Journal of Parkinson's Disease 11 (2021) 1381–1392
DOI 10.3233/JPD-202190
IOS Press

Research Report

Characteristics of Parkinson's Disease in Patients with and without Cognitive Impairment

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Accepted 23 February 2021
Pre-press 10 March 2021

Abstract.
Background: Characterizing patients with Parkinson's disease (PD) and cognitive impairment is important toward understanding their natural history.
Objective: Understand clinical, treatment, and cost characteristics of patients with PD pre- and post-cognitive impairment (memory loss/mild cognitive impairment/dementia or dementia treatment) recognition.
Methods: 2,711 patients with PD newly diagnosed with cognitive impairment (index) were identified using administrative claims data. They were matched (1:1) on age and gender to patients with PD and no cognitive impairment (controls). These two cohorts were compared on patient characteristics, healthcare resource utilization, and total median costs for 3 years pre- and post-index using Chi-square tests, *t*-tests, and Wilcoxon rank-sum tests. Logistic regression was used to identify factors predicting cognitive impairment.
Results: Comorbidity indices for patients with cognitive impairment increased during the 6-year study period, especially after the index. Enrollment in Medicare Advantage Prescription Drug plans vs. commercial (OR = 1.60), dual Medicare/Medicaid eligibility (OR = 1.36), cerebrovascular disease (OR = 1.24), and PD medication use (OR = 1.46) were associated with a new cognitive impairment diagnosis (all $p < 0.05$). A greater proportion of patients with cognitive impairment had hospitalizations and emergency department visits and higher median total healthcare costs than controls for each year pre- and post-index.
Conclusion: In patients with PD newly diagnosed with cognitive impairment, comorbidity burden, hospitalizations, emergency department visits, and total costs peaked 1-year pre- and post-identification. These data coupled with recommendations for annual screening for cognitive impairment in PD support the early diagnosis and management of cognitive impairment in order to optimize care for patients and their caregivers.

Keywords: Parkinson's disease, mild cognitive impairment, dementia, cost

INTRODUCTION

Parkinson's disease (PD), a neurogenerative disease, is typically defined as a movement disorder characterized by tremor, rigidity, bradykinesia, and postural instability [1–3]. Non-motor symptoms (affective disorders, psychosis, sleep disturbance,

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autonomic dysfunction, and cognitive impairment) are also important features of PD [1, 4, 5]. It is estimated that nearly 80% of patients with PD will develop dementia (i.e., cognitive impairment with functional impairment) during the course of the disease [6–9].

Cognitive impairment is associated with increased disability, reduced quality of life, and distress for patients with PD, as well as their caregivers [2, 10–12]. Detecting cognitive decline in patients with PD, namely, mild cognitive impairment (MCI) or dementia, is often challenging and largely based on recommended clinical and cognitive assessments [13]. MCI represents an intermediary cognitive deficit on the spectrum between normal cognition and dementia [2, 14, 15] with symptoms that are not severe enough to considerably impact the patient's ability to function normally [6]. Unlike MCI associated with Alzheimer's disease, which typically presents as an amnestic syndrome, MCI in patients with PD is often associated with a deficit in a single domain such as executive/attentional, visuospatial, and verbal fluency, albeit loss of memory may also occur [16]. PD-associated dementia, often identified within 20 years of the initial PD diagnosis [17], is insidious and progressive and defined as impairment in more than one cognitive domain, representing a decline from pre-morbid level, and deficits are severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms [1]. Clinical features associated with dementia in PD patients include impairment in attention, memory, executive and visuo-spatial functions, as well as behavioral symptoms such as affective changes, hallucinations, delusions, apathy, and excessive daytime sleepiness [1].

Published prevalence estimates of cognitive impairment in patients with PD vary widely due to differences in diagnostic criteria, methodology, and study populations. Approximately 25.0% to 30.0% of patients with PD satisfy criteria for MCI following onset of disease [18, 19]. A recent meta-analysis reported that the pooled prevalence of MCI was 40.0% based on 7,053 patients with PD without dementia [20]. The prevalence of PD-associated dementia estimated from community-based studies is 30.0%–40.0%, although the range is wide (10.0%–80.0%) [9, 21]. Overall, the prevalence of dementia in patients with PD increases with age and duration of the disease symptoms [21]. Among industrialized nations, the estimated prevalence of PD rises with age, 1.0% in those older than 60 years and 3.0% in those older than 80 years [3]. For females and males, a meta-analysis reported that incidence rates rose with age from approximately 3.26 to 3.57 per 100,000 person-year at age 40–49 to 103.48 to 258.47 per 100,000 person-years at age 80+, respectively [22]. Due to aging of the United States (US) population, it is estimated that the number of patients with co-existent PD and dementia will triple in US, suggesting that future burden will escalate dramatically [23]. Proposed risk factors for development of PD-associated dementia include rigidity and gait instability, MCI, and the presence of visual hallucinations [24].

The primary goal of this study was to understand the clinical, treatment, and cost characteristics of patients with confirmed PD prior to and following identification of cognitive impairment. Importantly, this study sought to include all possible indicators of cognitive impairment in patients with PD (MCI through dementia). Characterizing patients with PD and cognitive impairment using real-world data sources can help identify disease and treatment patterns, as well as predictors that may allow for early identification and management of this challenging aspect of PD. Overall, this analysis is hypothesis generating and may lead to interventions to reduce risk for cognitive impairment or to modify the impact of cognitive impairment on patients, families, and healthcare resource utilization.

METHODS

Study design and data source

This was a retrospective cohort study utilizing claims data for individuals with PD, enrolled in Humana, Inc.'s Medicare Advantage and Prescription Drug (MAPD) or commercial health plans. MAPD plans are insurance plans offered to US consumers through private companies that cover medical and hospital services included under Medicare Parts A and B and include additional coverage not available in Medicare, typically including a prescription drug plan [25]. Medicaid in the US is a jointly funded federal and state program that assists with medical costs for some individuals with limited income including eligible low-income adults, children, pregnant women, elderly adults, and individuals with disabilities [26]. The study did not include individuals enrolled only in Medicaid but those eligible for both Medicare and Medicaid. Commercial insurance, which is either employer-sponsored or privately

purchased, is defined as any type of healthcare benefit not provided by the government (Medicare/Medicaid) [27].

PD diagnosis was defined as those individuals with > 2 medical claims with a diagnosis code for PD (332.x, G32.x) or > 1 medical claim with a diagnosis code for PD and > 1 prescription claim for a PD medication between January 1, 2007 to December 31, 2014. Specifically, the database was initially searched to identify patients with PD based on diagnostic codes in medical claims or on the following PD medications in pharmacy claims: amantadine, apomorphine, benzotropine, bromocriptine, carbidopa, levodopa, carbidopa-levodopa, entacapone, ethopropazine, pergolide, pramipexole, procyclidine, rasagiline, ropinirole, rotigotine, safinamide, selegiline, tolcapone, and trihexyphenidyl. Among patients identified with PD, those with or without cognitive impairment for the entire study period were subsequently identified. Cognitive impairment was defined as a diagnosis of MCI, memory loss, dementia, or treatment for dementia. Specifically, we identified those newly diagnosed with MCI/memory loss/dementia based on > 1 medical claim or > 1 pharmacy claim for a prescription drug used to treat dementia between January 1, 2010 and December 31, 2014. MCI (331.83, G31.84), memory loss (780.93, R41.2, R41.3), and dementia (290.0–290.4, 294.1x, 294.9x, 331.0, 331.1, F02.8, F03.9x, F05.x, F06.8, G30.x, G31.0x) diagnoses were identified using ICD-9 and ICD-10 CM codes. Dementia was also identified based on medication use (acetylcarnitine, donepezil, galantamine, memantine, rivastigmine, or tacrine). The date of first medical claim for MCI/memory loss/dementia or the date of first pharmacy claim for a prescription drug used to treat dementia was set as the index date. This index date was required to occur after or at the time of the first PD diagnosis or PD prescription claim date in order to be included in this analysis.

Patients with PD with and without cognitive impairment were matched (1:1) on age (±3 years) and gender. The index date for the control group, PD without cognitive impairment, was based on the index date for the matched patient with cognitive impairment. Patients in all cohorts were 19–89 years of age on the index date and were enrolled in a MAPD or commercial plan for at least 3 years pre- and post-index date.

The study protocol was reviewed and approved by Advarra Institutional Review Board. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines.

Measures

Demographic characteristics included age, gender, race/ethnicity, and plan type (MAPD or commercial). Among those enrolled in MAPD, we identified individuals eligible for Medicare and Medicaid (dual eligible) and those eligible for low-income subsidy (Medicare beneficiaries with income below 150% of poverty and limited resources are eligible for additional premium and cost-share assistance for prescription drugs under the Medicare Part D program).

Comorbidity indices Deyo Charlson Comorbidity index (DCCI) [28–30] and RxRisk V score [31] were used to understand the comorbidity burden for these patients. The prevalence of specific comorbidities, including myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease (CVD), chronic obstructive pulmonary disease (COPD), diabetes mellitus with and without complications, renal disease, and cancer, was reported. The number of unique medications for all patients was calculated for each year. Additionally, use of specific classes of medications including PD medications, antipsychotics, antidepressants, and benzodiazepines/psychostimulants was evaluated separately. The proportion of patients in long-term care and skilled nursing facilities each year was identified. For healthcare resource use and costs, we calculated the proportion of patients with hospitalization and emergency department (ED) visits and median total median costs per person per year. Total cost is the sum of total medical and pharmacy costs (medications filled in retail or mail order pharmacy), adjusted to 2019 dollars.

Statistical analyses

Descriptive analyses were used to compare demographic characteristics of patients with PD with and without cognitive impairment. Clinical characteristics, including comorbidity indices, prevalence of specific comorbidities, medication use, long-term care, and skilled nursing facility use, were evaluated for the 3 years pre-and post-index (post-cognitive impairment identification). The Wilcoxon signed-rank test was used to assess differences in medians of continuous variables between baseline (pre-index) and post-index periods. The McNemar's test and the kappa coefficient were used to assess the statistical significance of paired categorical variables and the paired *t*-test for paired continuous variables. Comparisons between cohorts (PD with and without cognitive

impairment) on these clinical characteristics were conducted using Chi-square tests for categorical variables and *t*-tests and Wilcoxon rank-sum tests for continuous variables as appropriate.

Logistic regression was utilized to identify factors (pre-index demographic and clinical characteristics) associated with cognitive impairment. For potential prognostic factors, univariate logistic regression models were used to estimate the odds ratio (OR) for each of the demographic and clinical factors of interest. Variables with a p-value of < 0.05 in the univariate model were then fit into a multivariate logistic regression model. Variables responsible for multicollinearity were removed from consideration in the final model.

The proportion of patients hospitalized or with an ED visit in the cognitively impaired cohort was compared to the non-cognitively impaired cohort. Median total costs (adjusted to 2019) per year for each of the 3 years pre- and post-index were calculated and compared between the two cohorts.

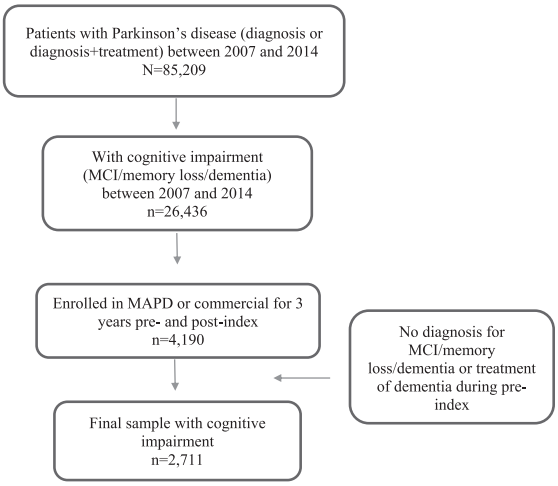

Fig. 1. Study Population Identification. MAPD, Medicare Advantage and Prescription Drug; MCI, mild cognitive impairment.

RESULTS

We identified 2,711 patients with PD and newly identified cognitive impairment (Fig. 1). Among these 2,711 patients with PD, 751 (27.7%) were newly diagnosed with MCI/memory loss only, 1,498 (55.3%) with dementia, and 462 (17.0%) with both MCI/memory loss and dementia.

Demographic and clinical characteristics

Patients with PD with and without cognitive impairment, respectively, were 75.3 years (standard deviation [SD] 8.1) and 75.1 years (SD 8.1) of age, mostly White (84.0% and 85.0%), living in urban areas (69.3% and 67.0%), and largely enrolled in MAPD plans (98.3% and 97.2%) (Table 1). Among patients with PD and cognitive impairment, a greater proportion were eligible for low-income subsidy (22.5% vs. 20.4%) and/or dual eligible (18.0% vs. 15.0%) compared to the non-cognitively impaired cohort ($p < 0.05$). Of note, during the 3 years prior to the index date, the proportions of patients with CVD were significantly greater in the PD with cognitive impairment cohort (9.3% to 17.6%) vs. the PD without cognitive impairment cohort (7.1% to 9.1%; $p < 0.02$) but similar for diabetes (with and without complications) between PD patients with and without cognitive impairment. In addition, a higher proportion of patients with PVD was observed in the PD with cognitive impairment cohort vs. the PD without cognitive impairment cohort 1 year prior to the index date (16.5% vs. 13.6%, respectively; $p = 0.002$).

The DCCI and RxRisk V score comorbidity indices for patients with cognitive impairment increased during the 6 years, especially after the index date (Table 1). The most common comorbidities included CVD, PVD, diabetes mellitus without complications, COPD, and renal disease. For these patients, the use of medications for PD increased from 45.4% during Year 3 pre-index to 87.2% in Year 3 post-index, whereas the proportion of patients treated with antidepressants increased from 35.3% to 71.9% and benzodiazepines/psychostimulants increased from 26.4% to 64.2% over the same time period. For patients with PD and cognitive impairment, the proportion of patients in a long-term care facility increased from 7.1% during the year prior to index date to 12.5% during the year immediately following index. Similarly, the proportion of patients with cognitive impairment in a skilled nursing facility increased from 8.0% during the year prior to index to 12.4% during the year immediately following index. By Year 3 post-index, 17.7% of patients with cognitive impairment were in a long-term care facility and 11.6% of patients were in a skilled nursing facility. Table 2 presents the clinical characteristics for the PD plus cognitive impairment cohort compared with control cohort (no cognitive impairment) at 1-, 2- and 3-years prior to index.

Table 1
Baseline Demographics and Clinical Characteristics Pre- and Post-Diagnosis of Cognitive Impairment Among Patients With Parkinson's Disease

Demographic Characteristics N	With Cognitive Impairment *n* = 2,711	No Cognitive Impairment *n* = 2,711
Age in years		
Mean (SD)	75.3 (8.1)	75.1 (8.1)
Median [Q1-Q3]	76 [71–81]	76 [71–81]
Min, Max	35, 89	36, 89
Age categories, *n* (%)		
<65	228 (8.4)	239 (8.8)
65–74	942 (34.8)	968 (35.7)
75–89	1,541 (56.8)	1,504 (55.5)
Sex, *n* (%)		
Female	1,271 (46.9)	1,271 (46.9)
Male	1,440 (53.1)	1,440 (53.1)
Race/ethnicity, *n* (%)		
White	2,279 (84.0)	2,304 (85.0)
Black	225 (8.3)	207 (7.6)
Other/unknown	207 (7.6)	200 (7.4)
Population density, *n* (%)		
Urban	1,879 (69.3)	1,815 (67.0)
Suburban	536 (19.8)	591 (21.8)
Rural	225 (8.3)	235 (8.7)
Unknown	71 (2.6)	70 (2.6)
Region, *n* (%)		
Northeast	56 (2.1)	66 (2.4)
Midwest	630 (23.2)	638 (23.5)
South	1,859 (68.6)	1,804 (66.5)
West	166 (6.1)	203 (7.5)
Plan type: MAPD or commercial, *n* (%)		
MAPD	2,665 (98.3)	2,634 (97.2)
Commercial	46 (1.7)	77 (2.8)
Low-income subsidy eligible, *n* (%¥)	599 (22.5)	538 (20.4)
Dual eligibility, *n* (%¥)	479 (18.0)	394 (15.0)

Clinical Characteristics of the Cognitively Impaired Cohort	Prior to Index			Post-Index		
N	Year 3 *n* = 2,711	Year 2 *n* = 2,711	Year 1 *n* = 2,711	Year 1 *n* = 2,711	Year 2 *n* = 2,711	Year 3 *n* = 2,711
DCCI						
Mean [SD]	1.3 [1.9]	1.5 [2.1]	1.9 [2.3]	2.4 [2.4]	2.3 [2.4]	2.5 [2.6]
Median [Q1–Q3]	1 [0–2]	1 [0–2]	1 [0–3]	2 [1–4]	2 [0–4]	2 [0–4]
Cumulative mean [SD]	1.3 [1.9]	2.1 [2.4]	2.8 [2.7]	3.7 [3.0]	4.3 [3.2]	4.9 [3.8]
Specific comorbidities, *n* (%)						
MI	134 (4.9)	216 (8.0)	297 (11.0)	370 (13.7)	419 (15.5)	482 (17.8)
CHF	199 (7.3)	332 (12.3)	471 (17.4)	619 (22.8)	723 (26.7)	845 (31.2)
PVD	269 (9.9)	480 (17.7)	677 (25.0)	917 (33.8)	1,115 (41.1)	1,272 (46.9)
CVD	253 (9.3)	469 (17.3)	776 (28.6)	1,076 (39.7)	1,225 (45.2)	1,375 (50.7)
COPD	361 (13.3)	547 (20.2)	721 (26.6)	884 (32.6)	999 (36.9)	1,106 (40.8)
Diabetes w/o complications	679 (25.1)	826 (30.5)	931 (34.4)	1,030 (38.0)	1,087 (40.1)	1,146 (42.3)
Diabetes with complications	260 (9.6)	361 (13.3)	460 (17.0)	556 (20.5)	633 (23.4)	697 (25.7)
Renal disease	310 (11.4)	480 (17.7)	689 (25.4)	866 (31.9)	991 (36.6)	1,107 (40.8)
Cancer	174 (6.4)	298 (11.0)	379 (14.0)	437 (16.1)	497 (18.3)	547 (20.2)
RxRisk V score						
Mean [SD]	5.7 [3.3]	6.0 [3.4]	6.4 [3.4]	7.1 [3.5]	7.0 [3.5]	6.7 [3.6]
Median [Q1–Q3]	6 [3–8]	6 [4–8]	6 [4–9]	7 [5–9]	7 [5–9]	7 [5–9]
Number of unique medications (class level)						
Mean [SD]	8.4 [6.2]	8.9 [6.4]	10.0 [6.5]	11.7 [6.7]	12.0 [6.7]	12.1 [6.8]
Median [Q1–Q3]	8 [4–12]	8 [4–13]	9 [5–14]	11 [7–16]	11 [7–16]	11 [7–16]

(*Continued*)

Table 1
(*Continued*)

	Prior to Index			Post-Index		
N	Year 3 $n = 2,711$	Year 2 $n = 2,711$	Year 1 $n = 2,711$	Year 1 $n = 2,711$	Year 2 $n = 2,711$	Year 3 $n = 2,711$
Use of PD medications, *n* (%)	1,231 (45.4)	1,437 (53.0)	1,796 (66.3)	1,936 (71.4)	1,835 (67.7)	2,365 (87.2)
Other drug classes of interest, *n* (%)						
Anti-psychotics	187 (6.9)	203 (7.5)	262 (9.7)	379 (14.0)	519 (9.6)	865 (31.9)
Anti-depressants	957 (35.3)	1,023 (37.7)	1,145 (42.2)	1,263 (46.6)	2,156 (39.8)	1,948 (71.9)
Benzodiazepines/ psychostimulants	715 (26.4)	787 (29.0)	876 (32.3)	938 (34.6)	1,592 (29.4)	1,741 (64.2)
Long-term care, *n* (%)	60 (2.2)	90 (3.3)	193 (7.1)	338 (12.5)	364 (13.4)	480 (17.7)
Skilled nursing facility, *n* (%)	81 (3.0)	120 (4.4)	216 (8.0)	337 (12.4)	257 (9.5)	315 (11.6)

DCCI scores and prevalence of comorbidities represent the prevalence in each year based on presence of a claim with the diagnosis code. CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DCCI, Deyo Charlson Comorbidity index; MAPD, Medicare Advantage and Prescription Drug Plan; Max, maximum; Min, minimum; MI, myocardial infarction; PD, Parkinson's disease; PVD, peripheral vascular disease; Q, quartile; SD, standard deviation; w/o = without.[¥] Calculated as a percentage of individuals enrolled in MAPD.

Predictors of a new cognitive impairment diagnosis

Table 3 depicts the results of the logistic regression evaluating factors associated with the identification of cognitive impairment. For the overall population, diagnosis of CVD (OR = 1.24; 95% confidence interval [CI] 1.01–1.51; $p = 0.036$) and use of PD medication (OR = 1.46; 95% CI 1.30–1.63; $p < 0.001$) increased the odds of cognitive impairment by 24.0% and 46.0%, respectively. Enrollment in an MAPD plan increased the odds of having a cognitive impairment by 60.0% compared to those enrolled in a commercial plan (OR = 1.60; 95% CI 1.10–2.33; $p = 0.013$). Furthermore, individuals eligible for both Medicare and Medicaid had a 36.0% higher chance to have cognitive impairment than individuals who were not dual eligible (OR = 1.36; 95% CI 1.07–1.72; $p = 0.012$).

Healthcare resource utilization and cost

The cohort with newly identified cognitive impairment had a higher proportion of patients with at least one hospitalization than the cohort without cognitive impairment (Fig. 2). The proportion of patients with cognitive impairment and ED visits increased especially during the year prior to (50.9%) and following index date (52.5%) compared to those without cognitive impairment (31.0% and 33.1%, respectively). However, the proportion of patients with cognitive impairment and ED visits declined slightly by Years 2 and 3 post-index (49.6% and 51.6%, respectively). Similar results were observed for proportion of patients with hospitalization. The proportion of patients with hospitalization in the cohort with cognitive impairment was nearly 2-fold greater than that of patients without cognitive impairment during the year prior to (31.5% vs. 17.6%) and following index (35.0% vs. 19.0%) (Fig. 2). The cohort without cognitive impairment saw a steady increase in proportion of patients with a hospitalization or ED visit from Year 3 pre-index to Year 3 post-index.

The cognitively impaired cohort had higher median total healthcare costs per patient compared with the non-cognitively impaired cohort for each year pre- and post-index (Fig. 3). For patients with a cognitive impairment, costs peaked during Year 1 post-index ($10,590) and declined during Years 2 ($8,965) and 3 post-index ($9,345), whereas the non-cognitively impaired cohort showed a much slower increase in costs over the observation period ($5,237 Year 1 pre-index, $5,763 Year 1 post-index, and $7,077 Year 3 post-index).

DISCUSSION

This retrospective cohort study utilizing claims data from a national health plan provides an in-depth examination of demographic and clinical characteristics, healthcare resource utilization, and costs during the 3-year span prior to and following identification of cognitive impairment among 2,711 individuals with PD compared to individuals with PD who did not develop cognitive impairment. Overall, our study findings suggest that even before a cognitive impairment diagnosis, patients with PD had increased

Table 2
Clinical Characteristics for the PD plus Cognitive Impairment Cohort Compared With Control Cohort (No Cognitive Impairment)

	Year 3 prior to Index			Year 2 prior to Index			1 Year Prior to Index		
	MCI/Memory Loss/Dementia	Matched Controls	*p*	MCI/Memory Loss/Dementia	Matched Controls	*p*	MCI/Memory Loss/Dementia	Matched Controls	*p*
N	*n* = 2,711	*n* = 2,711		*n* = 2,711	*n* = 2,711		*n* = 2,711	*n* = 2,711	
DCI									
Mean [SD]	1.3 [1.9]	1.3 [1.8]	0.533	1.5 [2.1]	1.5 [1.9]	0.481	1.9 [2.3]	1.6 [2.0]	<0.001
Median [Q1–Q3]	1 [0–2]	1 [0–2]		1 [0–2]	1 [0–2]		1 [0–3]	1 [0–3]	
Specific Comorbidities, n (%)									
MI	134 (4.9)	121 (4.5)	0.404	138 (5.1)	127 (4.7)	0.488	159 (5.9)	135 (5.0)	0.15
CHF	199 (7.3)	186 (6.9)	0.492	250 (9.2)	224 (8.3)	0.211	318 (11.7)	260 (9.6)	0.011
PVD	269 (9.9)	293 (10.8)	0.285	353 (13.0)	335 (12.4)	0.463	448 (16.5)	368 (13.6)	0.002
CVD	253 (9.3)	193 (7.1)	0.003	287 (10.6)	236 (8.7)	0.019	478 (17.6)	248 (9.1)	<0.001
COPD	361 (13.3)	348 (12.8)	0.600	423 (15.6)	418 (15.4)	0.851	499 (18.4)	427 (15.6)	0.009
Diabetes w/o complications	679 (25.1)	699 (25.8)	0.533	699 (25.8)	707 (26.1)	0.804	763 (28.1)	727 (26.8)	0.273
Diabetes with complications	260 (9.6)	262 (9.7)	0.927	288 (10.6)	277 (10.2)	0.625	345 (12.7)	318 (11.7)	0.263
Renal disease	310 (11.4)	303 (11.2)	0.764	377 (13.9)	395 (14.5)	0.484	515 (19.0)	469 (17.3)	0.105
Cancer	174 (6.4)	179 (6.6)	0.783	214 (7.9)	211 (7.8)	0.879	230 (8.5)	216 (8.0)	0.489
RxRisk V score									
Mean [SD]	5.7 [3.3]	5.3 [3.2]	0.006	6.0 [3.4]	5.5 [3.2]	0.002	6.4 [3.4]	5.8 [3.2]	0.001
Median [Q1–Q3]	6 [3–8]	5 [3–7]		6 [4–8]	5 [3–8]		6 [4–9]	6 [4–8]	
Number of unique medications (class level)									
Mean [SD]	8.4 [6.2]	7.6 [5.6]	<0.001	8.9 [6.4]	8.1 [5.7]	<0.001	10.0 [6.5]	8.8 [5.9]	<0.001
Median [Q1–Q3]	8 [4–12]	7 [4–11]		8 [4–13]	8 [4–11]		9 [5–14]	8 [5–12]	
Use of PD medications, *n* (%)	1,231 (45.4)	958 (35.3)	<0.001	1,437 (53.0)	1,128 (41.6)	<0.001	1,796 (66.3)	1,319 (48.7)	<0.001
Number of unique PD medication classes									
Mean [SD]	0.60 [0.87]	0.46 [0.77]	<0.001	0.71 [0.90]	0.55 [0.83]	<0.001	0.90 [0.93]	0.65 [0.85]	<0.001
Median [Q1–Q3]	0 [0–1]	0 [0–1]		0 [0–1]	0 [0–1]		1 [0–1]	0 [0–1]	
Long-term care, n (%)	60 (2.2)	38 (1.4)	0.025	90 (3.3)	47 (1.7)	<0.001	193 (7.1)	71 (2.6)	<0.001
Skilled nursing facility, *n* (%)	81 (3.0)	62 (2.3)	0.107	120 (4.4)	69 (2.6)	<0.001	216 (8.0)	95 (3.5)	<0.001

Note: Cell sizes less than 10 were suppressed. Where no comparisons could be made due to 1 or more cells being suppressed, *p*-values were removed (i.e., n/a). **matched on age (+/- 3 y) and gender CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DCI, Deyo-Charlson Comorbidity index,; MI, myocardial infarction; PD, Parkinson's disease; PVD, peripheral vascular disease; Q, quartile; SD, standard deviation; w/o, without.

Table 3
Logistic Regression of Factors Associated With a New Diagnosis of Cognitive Impairment in Patients With Parkinson's Disease

Parameter	Odds Ratio (95% Confidence Interval)	Pr>ChiSq
CVD	1.24 (1.01–1.51)	0.036
RxRisk V score	1.01 (0.98–1.03)	0.640
Number of unique medications (class level)	1.01 (1.00–1.03)	0.127
Use of Parkinson's disease medications	1.46 (1.30–1.63)	<0.0001
Plan type (MAPD vs. commercial)	1.60 (1.10–2.33)	0.013
Low-income subsidy eligible	0.84 (0.68–1.05)	0.126
Dual eligibility (Medicare and Medicaid)	1.36 (1.07–1.72)	0.012
Long-term care	1.34 (0.88–2.03)	0.173

ChiSq, Chi square; MAPD, Medicare Advantage and Prescription Drug plan; Pr, probability.

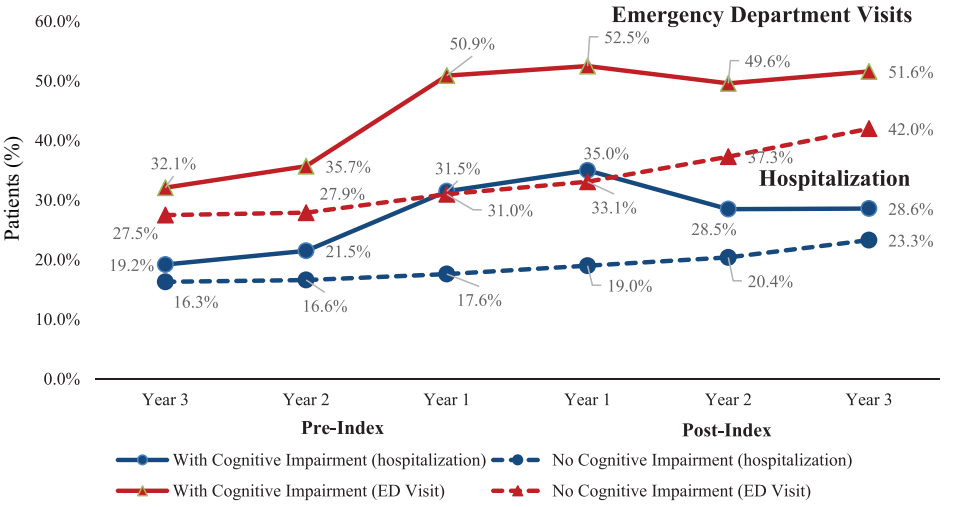

Fig. 2. Proportion of Patients with Hospitalization or Emergency Department Visits Prior to and Following Cognitive Impairment Diagnosis. ED visit, Emergency department visit.

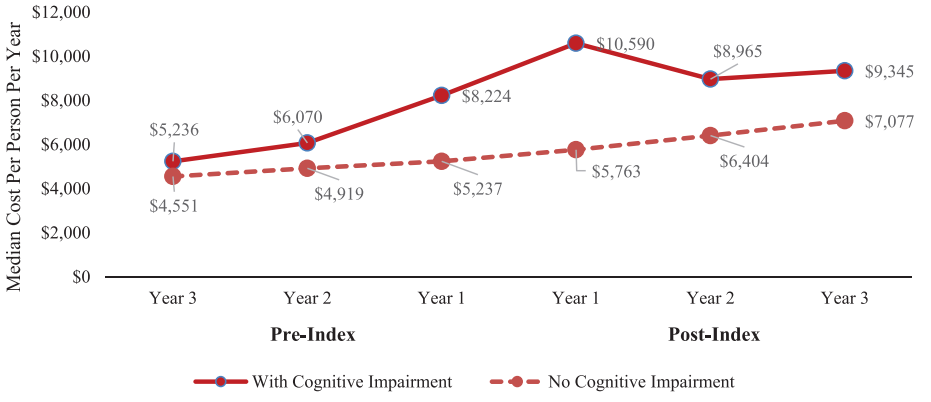

Fig. 3. Median Total Costs for Each Cohort Prior to and Following Cognitive Impairment Diagnosis. Note: In 2019 dollars.

comorbidities (i.e., CVD), need for long-term care or skilled nursing facility care, increased healthcare resource utilization (hospitalization and ED visits), and increased costs.

Among patients with PD who developed cognitive impairment, comorbidity burden increased during the 3 years prior to identification of cognitive impairment, especially the year prior, and continued to increase after identification. The increased DCCI and RxRisk V scores parallel the increasing proportions of patients with comorbidities closer to the diagnosis of one or more of these cognitive conditions. Among the specified comorbidities, notably, a greater proportion of patients had cardiovascular-related diagnoses (MI, CHF, CVD, and PVD). This aligns with reports of increased heart disease-related risks among patients with PD and cognitive impairment or dementia [32, 33].

Among the comorbidities, CVD was significantly associated with a diagnosis of cognitive impairment (i.e., 24.0% greater odds of cognitive impairment). In the literature, CVD has been consistently associated with dementia [34, 35], and our findings support the potential role of CVD in the development of cognitive impairment in PD. The increase in CVD and other select comorbidities in the year prior to the diagnosis of cognitive impairment-related to PD could also represent surveillance bias. That is, patients beginning to experience cognitive impairment symptoms may have more healthcare provider visits, which in turn may result in additional diagnostic tests/scans that uncover new diagnoses or vice versa. In addition, this analysis cannot imply causality, and it is plausible that the increasing severity of cognitive dysfunction over time may play a role in a patient's ability to manage chronic conditions and/or engage in health maintenance, resulting in the development of new physical ailments or the exacerbation of existing conditions. The increasing number of comorbidities in this cognitively impaired population with PD may indeed be greater with MCI or dementia and mandates clinical practice to focus more on risk factor management of these patients, as well as preventive care with appropriate medical support. In addition, earlier recognition of cognitive impairment in patients with PD may alter the management of care by the physician and caregiver to provide closer oversight of treatments and medications, thereby potentially reducing healthcare resource use such as ED visits.

In this study, admission to either long-term care or a skilled nursing facility increased each year prior to identification of cognitive impairment and was almost doubled by the third year after identification. These findings likely reflect the increasing care needs of these patients as the disease progresses, especially in those with dementia, which was high in our sample population. However, the increased admissions to long-term care or skilled nursing facilities may also be partly due to the increase of other comorbidities (e.g., CVD). Safarpour et al. reported that a quarter of Medicare-enrolled patients with PD and dementia resided in a long-term care facility and dementia was among the strongest predictors of use of long-term care facilities [36].

Cognitive impairment was associated with a greater proportion of patients prescribed medications for PD, such as levodopa, compared to non-cognitively impaired cohort. While we did not evaluate the specific regimens and their respective doses, it has been suggested that higher daily doses of levodopa may be an independent risk factor for the development of dementia [37]. In contrast, several studies indicate that the use of levodopa is not associated with, or may even prevent, cognitive decline in patients with PD [38, 39]. Greater healthcare utilization, such as increased hospitalizations/ED visits and long-term/skilled nursing facility care, due to comorbidities may account for more intensive interactions with prescribers and greater likelihood of being treated. The association of increased PD medications may not be related to a new diagnosis of cognitive impairment but rather other progressive disease signs and symptoms. It is also possible that patients with PD and cognitive impairment may have more severe disease and require more treatment. Published literature on the influence of PD medications on dementia risk is mixed, and further research is needed to elucidate the apparent association between PD treatment and cognitive impairment.

Enrollment in MAPD and dual eligibility (Medicare and Medicaid) were associated with increased detection of cognitive impairment. The risk associated with MAPD enrollment may be due to the fact that $>90\%$ patients with these diagnoses were enrolled in MAPD in this study. Additionally, it may also be reflective of age and its influence on cognitive impairment risk. It is notable that patients with PD eligible for Medicare and Medicaid had a 36.0% greater chance of being diagnosed with a cognitive impairment. With the increased need for long-term care services and disabilities among patients with dementia, Medicaid is often needed to cover gaps in coverage with Medicare. This dual eligibility also could reflect the impact of socioeconomic factors on

dementia risk and the impact of other illnesses that lead to disability.

Finally, these study findings suggest that during each of the 3 years prior to and following a cognitive impairment diagnosis, patients had increased hospitalizations and ED visits and higher costs compared to patients in the non-cognitively impaired cohort. The proportion of patients with hospitalization or ED visit peaked during the year pre- and post-identification of cognitive impairment. Healthcare costs for patients with PD and newly identified with cognitive impairment peaked during the year immediately following the identification and declined slightly during Years 2 and 3 post-identification. Overall, costs for patients with cognitive impairment were higher than those of the non-cognitively impaired cohort. Approaches to identify those at highest risk for cognitive impairment may allow interventions to minimize healthcare utilization and costs prior to dementia onset. Several studies have reported similar trends in healthcare resource utilization and costs in newly diagnosed Alzheimer's patients [40–43]. Albrecht and coworkers reported that HCRU was highest in the outpatient setting, which in part was related to increased neuropsychiatric comorbidities during the year prior to dementia diagnosis [42]. Our study corroborates the findings of Desai et al. who reported increased costs secondary to all-cause hospitalizations and all-cause ED visits compared to the control group each year preceding a diagnosis of Alzheimer's disease [43]. Marešová et al. reported costs in patients with PD and dementia to be 3 times higher than those in patients with PD and no dementia [44]. In the current study, costs in the cognitive impairment cohorts were 15% to 45% higher than the non-cognitively impaired cohort. This observation may be due to differences in the population, duration of disease (newly diagnosed), methodology, and the healthcare system.

Limitations

The findings of these analyses need to be interpreted within the context of the study limitations described below. Limitations common to studies using administrative claims data, such as potential errors in coding, omissions in claims data, and unmeasured clinical, economic, or behavioral factors, may impact the results. This study utilized data with a Medicare-rich member population, thus the results may not be generalizable, particularly for younger patients in commercial plans. However, given the lower risk of PD and cognitive impairment for these younger individuals, this is unlikely to have a significant impact in the overall findings. No causal inference can be ascertained from this study since it was a non-interventional study using existing data. Accordingly, the root cause of cognitive impairment could not be addressed in this study. Yet, it is acknowledged that 1) cognitive impairment is a common sequelae in PD, and 2) etiology of cognitive impairment, as with many forms of dementias, may be multifactorial, including vascular and other risk factors as well as primary PD pathology.

The definitions of PD and cognitive impairment used in this study, while imperfect, were an attempt to identify the populations of interest. It is possible that patients with only 1 medical claim with a diagnosis code for PD and 1 prescription claim for a PD medication were misclassified as having PD. It is also recognized that PD medications were not completely captured and only included representative medications for each class. Likewise, it is also possible that the definition used to identify cognitive impairment in PD patients either missed some patients who had cognitive impairment or classified some patients with cognitive impairment who did not have true cognitive impairment issues. This analysis employed a lower threshold for identifying cognitive impairment for several reasons: 1) In a patient with PD, new onset cognitive impairment is likely to be relevant as they are at higher risk for cognitive impairment, and therefore, the finding is less likely to be a false negative despite being less strict; 2) Providers may be less likely to diagnose cognitive impairment or prescribe cognitive impairment medications in a PD patient for a variety of reasons; therefore, stricter criteria may have missed individuals with cognitive impairment; and 3) Since PD identification had to predate cognitive impairment in these analyses, we were interested in changes up to the initial cognitive impairment diagnosis and used the first cognitive impairment diagnosis to understand clinical and HCRU prior to and at the time of cognitive impairment diagnosis.

Lack of medical records makes it difficult to fully understand diagnosis and treatment choices and reasons behind physicians' decisions. Although the study data were drawn from a large national health plan with persons enrolled throughout the US, the results may not be generalizable to the overall US population or to specific subpopulations in certain geographic regions. Moreover, the results may not be generalizable to all beneficiaries due to differences in benefit structures of MAPD vs. non-MAPD health plans. Finally, a potential bias is that this analysis

was limited to PD patients with 6 years of follow-up in the database; thus, patients who disenrolled prior to 6 years may be different from those included in the analysis.

Despite these limitations, to the best of our knowledge, this is the first study to longitudinally examine the characteristics of patients with PD before and after being newly diagnosed with cognitive impairment. The findings from this study should be replicated using additional data sources that include other populations of patients with PD.

CONCLUSION

In patients with PD who were newly diagnosed with cognitive impairment, comorbidity burden and use of long-term care or skilled nursing facilities increased over the years, especially the year prior to the cognitive impairment diagnosis. Furthermore, HCRU and total costs peaked 1-year pre- and post-cognitive impairment identification. These data coupled with recommendations for annual screening for cognitive impairment in PD [13] support the early diagnosis and management of cognitive impairment in order to optimize care for patients and their caregivers.

ACKNOWLEDGMENTS

Eli Lilly and Company and Humana, Inc. collaboratively designed the study and interpreted results. Data analyses were performed by Humana. Writing support was provided by Teresa Tartaglione, PharmD (Synchrogenix, a Certara Company, Wilmington, Delaware).

CONFLICT OF INTEREST

JC, KB, and LM are employees and minor stockholders for Eli Lilly and Company; RN, EAF, and NP are employees of Humana Healthcare Research, Inc.; and TC is an employee of Humana, Inc.

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