



Healthcare resource utilization among nursing home residents with Parkinson's disease psychosis: an analysis of Medicare beneficiaries treated with pimavanserin or other-atypical antipsychotics

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Aim: Real-world healthcare resource use (HCRU) burden among patients with Parkinson's disease psychosis (PDP) treated with pimavanserin (PIM) versus other atypical antipsychotics (other-AAPs) including quetiapine (QUE) in long term care (LTC) and nursing home (NH) settings are lacking. This analysis examines HCRU differences among residents in LTC/NH settings who initiate PIM versus QUE or other-AAPs. **Methods:** A retrospective analysis of LTC/NH residents with PDP from the 100% Medicare claims between 1 April 2015 and 31 December 2021 was conducted. Treatment-naïve residents who initiated ≥ 6 months continuous monotherapy with PIM or QUE or other-AAPs between 04/01/16 and 06/30/2021 were propensity score matched (PSM) 1:1 using 31 variables (age, sex, race, region and 27 Elixhauser comorbidity characteristics). Post-index (i.e., 6 months) HCRU outcomes included: proportion of residents with ≥ 1 all-cause inpatient (IP) hospitalizations and emergency room (ER) visits. HCRU differences were assessed via log binomial regression and reported as relative risk ratios (RR) and 95% confidence intervals after controlling for dementia, insomnia and index year. **Results:** From a total of PIM ($n = 1827$), QUE ($n = 7770$) or other-AAPs ($n = 9557$), 1:1 matched sample ($n = 1827$) in each cohort were selected. All-cause IP hospitalizations (PIM [29.8%]) versus QUE [36.7%]) and ER visits (PIM [47.3%] versus QUE [55.8%]), respectively, were significantly lower for PIM. PIM versus QUE cohort also had significantly lower RR for all-cause IP hospitalizations and ER visits, respectively, (IP hospitalizations RR: 0.82 [0.75, 0.9]; ER visits RR: 0.85 [0.8, 0.9]). PIM versus other-AAPs also had lower likelihood of HCRU outcomes. **Conclusion:** In this analysis, LTC/NH residents on PIM monotherapy (versus QUE) had a lower likelihood of all-cause hospitalizations (18%) and ER (15%) visits. In this setting, PIM also had lower likelihood of all-cause HCRU versus other-AAPs.

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Keywords: atypical antipsychotics • healthcare resource utilization • long-term care • nursing homes • Parkinson's disease psychosis • pimavanserin • quetiapine

Background

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease affecting up to 1 million people in the US [1,2]. With nearly 90,000 new cases each year of PD diagnosis in the US, it is expected to rise to 1.2 million by 2030 [2]. The combined direct and indirect costs of PD, including treatment, Social Security payments and lost income from inability to work, is estimated to be nearly \$25 billion per year in the US alone [2,3]. While PD is widely known to result in motor changes, nonmotor changes, including neuropsychiatric symptoms, are often considered to be a greater burden associated with the treatment and management of these patients [4,5]. Current literature suggests that non-motor neuropsychiatric symptoms such as hallucinations and delusions, a characteristic hallmark of Parkinson's disease psychosis (PDP), are often unrecognized and untreated [6].

Diagnosis of PDP is often complicated due to multiple factors such as difficulty in diagnosis, absence of diagnostic criteria and frequency of misdiagnosis [7–9].

In prior research, PDP is known to occur about 10 years or more after initial diagnosis of PD [10]. However, other studies suggest that a diagnosis of PDP may occur within 4 years of a PD diagnosis in nearly 60% PD patients [11]. Some estimates suggest a lifetime prevalence rate for PDP of 25% in community-based populations and nearly 50% in clinic-based or institutional populations [12]. Overall, PDP treatment and management is challenging since it is associated with a significantly diminished quality of life, worsening patient outcomes, increased caregiver burden and increased patient mortality rates [13]. Additionally, PDP is strongly associated with higher rates of nursing home placement, regardless of age [14]. In fact, research from the literature suggests that ~75% of patients with PDP compared with ~56% of patients with PD without psychosis spent time in long-term care (LTC) or nursing homes (NHs). On average, patients with PDP spent nearly six months while those with PD-only spent less than three months in LTC/NH [15]. Patients with PDP also incur greater economic costs; with twice the annual all-cause medical costs versus patients with PD-only in LTC settings (\$31,178 vs \$14,461) [15].

Currently, pimavanserin (PIM) remains the only atypical antipsychotic that has been approved by the US Food and Drug Administration (FDA) to treat hallucinations and delusions associated with PDP. Evidence based review of treatments for non-motor symptoms by Movement Disorders Society (MDS), published in 2019, suggests that PIM is clinically useful for treating psychosis symptoms among patients with PDP. It has demonstrated effectiveness in improving psychotic symptoms of PDP, is well-tolerated and displays no worsening of motor symptoms. On the other hand, AAPs such as clozapine and quetiapine (QUE) may possibly be useful since they have demonstrated moderate, yet inconsistent, effects in improving hallucinations and delusions associated with PDP despite the absence of FDA approval and lack of Class I evidence [16]. Moreover, recently published research has demonstrated that PIM is associated with significantly lower rates of hospitalizations, emergency (ER) visits and overall healthcare resource use (HCRU) versus other-AAPs or versus QUE among patients with PDP in community settings [17–19]. Given that PDP contributes to nursing home placement in SNF with the increasing symptom severity, it is likely a significant number of patients with PDP may be in LTC/NH settings. Therefore, it is important to understand the HCRU burden such as inpatient hospitalizations among those already institutionalized patients in LTC/NH settings. However, studies comparing HCRU among LTC residents treated with PIM versus other AAPs in LTC/NH settings are lacking. This analysis examines HCRU differences among residents with PDP in LTC/NH settings that initiate treatment PIM versus QUE, and PIM versus other-AAPs.

Methods

Study design & data source

A retrospective database analysis of the Center for Medicare and Medicaid Services (CMS) 100% Medicare Fee-for-service (FFS) claims of residents with PDP in LTC/NH facilities were conducted. FFS refers to the traditional Medicare program, where healthcare providers are paid on a fee schedule for services provided to the beneficiary, and reimbursement is based on a Medicare annual established fee schedule. The US Medicare program serves as the primary public health insurer for all US residents 65 years and older, selected individuals that are physically disabled or have end-stage renal disease. The Medicare dataset represents 100% Medicare beneficiaries with claims for all inpatient (Part A), outpatient (Part B) and pharmacy services (Part D) incurred. Of note, Medicare Parts A, B and D covers hospital insurance (i.e., inpatient hospitalizations), medical insurance (i.e., doctor visits, outpatient care, preventive services and durable medical equipment) and pharmacy insurance (i.e., prescription medication coverage through private insurance plans), respectively. This analysis was conducted in accordance with the CMS data use agreement that was established after the New England Institutional Review Board review and approval.

Study population

In the current study, eligible PDP residents within the LTC/NH setting were identified using a combination of Parts A, B and D claims from 1 April 2015 to 31 December 2021. The PDP population included residents with PD that were identified from ≥ 1 ICD-9 and ICD-10 diagnostic claim of 332.0 and G20, respectively, with a concurrent psychosis diagnosis (occurrence of ≥ 1 psychosis or psychotic disorder diagnostic claim: F06.0, F06.2, F22, F23, F28, F29, H53.16, R44.0, R44.1, R44.2, R44.3) (See [Supplementary Table 1](#) in Appendix for cohort selection and sample identification).

Of the residents with PDP in the LTC/NH setting, those who initiated continuous monotherapy with PIM, QUE-only or other-AAPs, between 1 April 2016 and 30 June 2021, for at least 6 months (post-index date) formed

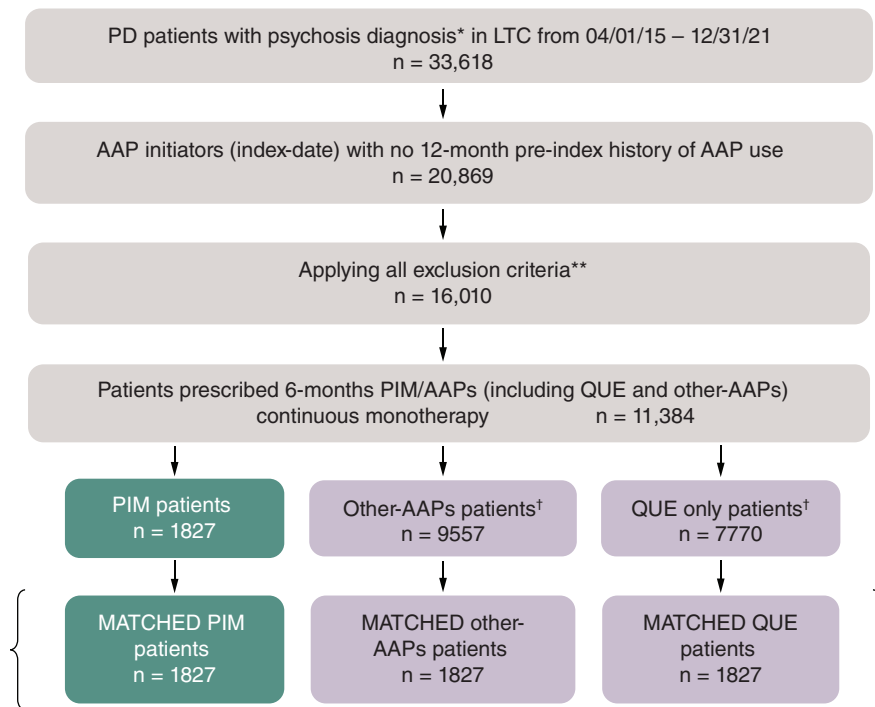


Figure 1. Patient selection.

*The diagnosis of psychosis should occur post Parkinson's disease diagnosis.

**PDP patients (n = 4626) with a pre-index diagnosis of psychosis, secondary parkinsonism, delirium, other psychotic disorders, HIV, alcohol/drug-induced psychosis, schizophrenia, paranoia or personality disorders were also excluded.

†Patients treated with other-AAPs (n = 9557), i.e., risperidone (n = 855), olanzapine (n = 496), aripiprazole (n = 436) and quetiapine (n = 7770)

AAP: Atypical antipsychotic; PD: Parkinson's disease; PDP: Parkinson's disease psychosis; PIM: Pimavanserin; QUE: Quetiapine.

the final study sample. Residents without prior use of any AAPs or PIM for at least 12 months prior to index date (i.e., baseline) were included. The index date was identified as the date of first prescription for PIM-only, QUE-only, or other-AAPs for the three respective cohorts. LTC/NH residents with a pre-index diagnosis of psychosis, secondary parkinsonism, delirium, other psychotic disorders, alcohol/drug-induced psychosis, schizophrenia, paranoia or personality disorders, were excluded from the study population. Diagnosis codes used for the inclusion/exclusion criteria are listed in [Supplementary Table 1](#). [Figure 1](#) presents the study population and attrition. Primary analysis focused on comparisons of the PIM versus QUE cohort and secondary analysis focused on the PIM versus other-AAPs cohort.

Covariates

Baseline characteristics including age, sex, race or ethnicity, region, clinical comorbidities (Elixhauser comorbidities), as well as presence of other co-existing conditions such as insomnia or dementia were examined during six months prior to index date.

Study outcomes

All-cause & psychiatric-related healthcare resource utilization

Healthcare resource utilization (HCRU) outcomes related to any all-cause and psychiatric-related inpatient hospitalizations, and ER visits were analyzed for the six-month post-index period. While all-cause outcomes were defined as admissions or visits to a healthcare facility or a professional healthcare provider for any reason, psychiatric-related admissions or visits were defined as an admission/visit for any of the diagnostic (i.e., primary or secondary) positions for psychotic disorders described in Appendix. An inpatient hospital admission is when a resident is formally admitted to the hospital with a doctor's order. In Medicare claims, inpatient hospital admissions can be further categorized into three types of setting based on provider type/facility characteristics (i.e., facilities characterized by

allowable length of stay): short-term stay (ST-stay: any hospitalizations in a facility/hospital that provides care to patients that require an acute or critical setting following surgery, or flare-up of a chronic sickness); long-term care stay (LTC-stay: hospitalizations in certified long-term acute care hospitals [LTACHs] among patients who may transfer from intensive care units to LTACHs of stay >25 days upon admission; and skilled nursing facility stay (SNF-stay: hospitalizations that are longer than LTC-stays and may house patients for up to 100 days).

Propensity score matching

Residents initiating PIM or QUE-only or other-AAPs were propensity score-matched in a 1:1 ratio to create a balanced sample. Propensity scores were calculated using multivariate logistic regression on resident age, sex, race, region and 27 of 31 Elixhauser comorbidity characteristics. Four Elixhauser comorbidities such as psychosis, HIV, alcohol abuse and substance abuse were not used in the propensity score matching (PSM). Residents with psychosis in the pre-index (i.e., baseline) were excluded in this analysis as data for those with HIV, alcohol abuse and substance use may be suppressed by CMS to accommodate confidentiality and would not have allowed an appropriate method of matching [20–23]. A greedy nearest neighbor matching algorithm was used for matching and has been described elsewhere [17]. Covariate balances were assessed using standardized mean differences (SMDs) value of <0.1 between PIM versus QUE cohort. The same methodology was repeated for the secondary analyses of PIM and other-AAPs cohort as well. Missing data were excluded prior to matching and the final, matched sample had no missing data.

Statistical analysis

Baseline resident demographics and clinical characteristics such as sex, age, Elixhauser comorbidities and other comorbidity status (i.e., dementia or insomnia) among residents were described prior to match and after matching was conducted. Covariate balance was assessed between PIM versus QUE cohort and PIM versus other-AAPs cohort by calculating frequencies and proportions before and after propensity score matching. Descriptive statistics were reported as frequencies and percentages for categorical variables; mean, median and range for continuous variables. Among the pre-matched groups, covariates that were categorical measures were evaluated by chi-square tests and those that were continuous parametric measures were evaluated by t-tests, and non-parametric measures were evaluated by Wilcoxon-rank sum tests. Among the matched groups, covariates were evaluated using McNemar or paired t-test (parametric), or Wilcoxon-sign sum tests (for nonparametric) continuous measures. SMDs among the covariates used in cohort matching were also used to assess cohort balance. It should be noted that covariates such as coexisting insomnia and dementia as well as demographic variables used for matching were used as controlling variables in the regression analysis of outcomes to address any residual confounding.

Rates of HCRU among PIM versus QUE and PIM versus other-AAPs cohorts were compared using log binomial regression models, controlling for index year, insomnia and dementia. Relative risk ratios and 95% confidence intervals are reported. Unless otherwise specified, the statistical significance was set to a threshold of $p < 0.05$. All analyses were conducted using SAS[®] Enterprise Server via the CMS Virtual Research Data Center.

Results

There were 11,384 resident beneficiaries identified from 1 April 2016 to 30 June 2021; 1827 resident beneficiaries were prescribed PIM continuous monotherapy and 9557 were other-AAPs continuous monotherapy (of which 7770 were on QUE on continuous monotherapy). Prior to matching, the different cohorts were not balanced with respect age, sex, region and comorbidities. Mean age of the beneficiaries in the PIM cohort was statistically lower compared with QUE (75 vs 76 years, $p < 0.05$) cohort. Additionally, the PIM cohort also had lower rates of comorbidities, dementia and insomnia compared with QUE cohort (Table 1).

After 1:1 matching PIM with QUE cohort and with other-AAPs cohort ($n = 1827$ each group), distribution of age, gender, race and comorbidities were balanced between the cohorts. However, PIM cohort still had lower rates of dementia (88.7% vs 90.5%, $p = 0.075$) and insomnia (41.9% vs 50.6%, $p < 0.05$) compared with QUE cohort. During the post-index follow-up period, mean and median daily dose of QUE cohort prescribed was 40.6 mg and 25 mg (IQR: 25, 50), respectively. Details about the demographic and baseline comorbidities before and after PSM for PIM versus QUE cohort and PIM versus other-AAPs cohort are described in Tables 1, 2, 3 & 4, respectively.

In the matched sample of residents treated with PIM compared with QUE, beneficiaries on PIM treatment exhibited significantly lower risk for any all-cause inpatient hospitalizations (RR: 0.82 [95% CI: 0.75–0.9], $p < 0.05$), all-cause short-term stays (RR: 0.80 [95% CI: 0.72–0.88], $p < 0.05$), all-cause SNF stays (RR: 0.79 [95% CI: 0.69–0.90], $p < 0.05$), and all-cause long term stays (RR: 0.71 [95% CI: 0.53–0.93], $p < 0.05$). Lower

Table 1. Patient demographics: pre-matched and post-matched PIM versus QUE cohorts (primary analysis).

	Pre-matched				Post-matched			
	PIM (n = 1827)	QUE (n = 7770)	p-value	SMD	PIM (n = 1827)	QUE (n = 1827)	p-value	SMD
Age (years)								
Mean (SD)	74.98 (7.03)	75.89 (7.03)	0.008	0.093	74.98 (7.03)	75.33 (7.14)	0.0056	0.049
Sex, n (%)								
			0.4448	0.02			0.7122	0.012
Male	965 (52.8%)	4181 (53.8%)			965 (52.8%)	954 (52.2%)		
Female	862 (47.2%)	3589 (46.2%)			862 (47.2%)	873 (47.8%)		
Race, n (%)								
Unknown	26 (1.4%)	93 (1.2%)	0.4318	0.02	†	†	NA	NA
White	1661 (90.9%)	7009 (90.2%)	0.3565	0.024	1661 (90.9%)	1668 (90.86%)	0.6773	0.013
Black	62 (3.4%)	297 (3.8%)	0.3847	0.023	62 (3.4%)	80 (4.4%)	0.1172	0.051
Other	25 (1.4%)	96 (1.2%)	NA	NA	25 (1.4%)	25 (1.4%)	1	0
Asian	26 (1.4%)	135 (1.7%)	0.3465	0.025	26 (1.4%)	22 (1.2%)	0.5465	0.019
Hispanic	21 (1.1%)	113 (1.5%)	0.3176	0.027	21 (1.1%)	17 (0.9%)	0.505	0.022
American native	†	†	NA	NA	†	†	NA	NA
Geographic region of the US, n (%)								
Midwest	384 (21.0%)	1974 (25.4%)	0.977	0.104	384 (21.0%)	391 (21.4%)	0.4861	0.009
Northeast	409 (22.4%)	1737 (22.4%)	<0.0001	0.001	409 (22.4%)	426 (23.3%)	0.1253	0.022
South	744 (40.7%)	2839 (36.5%)	0.0009	0.086	744 (40.7%)	729 (39.9%)	0.1762	0.017
West	290 (15.9%)	1220 (15.7%)	0.8562	0.005	290 (15.9%)	281 (15.4%)	0.3454	0.014
Index year								
2016	185 (10.1%)	1234 (15.9%)	<0.0001	0.172	185 (10.1%)	304 (16.6%)	<0.0001	0.192
2017	453 (24.8%)	1591 (20.5%)	<0.0001	0.103	453 (24.8%)	395 (21.6%)	0.0233	0.075
2018	387 (21.2%)	1716 (22.1%)	0.4013	0.022	387 (21.2%)	400 (21.9%)	0.6087	0.017
2019	425 (23.3%)	1425 (18.3%)	<0.0001	0.121	425 (23.3%)	350 (19.2%)	0.0019	0.101
2020	285 (15.6%)	1350 (17.4%)	0.0694	0.048	285 (15.6%)	282 (15.4%)	0.8923	0.005
2021	92 (5.0%)	454 (5.8%)	0.1801	0.036	92 (5.0%)	96 (5.3%)	0.7617	0.01

† Cells with sample size of <11 are suppressed per CMS requirements.

IQR: Interquartile range; PIM: Pimavanserin; QUE: Quetiapine; SD: Standard deviations; SMD: Standardized mean difference.

risk of all-cause ER visits (RR: 0.85 [95% CI: 0.8–0.9], $p < 0.05$) were observed for PIM compared with QUE cohort, respectively. All comparative HCRU results between PIM and QUE treatment are described in Figure 2A & 2B.

Similar patterns were observed with the risk of psychiatric-related hospitalizations. PDP residents receiving PIM monotherapy demonstrated significantly lower risk of psychiatric-related inpatient hospitalizations (RR: 0.71, 95% CI: 0.58–0.85), psychiatric-related short-term stays (RR: 0.62, 95% CI: 0.47–0.82) and psychiatric-related ER visits (RR: 0.52, 95% CI: 0.39–0.68). Although rates for psychiatric-related SNF and long-term inpatient hospitalization were also lower in the PIM cohort compared with QUE, these differences did not reach statistical significance.

In this study, the results from a secondary analysis of PIM versus other-AAPs, reported in Tables 3 & 4, were consistent with the results observed for PIM versus QUE comparisons and demonstrated that PIM may have favorable HCRU results regardless of the type of AAP prescribed to patients with PDP in LTC/NH settings. The matched cohorts comparing PIM versus other-AAPs treatment, resident beneficiaries on PIM treatment also showed significantly lower risks for any all-cause inpatient hospitalizations (RR: 0.78 [95% CI: 0.71–0.86], $p < 0.05$), all-cause short-term stays (RR: 0.80 [95% CI: 0.72–0.88], $p < 0.05$), all-cause SNF stays (RR: 0.75 [95% CI: 0.66–0.86], $p < 0.05$) and all-cause long-term stays (RR: 0.66 [95% CI: 0.53–0.87], $p < 0.05$). Additionally, resident beneficiaries on PIM treatment had a lower risk of all-cause ER visits (RR: 0.85 [95% CI: 0.79–0.90], $p < 0.05$) compared with those on other-AAPs (Figure 3A). Significantly lower risk of psychiatric-related HCRU outcomes, including psych-related inpatient hospitalizations (RR: 0.67 [95% CI: 0.56–0.81], $p < 0.05$), psych-related short-term stays (RR: 0.61 [95% CI: 0.46, 0.81], $p < 0.05$), psych-related long-term stays (RR: 0.54 [95% CI: 0.31, 0.95], $p < 0.05$) and psych-related ER visits (RR: 0.5 [95% CI: 0.38, 0.66], $p < 0.05$), were also

Table 2. Baseline comorbidities, Pre-matched and Post-matched PIM versus QUE cohorts.

	PIM (n = 1827)	QUE, Pre-matched (n = 7770)	SMD [†]	QUE, Post-matched (n = 1827)	SMD [‡]
Congestive heart failure	250 (13.7%)	1443 (18.6%)	0.133	258 (14.1%)	0.013
Cardiac arrhythmia	431 (23.6%)	2305 (29.7%)	0.138	434 (23.8%)	0.004
Valvular disease	185 (10.1%)	984 (12.7%)	0.08	198 (10.8%)	0.023
Pulmonary circulation disorder	66 (3.6%)	380 (4.9%)	0.063	61 (3.3%)	0.015
Peripheral vascular disease	475 (26.0%)	1942 (25.0%)	0.023	448 (24.5%)	0.034
Hypertension uncomplicated	1309 (71.6%)	5788 (74.5%)	0.064	1289 (70.6%)	0.024
Hypertension complicated	325 (17.8%)	1802 (23.2%)	0.134	314 (17.2%)	0.016
Paralysis	31 (1.7%)	255 (3.3%)	0.102	21 (1.1%)	0.046
Other neurological disorders	1812 (99.2%)	7356 (94.7%)	0.263	1813 (99.2%)	0.006
Chronic pulmonary disease	256 (14.0%)	1477 (19.0%)	0.135	246 (13.5%)	0.016
Diabetes uncomplicated	387 (21.2%)	1901 (24.5%)	0.078	406 (22.2%)	0.025
Diabetes complicated	291 (15.9%)	1430 (18.4%)	0.066	293 (16.0%)	0.003
Hypothyroidism	419 (22.9%)	1799 (23.2%)	0.005	408 (22.3%)	0.014
Renal Failure	256 (14.0%)	1573 (20.2%)	0.166	252 (13.8%)	0.006
Liver disease	23 (1.3%)	206 (2.7%)	0.101	19 (1.0%)	0.021
Peptic ulcer disease excluding bleeding	21 (1.1%)	102 (1.3%)	0.015	12 (0.7%)	0.052
Lymphoma	16 (0.9%)	102 (1.3%)	0.042	19 (1.0%)	0.017
Metastatic cancer	12 (0.7%)	85 (1.1%)	0.047	19 (1.0%)	0.042
Solid tumors without metastasis	169 (9.3%)	793 (10.2%)	0.032	170 (9.3%)	0.002
Rheumatoid arthritis	88 (4.8%)	426 (5.5%)	0.03	102 (5.6%)	0.035
Coagulopathy	105 (5.7%)	548 (7.1%)	0.053	95 (5.2%)	0.024
Obesity	159 (8.7%)	748 (9.6%)	0.032	153 (8.4%)	0.012
Weight loss	205 (11.2%)	1068 (13.7%)	0.076	215 (11.8%)	0.017
Fluid and electrolyte disorders	435 (23.8%)	2423 (31.2%)	0.166	420 (23.0%)	0.019
Blood loss anemia	32 (1.8%)	171 (2.2%)	0.032	30 (1.6%)	0.008
Deficiency anemia	195 (10.7%)	926 (11.9%)	0.039	197 (10.8%)	0.004
Depression	810 (44.3%)	3639 (46.8%)	0.05	814 (44.6%)	0.004
Insomnia	766 (41.9%)	3865 (49.7%)	NA	925 (50.6%)	NA
Dementia	1620 (88.7%)	7007 (90.2%)	NA	1653 (90.5%)	NA

[†] Compares QUE Pre-matched to PIM.
[‡] Compares matched QUE to Post-matched PIM.
PIM: Pimavanserin; QUE: Quetiapine; SMD: Standardized mean difference. If SMD is <0.1 then covariate is balanced across both treatments.

observed in PIM compared with other-AAPs cohort comparison. Details of all (HCRU) results between PIM and other-AAPs cohort are provided in [Figure 3B](#).

Discussion

In this observational study of LTC/NH residents within the Medicare 100% sample, resident beneficiaries initiating PIM compared with QUE (or other-AAPs) continuous monotherapy had significantly lower rates of all-cause and psychiatric inpatient hospitalizations as well as ER visits; however, these differences were not significant for all types of hospitalization stay. While the risk of all-cause inpatient hospitalizations (and by type of hospitalization) and ER visits were 20–30% lower in the PIM cohort compared with QUE, the risk of psych-related HCRU was lower; nearly 40–50% lower risk of hospitalizations by all types, and for ER visits was observed in the PIM cohort. These results are consistent with other comparative studies that have demonstrated lower rates of all-cause or psychiatric-related hospitalizations and ER visits among patients using PIM in community settings [17–19]. These results are not surprising given that research studies have indicated that PIM treated patients may have better clinical outcomes including fewer falls or fractures, both in community and LTC/NH [24,25]. While this study did not examine the reasons for all-cause hospitalizations or ER visits, it is plausible that PIM patients may have fewer all-cause hospitalizations or ER visits due to fewer falls or fractures. Interestingly, nearly 50% lower risk of psych-related hospitalizations or ER visits was observed among LTC resident beneficiaries initiating PIM continuous

Table 3. Patient demographics: Pre-matched and Post-matched PIM versus other-AAP cohorts (secondary analysis).

	Pre-matched				Post-matched			
	PIM (n = 1827)	QUE (n = 9557)	p-value	SMD	PIM (n = 1827)	QUE (n = 1827)	p-value	SMD
Age in years								
Mean (SD)	74.98 (7.03)	75.95 (7.46)	<0.0001	0.133	74.98 (7.03)	75.33 (7.14)	0.0015	0.058
Sex, n (%)								
			0.5719	0.014			0.608	0.016
Male	965 (52.8%)	4979 (52.1%)			965 (52.8%)	954 (52.2%)		
Female	862 (47.2%)	4578 (47.9%)			862 (47.2%)	873 (47.8%)		
Race, n (%)								
Unknown	26 (1.4%)	109 (1.1%)	0.3066	0.025	26 (1.4%)	18 (1.0%)	0.2278	0.04
White	1661 (90.9%)	8602 (90.0%)	0.2333	0.031	1661 (90.9%)	1650 (90.3%)	0.1045	0.021
Black	62 (3.4%)	375 (3.9%)	0.2797	0.028	62 (3.4%)	85 (4.7%)	0.0879	0.064
Other	†	†		NA	†	†		NA
Asian	26 (1.4%)	164 (1.7%)	0.3705	0.024	26 (1.4%)	19 (1.0%)	0.2858	0.035
Hispanic	21 (1.1%)	146 (1.5%)	0.2179	0.033	21 (1.1%)	24 (1.3%)	0.1174	0.015
American native	†	†		NA	†	†		NA
Geographic region of the US, n (%)								
Midwest	384 (21.0%)	2402 (25.1%)	0.0002	0.098	384 (21.0%)	393 (21.5%)	0.4579	0.012
Northeast	409 (22.4%)	2102 (22.0%)	0.7111	0.009	409 (22.4%)	431 (23.6%)	0.1198	0.029
South	744 (40.7%)	3595 (37.6%)	0.0123	0.064	744 (40.7%)	743 (40.7%)	0.9429	0.001
West	290 (15.9%)	1458 (15.3%)	0.5026	0.017	290 (15.9%)	260 (14.2%)	0.013	0.046
Index year								
2016	185 (10.1%)	1623 (17.0%)	<0.0001	0.201	185 (10.1%)	356 (19.5%)	<0.0001	0.266
2017	453 (24.8%)	1050 (21.5%)	0.0016	0.079	453 (24.8%)	394 (21.6%)	0.0221	0.077
2018	387 (21.2%)	2115 (22.1%)	0.3699	0.023	387 (21.2%)	388 (21.2%)	0.9676	0.001
2019	425 (23.3%)	1701 (17.8%)	<0.0001	0.136	425 (23.3%)	327 (17.9%)	<0.0001	0.133
2020	285 (15.6%)	1551 (16.2%)	0.5026	0.017	285 (15.6%)	276 (15.1%)	0.679	0.014
2021	92 (5.0%)	517 (5.4%)	0.515	0.017	92 (5.0%)	86 (4.7%)	0.6492	0.015

† Cells with sample size of <11 are suppressed per CMS requirements.

AAP: Atypical antipsychotic; IQR: Interquartile range; PIM: Pimavanserin; QUE: Quetiapine; SD: Standard deviations; SMD: Standardized mean difference.

monotherapy versus QUE or other-AAPs. While administration claims data lack clinical information about the frequency and severity of psychiatric symptoms (i.e., hallucinations and delusions) that can allow the examination of potential association between psych-related hospitalizations and ER visits, the above results may be suggestive of the effectiveness of PIM in treating psychotic symptoms compared with QUE or other-AAPs.

In this analysis of LTC resident beneficiaries from the Medicare sample, PIM versus QUE comparisons was conducted as the primary analysis since it was the most frequently used off-label AAPs (i.e., nearly 75% of resident beneficiaries with PDP). However, we also examined a pooled secondary analysis using any one of the four commonly used off-label AAPs (quetiapine, risperidone, olanzapine and aripiprazole). It should also be noted that the study period included the pandemic period between March 2020 and December 2021. In the current analysis we controlled for the index year to address any confounding by year.

This study included only patients diagnosed with PDP to avoid confounding by indication among the eligible patient population; however, it cannot be ruled out that PDP patients with concurrent dementia or insomnia may be prescribed AAPs for treating insomnia or agitation associated dementia instead of being treated for PDP. The median dose of quetiapine was ~50 mg. While standardized AAPs dose range for patients with PD has not been well-established, a dose of 100–150 mg has been hypothesized to be a reasonable therapeutic dose in PD patients. Given that these patients are in LTC/NH settings, it is expected that their doses will be lower than patients in the community. It should be noted that the median dose of QUE indicated that it may also have been prescribed for reasons other than PDP (i.e., insomnia). Notwithstanding this, after controlling for co-existing insomnia as a potential confounder, PIM treatment resulted in lower risk of psych-related HCRU outcomes. In the current study, researchers have examined the HCRU burden among LTC residents with PIM or other-AAPs monotherapy. While the association between treatment initiation and outcomes post-treatment initiation can be examined more clearly

Table 4. Baseline comorbidities, Pre-matched and Post-matched PIM versus other-AAPs cohorts.

	PIM (n = 1827; %)	Other-AAPs, pre-matched (n = 9557; %)	SMD [†]	Other-AAPs, post-matched (n = 1827; %)	SMD [‡]
Congestive heart failure	250 (13.7%)	1859 (19.5%)	0.156	283 (15.5%)	0.051
Cardiac arrhythmia	431 (23.6%)	2899 (30.3%)	0.152	405 (22.2%)	0.034
Valvular disease	185 (10.1%)	1207 (12.6%)	0.079	196 (10.7%)	0.02
Pulmonary circulation disorder	66 (3.6%)	477 (5.0%)	0.068	62 (3.4%)	0.012
Peripheral vascular disease	475 (26.0%)	2468 (25.8%)	0.004	454 (24.8%)	0.026
Hypertension uncomplicated	1309 (71.66%)	7258 (75.9%)	0.098	1273 (69.7%)	0.043
Hypertension complicated	325 (17.8%)	2272 (23.8%)	0.148	322 (17.6%)	0.004
Paralysis	31 (1.7%)	335 (3.5%)	0.114	25 (1.4%)	0.027
Other neurological disorders	1812 (99.2%)	8730 (91.3%)	0.375	1812 (99.2%)	0
Chronic pulmonary disease	256 (14.02%)	1902 (19.9%)	0.157	259 (14.2%)	0.005
Diabetes uncomplicated	387 (21.2%)	2490 (26.1%)	0.115	417 (22.8%)	0.04
Diabetes complicated	291 (15.9%)	1881 (19.7%)	0.098	295 (16.1%)	0.006
Hypothyroidism	419 (22.9%)	2318 (24.3%)	0.031	403 (22.1%)	0.021
Renal failure	256 (14.0%)	1997 (20.9%)	0.182	256 (14.0%)	0
Liver disease	23 (1.3%)	262 (2.7%)	0.106	17 (0.9%)	0.032
Peptic ulcer disease excluding bleeding	21 (1.1%)	135 (1.4%)	0.023	16 (0.9%)	0.027
Lymphoma	16 (0.9%)	117 (1.2%)	0.034	18 (1.0%)	0.011
Metastatic cancer	12 (0.7%)	98 (1.0%)	0.04	12 (0.7%)	0
Solid tumors without metastasis	169 (9.3%)	966 (10.1%)	0.029	177 (9.7%)	0.015
Rheumatoid arthritis	88 (4.8%)	549 (5.7%)	0.041	111 (6.1%)	0.055
Coagulopathy	105 (5.7%)	663 (6.9%)	0.049	107 (5.9%)	0.005
Obesity	159 (8.7%)	976 (10.2%)	0.052	142 (7.8%)	0.034
Weight loss	205 (11.2%)	1316 (13.8%)	0.077	192 (10.5%)	0.023
Fluid and electrolyte disorders	435 (23.8%)	3024 (31.6%)	0.176	427 (23.4%)	0.01
Blood loss anemia	32 (1.8%)	222 (2.3%)	0.04	34 (1.9%)	0.008
Deficiency anemia	195 (10.7%)	1178 (12.3%)	0.052	194 (10.6%)	0.002
Depression	810 (44.3%)	4737 (49.6%)	0.105	794 (43.5%)	0.018
Insomnia	766 (41.9%)	4736 (49.6%)	NA	907 (49.6%)	NA
Dementia	1620 (88.7%)	8597 (90.0%)	NA	1644 (90.0%)	NA

[†] Compares QUE Pre-matched to PIM.
[‡] Compares matched QUE to Post-matched PIM.
 If SMD is <0.1 then covariate is balanced across both treatments.
 AAP: Atypical antipsychotic; PIM: Pimavanserin; SMD: Standardized mean difference.

with monotherapy patients, it is possible that patients may have adjunctive AAPs therapy. Therefore, future studies examining the HCRU burden among patients on adjunctive therapy for PDP may also be needed.

Limitations

As with any retrospective studies involving administrative claims data, this analysis is subject to limitations related to potential miscoding, under-coding, or other issues associated with data used for billing and reimbursement purposes. While administrative claims are excellent measures to assess HCRU outcomes, they are unable to account for unobservable patient characteristics such as clinical data related to symptomatology, other factors related to socioeconomic status, psychosocial support, BMI, smoking, facility characteristics, or others that may bias the results. Despite adopting PSM to ensure balanced cohorts, it is possible that residual confounding may exist. Of note, only twenty-seven of the Elixhauser comorbidities (HIV, alcohol-abuse, substance-abuse and psychoses were excluded) were used in the PSM; however, residual confounding may exist.

After matching, residents on PIM treatment had higher mean and median Elixhauser comorbidity index scores and yet had a larger number of patients with no difference in majority of comorbidities compared with other-AAPs cohort. We posit that since our PSM algorithm matched PIM and other-AAPs treated cohorts based on individual

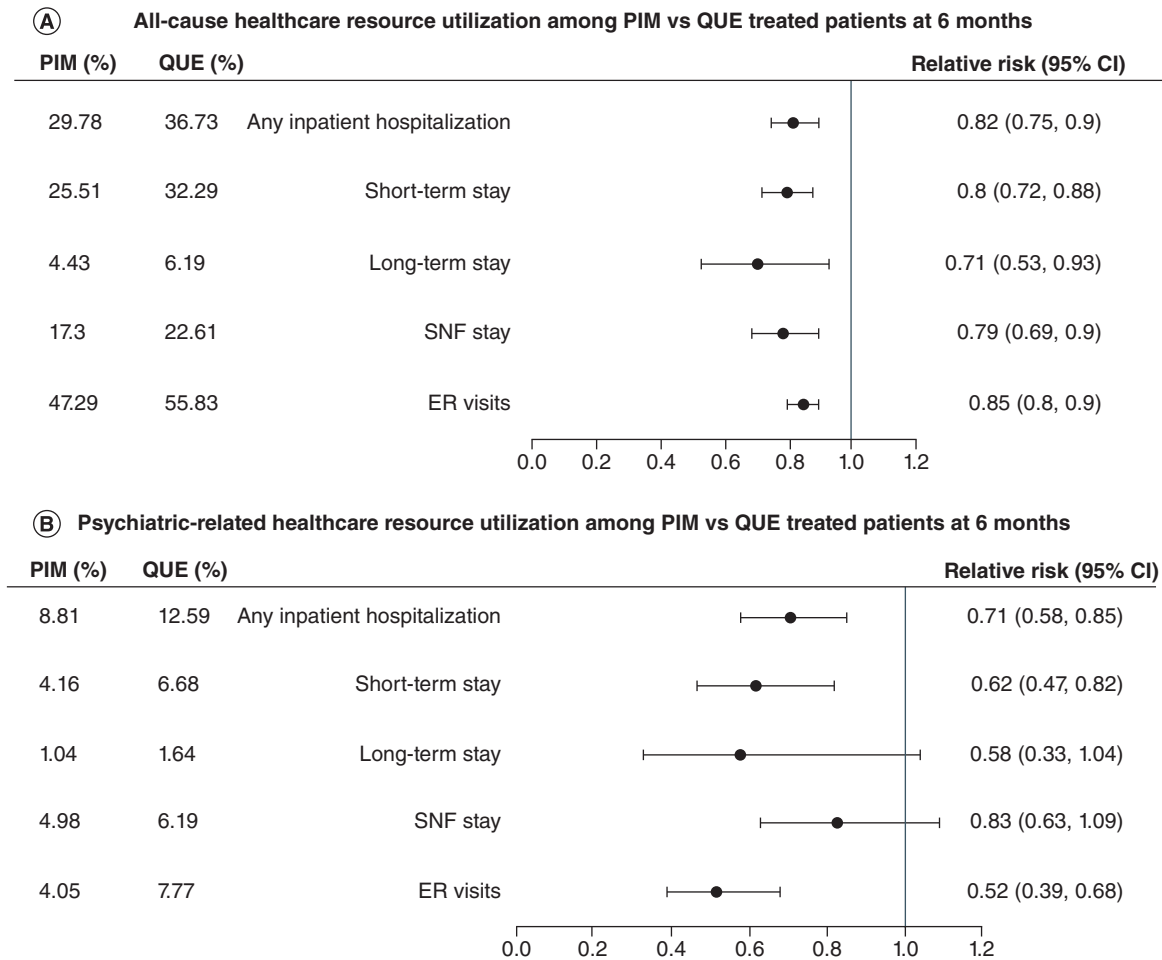


Figure 2. Healthcare resource utilization among pimavanserin vs quetiapine.
ER: Emergency room; PIM: Pimavanserin; QUE: Quetiapine; SNF: Skilled nursing facility.

27 Elixhauser comorbidities instead of the comorbidity index score, it cannot be assumed that the cohorts would have a balanced match on the index score as well.

While this analysis included all those receiving PIM or QUE (or other-AAPs) in LTC/nursing home setting, the PIM cohort was younger and had fewer comorbidities at time of treatment initiation. Additionally, it is possible that patients in the other-AAPs cohort, specifically QUE, may potentially be prescribed for treating other symptoms of dementia or insomnia despite ensuring that all the eligible patients have confirmed diagnosis of PD with conjunctive psychosis. Given, these potential for imbalances, future comparative analysis of PIM versus QUE (or other-AAPs) should include patients of therapeutically equivalent dose of QUE or other comparators based on chlorpromazine equivalents or some form of defined therapeutic daily dose. In this analysis, the other-AAPs cohort comprised patients who initiate four of the commonly used other-AAPs only. While other-AAPs such as clozapine or brexpiprazole were considered for inclusion into the other-AAPs cohort, their small sample sizes precluded the ability to consider their inclusion in the analysis. It is, therefore, possible that the HCRU results for other-AAPs cohort may be different if clozapine or brexpiprazole had been included.

As in any regression analysis, it is important not to control variables in the causal pathway. Similarly, in comparing PIM or QUE (or other-AAPs), adjusting for baseline HCRU in the previous year in the same treatment cohort would have masked the differences between the treatment cohorts [26]. Additionally, given the large standard deviations in HCRU outcomes, it is possible that inter-individual variability among patients may be skewed by heavy service users. Although dually eligible patients and patients with low-income subsidies may not be adequately represented in our analysis, they were not actively excluded in the analysis. Therefore, despite this limitation, it is possible to generalize these results to the broader LTC resident population. Since our research examined only

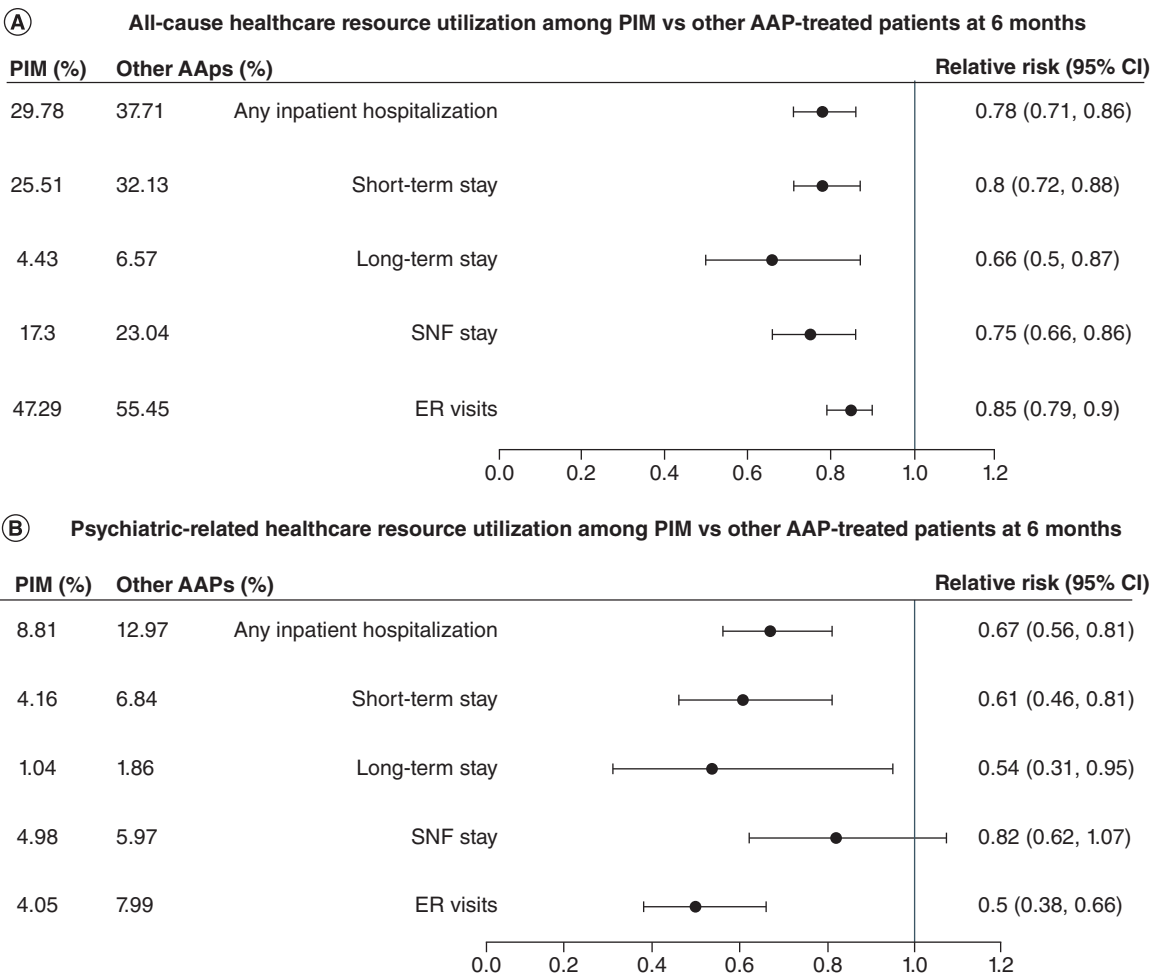


Figure 3. Healthcare resource utilization among pimavanserin vs other atypical antipsychotics.
AAP: Atypical antipsychotic; ER: Emergency room; PIM: Pimavanserin; SNF: Skilled nursing facility.

patients on monotherapy, the findings may not be generalizable to patients who may be receiving combination therapy of various antipsychotics.

Notwithstanding the limitations of the study, this study has several strengths. First, the data is based on the 100% Medicare sample of patients during a long study period (i.e., nearly 8 years). Second, we used a propensity score matching technique to yield a balanced matched sample of patients, thereby increasing the robustness of the findings. Lastly, results of this study may provide important insights about the role of pimavanserin versus other off-label antipsychotics in reducing incidence of hospitalizations among resident beneficiaries in LTC/NH settings.

Conclusion

This analysis of LTC resident beneficiaries with PDP on 6-month PIM continuous monotherapy (versus QUE) have a lower likelihood of all-cause hospitalizations (18%) and ER visits (15%). They are also less likely to have all cause ST-stays (20%), LT-stays (29%) and SNF-stays (21%), respectively, versus QUE cohort. Similar patterns were observed with other-AAPs comparisons; PIM cohort was less likely to have all-cause hospitalizations (22% lower) and ER visits (15% lower). PIM cohort also had lower likelihood for all-cause ST-stays (22% lower), LT-stays (34% lower) and SNF-stays (25% lower), respectively, versus other-AAPs. PIM treatment versus QUE were also less likely to have psych-related IP hospitalizations (29% lower) and ER visits (48% lower). Similarly, PIM treatment versus other-AAPs were less likely to have psych-related IP hospitalizations (33% lower) and ER visits (50% lower). Overall, these findings show that PIM treated cohort had lower HCRU burden in LTC/NH settings. While not causal in nature, they demonstrate the potential real-world association between HCRU patterns and prescribing of

PIM compared with QUE or other-AAPs use among patients with PDP. Overall, these results may provide guidance to policymakers given their concern about the potential over-use of off-label antipsychotics and can provide support to informing clinical and formulary decision-making for Medicare patients in future.

Summary points

- Real world evidence on healthcare service utilization for Parkinson's disease psychosis (PDP) patients using pimavanserin (PIM) versus other-atypical antipsychotics (other-AAPs) like quetiapine (QUE) in long term care (LTC) and nursing home (NH) settings is limited.
- This retrospective cohort analysis, using a 100% Medicare sample, compared healthcare resource utilization (HCRU) among LTC/NH residents with PDP initiating PIM versus QUE or other-AAPs.
- Treatment-naïve residents who initiated ≥ 6 months continuous monotherapy with PIM, QUE, or other-AAPs between April 2016 and June 2021 were included in the analysis.
- Propensity score matching (PSM) was employed using 31 variables to create a balanced sample for comparison.
- Post-index (6 months) HCRU outcomes included all-cause inpatient hospitalizations (by types of inpatient hospitalization stays: short term, SNF, long-term) and emergency room (ER) visits.
- After matching, the PIM cohort exhibited significantly lower rates of all-cause IP hospitalizations and ER visits compared with QUE and other-AAP cohorts. Specifically, the PIM cohort had an 18% lower likelihood of all-cause hospitalizations and a 15% lower likelihood of ER visits compared with QUE.
- PIM-treated patients were also less likely to have all-cause short-term, long-term and skilled nursing facility stays compared with QUE-treated patients.
- Similar trends were observed when comparing PIM to other-AAPs, indicating lower HCRU burden for PIM-treated patients in LTC/NH settings overall.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2024-0038>

Author contributions

K Rajagopalan, N Rashid and D Doshi were responsible for study conception and design; author K Rajagopalan was responsible for acquisition of data; authors K Rajagopalan, N Rashid, D Gopal and D Doshi were responsible for data analysis and drafting and revision of the manuscript.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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