)	0.004	*
CHF	553	(40.8%)	281	(37.5%)	272	(45.0%)	0.001	*

[1]Demographics and health insurance plans were measured on or during the 6-mon pre-index period. Comorbidities were measured during the baseline period, defined as the 6 month period prior to the index date.

[2]Chi-squared tests were used for comparisons of categorical variables (Fisher's Exact tests were used for outcomes with small cell counts). Wilcoxon rank-sum tests were used for comparisons of continuous variables.

Table 3.3. Comparison of 3-Mon EOL Direct Healthcare Costs Between the Cohorts

	Unadjusted cost, mean (SD)							
Direct Healthcare Costs[1]	**All** **N = 1,354**		**Non-hospice cohortpatients** **N = 749**		**Institutional hospice cohort patients** **N = 605**		**P-value[2]**	
All-cause Costs								
Total costs	$20,041	($17,557)	$18,530	($16,457)	$21,912	($18,675)	<.0001	*
Inpatient costs	$9,686	($16,013)	$8,191	($15,143)	$11,537	($16,858)	<.0001	*
Outpatient costs	$2,704	($3,195)	$2,270	($3,019)	$3,242	($3,324)	<.0001	*
Pharmacy costs	$822	($1,958)	$798	($2,072)	$852	($1,807)	0.0029	*
Palliative care costs	$6,828	($4,926)	$7,270	($4,955)	$6,281	($4,839)	0.0002	*

[1]Corresponds to all-cause healthcare costs

[2]Wilcoxon rank sum test was used for the comparison of unadjusted costs

Table 3.4. Comparison of 9-Mon EOL Direct Healthcare Costs Between the cohorts

	Unadjusted cost, mean (SD)							
Direct Healthcare Costs[1]	**All** **N = 1,354**		**Non-hospice cohort patients** **N = 749**		**Institutional hospice cohort patients** **N = 605**		**P-value[2]**	
All-cause Costs								
Total costs	$50,116	($33,616)	$47,316	($32,095)	$53,581	($35,128)	0.0001	*
Inpatient costs	$18,760	($26,253)	$16,810	($25,219)	$21,174	($27,307)	<.0001	*
Outpatient costs	$6,037	($5,813)	$5,383	($5,918)	$6,847	($5,579)	<.0001	*
Pharmacy costs	$2,809	($5,491)	$2,802	($5,744)	$2,817	($5,166)	0.0497	*
Palliative care costs	$13,506	($12,394)	$15,105	($12,902)	$11,526	($11,439)	<.0001	*

[1]Corresponds to all-cause healthcare costs
[2]Wilcoxon rank sum test was used for the comparison of unadjusted costs

Table 3.5. Pairwise correlations between EOL care choice and instrumental variables

	EOL Choice (HHA)	IV 1	IV 2	IV 3
EOL Choice (HHA)	1.000			
IV 1	0.012	1.000		
r (p value)	(0.663)			
IV 2	0.092	0.102	1.000	
r (p value)	(0.001)	(0.0002)		
IV 3	-0.068	0.129	-0.023	1.000
r (p value)	(0.012)	(<.0001)	(0.407)	

Table 3.6. First stage regression demonstrating whether instrumental variables predict variance in the independent variable - Test of individual significance

Characteristic	Parameter Estin	T-Value	P-value	
Age	-0.005	-2.39	0.017	*
Female (Ref: Male)	0.003	-0.11	0.912	
Region				
S	0.06	1.63	0.103	
MW	-0.04	-0.94	0.349	
W	0.12	2.54	0.011	*
NE (Ref)				
Race				
African American	0.08	0.97	0.334	
Other	0.10	1.22	0.221	
Non-Hispanic White (Ref)				
CCI Category				
CCI Category: 1	-0.01	-0.18	0.854	
CCI Category: 2	-0.07	-1.17	0.242	
CCI Category: 3	-0.13	-2.30	0.021	*
CCI Category: 4	-0.08	-1.50	0.133	
CCI Category: 0 (Ref)				
Comorbidities				
Alzheimer's Disease	-0.04	-1.00	0.316	
Dementia	-0.06	-1.60	0.110	
Pneumonia	-0.09	-2.83	0.005	*
Stroke	-0.03	-0.88	0.380	
Congestive Heart Failure	-0.01	-0.42	0.672	
Stage		.	.	
Stage Moderate	0.03	1.03	0.305	
Stage Advanced	-0.05	-0.67	0.500	
Stage Unknown	0.00	0.07	0.946	
Stage Mild (Ref)				
IV 1	0.03	0.25	0.806	
IV 3	-0.14	-1.76	0.079	

*P-value < 0.05

Abbreviations: CI, Confidence Interval.

Table 3.7. Hausman Test for Endogeneity

Variable	Estimate	t Value	p value	
EOL Choice: HHA	-1.800	-2.57	0.0104	*
Age	-0.023	-5.52	<.0001	*
Female (Ref: Male)	-0.050	-1.47	0.141	
Region				
S	0.089	1.4	0.1608	
MW	-0.211	-3.31	0.0009	*
W	0.226	2.18	0.0295	*
NE (Ref)				
Race				
African American	0.441	3.66	0.0003	*
Other	0.232	1.89	0.0586	
Non-Hispanic White (Ref)				
CCI Category				
CCI Category: 1	-0.028	-0.41	0.6837	
CCI Category: 2	0.006	0.07	0.946	
CCI Category: 3	-0.075	-0.67	0.5001	
CCI Category: 4	0.216	2.49	0.0129	*
CCI Category: 0 (Ref)				
Comorbidities				
Alzheimer's Disease	-0.118	-2.31	0.0209	*
Dementia	-0.078	-1.31	0.1895	
Pneumonia	-0.026	-0.36	0.7177	
Stroke	0.100	2.37	0.0179	*
Congestive Heart Failure	0.142	3.53	0.0004	*
Stage				
Stage Moderate	0.094	1.98	0.048	*
Stage Advanced	-0.151	-1.47	0.1426	
Stage Unknown	-0.046	-1.15	0.2509	
Stage Mild (Ref)				
Residual	1.733	2.47	0.0137	*

Table 3.8. OLS model and 2SLS models Assessing the Relationship Between EOL Care Type and Allcause Healthcare Costs During the 3 Mon EOL Period

	OLS Regression				2SLS Regression			
Characteristic	**Parameter**	**T-Value**	**P-value**		**Parameter**	**T-Value**	**P-value**	
EOL Choice: HHA	-0.10	-2.46	0.014	*	-0.04	-0.1	0.921	
Age	-0.02	-5.93	<.0001	*	-0.02	-5.07	<.0001	*
Female (Ref: Male)	-0.10	-2.32	0.02	*	-0.10	-2.34	0.019	*
Region								
S	-0.09	-1.49	0.138		-0.09	-1.47	0.141	
MW	-0.14	-2.14	0.032	*	-0.14	-2.02	0.043	*
W	-0.02	-0.35	0.728		-0.03	-0.4	0.692	
NE (Ref)								
Race								
African American	0.36	2.81	0.005	*	0.35	2.69	0.007	*
Other	0.05	0.41	0.684		0.05	0.35	0.73	
Non-Hispanic White (Ref)								
CCI Category								
CCI Category: 1	0.07	0.84	0.402		0.07	0.85	0.397	
CCI Category: 2	0.21	2.47	0.014	*	0.22	2.45	0.014	*
CCI Category: 3	0.20	2.38	0.017	*	0.21	2.21	0.027	*
CCI Category: 4	0.45	5.5	<.0001	*	0.46	5.28	<.0001	*
CCI Category: 0 (Ref)								
Comorbidities								
Alzheimer's Disease								
Dementia	-0.07	-1.3	0.194		-0.07	-1.23	0.217	
Pneumonia	-0.06	-1.03	0.301		-0.05	-0.9	0.369	
Stroke	0.14	3.08	0.002	*	0.15	2.69	0.007	*
Congestive Heart Failure	0.09	2	0.045	*	0.09	2.01	0.044	*
Stage	0.21	4.27	<.0001	*	0.21	4.3	<.0001	*
Stage Moderate								
Stage Advanced	-0.05	-0.99	0.323		-0.05	-1.01	0.311	
Stage Unknown	-0.17	-1.41	0.159		-0.17	-1.38	0.169	
Stage Mild (Ref)	-0.05	-0.93	0.351		-0.05	-0.94	0.348	

* P-value < 0.05

Abbreviations: CI, Confidence Interval.

Table 3.9. OLS model and 2SLS model assessing the relationship between EOL Care Type and Allcause Healthcare Costs During the 9 Mon EOL Period

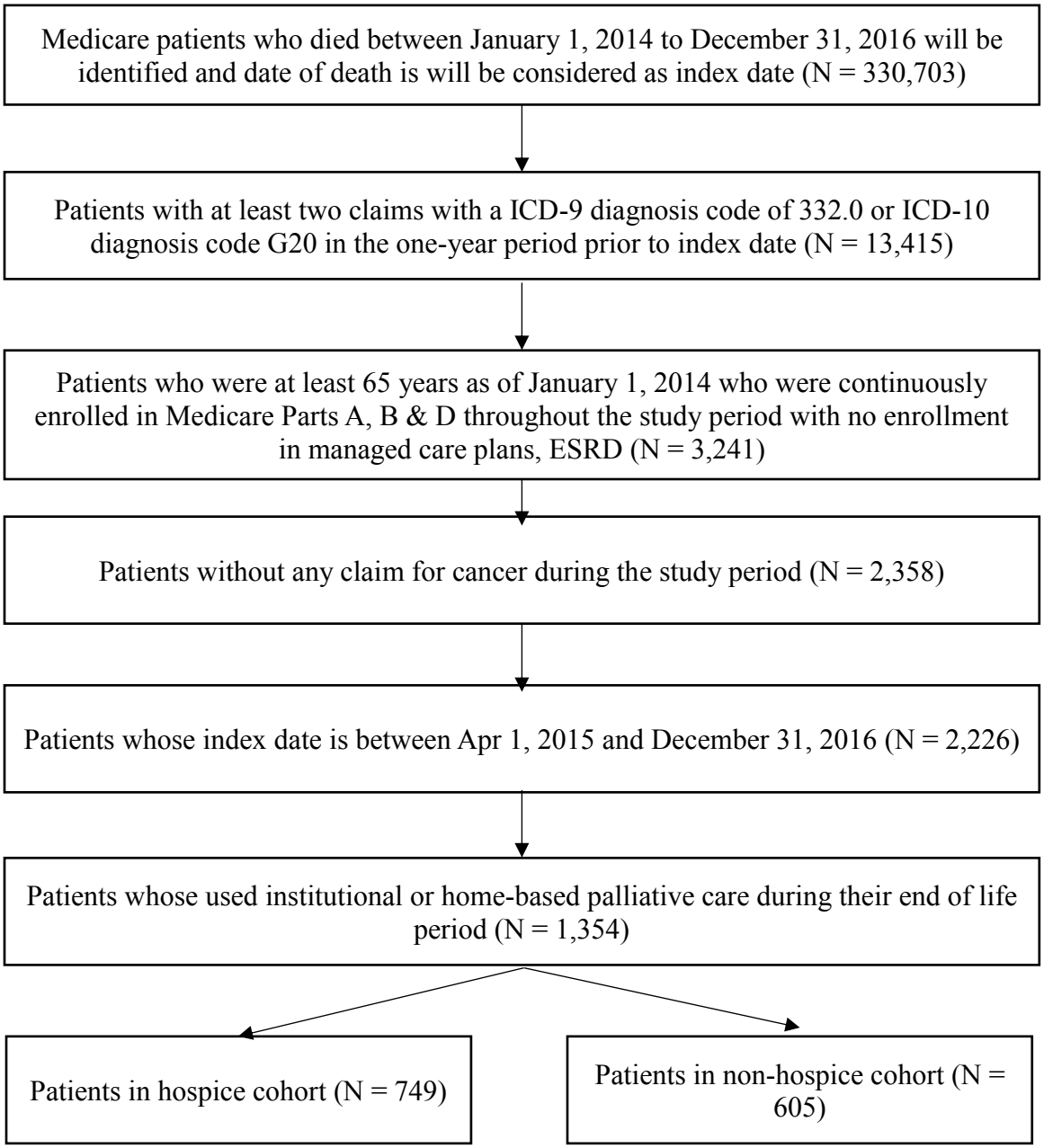
	OLS Regression				2SLS Regression			
Characteristic	**Parameter**	**T-Value**	**P-value**		**Parameter**	**T-Value**	**P-value**	
EOL Choice: HHA	-0.07	-2.09	0.036	*	0.24	0.79	0.431	
Age	-0.01	-6	<.0001	*	-0.01	-4.56	<.0001	*
Female (Ref: Male)	-0.06	-1.73	0.085		-0.06	-1.73	0.084	
Region								
S	-0.01	-0.24	0.809		-0.03	-0.56	0.573	
MW	-0.12	-2.31	0.021	*	-0.10	-1.88	0.06	
W	0.01	0.23	0.819		-0.02	-0.36	0.722	
NE (Ref)								
Race								
African American	0.29	2.77	0.006	*	0.26	2.37	0.018	*
Other	0.07	0.64	0.52		0.04	0.33	0.739	
Non-Hispanic White (Ref)								
CCI Category								
CCI Category: 1	-0.02	-0.32	0.75		-0.02	-0.3	0.767	
CCI Category: 2	0.11	1.63	0.103		0.13	1.8	0.071	
CCI Category: 3	0.14	2.01	0.045	*	0.18	2.22	0.027	*
CCI Category: 4	0.35	5.33	<.0001	*	0.38	5.25	<.0001	*
CCI Category: 0 (Ref)								
Comorbidities								
Alzheimer's Disease	-0.06	-1.28	0.199		-0.05	-1	0.32	
Dementia	0.02	0.54	0.592		0.04	0.87	0.386	
Pneumonia	0.12	3.25	0.001	*	0.15	3.22	0.001	*
Stroke	0.15	3.91	<.0001	*	0.15	3.95	<.0001	*
Congestive Heart Failure	0.16	4.12	<.0001	*	0.17	4.1	<.0001	*
Stage								
Stage Moderate	0.04	0.87	0.383		0.03	0.59	0.553	
Stage Advanced	-0.07	-0.68	0.495		-0.05	-0.51	0.61	
Stage Unknown	-0.04	-1.09	0.275		-0.04	-1.06	0.29	
Stage Mild (Ref)								

* P-value < 0.05

Abbreviations: CI, Confidence Interval.

APPENDIX B

Figure 3.1: Patient selection



CHAPTER 5

Dissertation Summary and Future Research

Summary

Our study used Joinpoint regression to model all-cause healthcare costs prior to death. We found that there is a significant change in the trend of all-cause costs in PD patients at months 3 and 9 prior to death indicating possible shift in the focus on patient's care to palliative care. Using results from Joinpoint regression and clinical judgement we determined the EOL period in PD patients to be the 9-month period prior to death. While previous studies defined EOL period arbitrarily or based on clinical judgement, our study used a data-driven approach which can be used on a consistent basis to identify EOL phase.

Results from our study also indicate that direct healthcare costs during EOL period in PD patients were significantly higher when compared to non-PD patients of similar demographics and comorbidity burden. EOL costs in PD patients were driven by hospitalization costs and palliative care costs where as EOL costs in non-PD cohort were driven by hospitalizations costs and outpatient visit costs. Our study results also highlighted racial and geographic variation in EOL costs in PD patients.

We assessed EOL costs among patients who used hospice services in EOL period and patients who used non-hospice services. While previous studies found that patients with non-cancer conditions and patients in general are more likely to use hospice care during EOL period, our study found that the use of non-hospice EOL care is higher in PD patients when compared to

hospice based EOL care. We also assessed the relationship between place at death and EOL costs using two approaches. In the first approach, results from OLS regression indicated that all-cause costs in the non-hospice cohort were significantly lower than hospice cohort. However, due to the presence of several unobserved confounders we used an instrumental variable approach to assess the relationship between place at death and EOL costs. Results from IV model suggested that EOL costs were higher in non-hospice cohort when compared to hospice cohort but the results did not reach statistical significance.

Future Directions

Our study assessed the duration of EOL period in PD patients using a data-driven approach. Future studies can use longer follow-up periods to identify phases of care during early stages of PD so that phase-based costing models can be built to estimate life time costs of PD. Future studies can assess EOL costs among PD patients who died before attaining age 65. Also, our current study excluded patients who had cancer anytime during the study period. Further studies are required to assess the incremental burden in PD patients with comorbid cancer. Last, our study assessed association between place at death and EOL costs. Future studies can examine the association between type of EOL care (hospice, home health etc.) and EOL costs so that novel EOL care programs can be designed to reduce costs and improve patient's EOL care experience.

CURRICULUM VITAE

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EDUCATION:

- **The University of Mississippi**
  Aug 2012 – Dec 2019
  Ph.D in Health Economics and Outcomes Research
  Master's in Health Economics and Outcomes Research (2016)

- **Birla Institute of Technology and Science (2006 – 2010)**
  Bachelors in Pharmacy (Hons.)

TECHNICAL SKILLS:

- Around 4 years of professional experience in pharmaceutical industry and consulting
- Identifying evidence require
- ments and implementing health economics studies
- Design and execution of HEOR studies
- Network meta-analysis
- PRO measure validation, analysis of PRO data from clinical trials, selection of PRO endpoints in clinical trials
- Understanding and applying appropriate biostatistical and econometric techniques to research
- Pharmacoeconomic modeling using TreeAge, budget impact models using excel

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WORK EXPERIENCE:

- Consultant (HEOR) at IQVIA (previously QuintilesIMS, IMS Health)
  Sep 2017 – Current
  - Working with HEOR/ Market Access teams from pharmaceutical companies to understand their evidence generation needs and support HEOR strategies
  - Design and execution of HEOR studies including writing proposals, study protocols, SAPs
  - Dissemination of HEOR evidence: Presentations, reports, manuscripts and posters

- HEOR Analyst at AbbVie (short-term contractor)
  Sep 2016 – Dec 2016
- Graduate Intern, HEOR at AbbVie
  Jun 2016 – Aug 2016
    - Worked in the immunology/pipeline immunology HEOR team
    - Initiated and worked on several ongoing HEOR activities to support marketed/pipeline assets in immunology TA

- HEOR Intern, Applied Data Analytics at Xcenda LLC
  Jun 2015 – Aug 2015
    - Retrospective database analysis to identify end of life (EOL) costs in advanced melanoma
        - Worked on database analysis, study report, podium and manuscript
    - Clinical study reports (CSR)
    - Worked on electronic medical records (EMR) databases

- Graduate Assistant – Center for Pharmaceutical Marketing and Management (CPMM) at the University of Mississippi
  Jan 2013 – May 2016
    - Currently working in the MS evidence-based drug utilization review (DUR) initiative as an analyst
    - Generate RWE support for MS Medicaid using Medicaid pharmacy and medical claims data
    - Projects related to healthcare utilization, medication adherence, opioid abuse, exceptions monitoring
    - Access to care using SAS geocoding and other procedures
    - Assessed the performance of Mississippi Medicaid on various PQA/NCINQ/HEDIS measures and worked on a PQA measure update panel

- Junior Consultant - IMS Health
  Jul 2011 – Jul 2012
    - Worked as a junior consultant at IMS Health and supported analytics teams and IMS consulting group
    - Studies to assess adherence and persistence using IMS claims data
    - Treatment patterns in oncology using IMS claims data
    - Worked extensively on IMS prescription data using to assess prescription and payer activity across various therapeutic areas
    - Performed post-launch brand performance tracking in US using prescription, sales data and longitudinal data of IMS

- Associate Analyst – Global Data
  Jun 2010 to Jul 2011
  - Worked in forecasting team at Hyderabad, India; Developed patient based models to forecast market size and drug sales in US, EU-5 and Japan
  - Responsibilities included analysis of prescription and claims data for inputs to the models, KOL interviews and building excel based models to forecast market size and drug sales

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MANUSCRIPTS & PODIUM PRESENTATIONS:

- **Nunna S,** Yang Y, Khanna R, Banahan B, Carithers T. Biological and psychosocial risk factors of stroke in African Americans enrolled in the Jackson Heart Study (JHS) (Podium presentation at ISPOR 2017)
- Atkins M, Coutinho AD, **Nunna, S**, Gupte-Singh K, & Eaddy M. (2017). Confirming the timing of phase-based costing in oncology studies: a case example in advanced melanoma. Journal of medical economics, 1-6. (Also podium at ISPOR 2016)
- Hu E, **Nunna S**, Bhattacharya K, Ramachandran S. Obesity among high school students in the United States: risk factors and their population attributable fraction. Preventing Chronic Disease, 15.
- Baum, S. J., Wade, R. L., Xiang, P., Arellano, J., Olmos, C. C., **Nunna, S**., & Desai, N. R. (2019). Demographic And Clinical Characteristics Of Patients Prescribed Proprotein Convertase Subtilisin/kexin Type 9 Inhibitor Therapy And Patients Whose Current Lipid-Lowering Therapy Was Modified. Therapeutics and Clinical Risk Management, 15, 1325-1332.
- Shah R, **Nunna S**, Banahan III B, Hardwick SP, Clark JP. Use of multiple concurrent antipsychotics in children enrolled in the Mississippi Medicaid program. (Podium at ISPOR 2015)

LEADERSHIP AND HONOR SOCIETIES:

- Recipient of William E. Farlow fellowship for the year 2015
- Member of Rho Chi Academic Honors Society in Pharmacy, Chi Chapter
- Who's Who Among Students in American Universities and Colleges
- International student representative on two Chancellor's standing committees (International Student Programs and Recruitment Admissions Orientation and Advising), 2013-15
- Secretary, Graduate Student Council, 2013-14