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ASTHMA CONTROL



Determining the optimal threshold for medication adherence in adult asthma patients: an analysis of British Columbia administrative health database in Canada

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ABSTRACT

Objective: This study investigated the association between varying cutoffs for Medication Adherence (MA) among physician-diagnosed asthma patients and subsequent association with asthma exacerbation.

Methods: We linked four administrative health databases obtained from the Population Data in British Columbia. Index cases were physician-diagnosed asthma patients between January 1, 1998, to December 31, 1999, aged 18 years and older. Patients were prospectively assessed in the follow-up period from January 1, 2000, to December 31, 2018, to identify asthma exacerbation. Two proxy measures were used to assess MA: the proportion of days covered (PDC) and the medication possession ratio (MPR). Using the generalized estimating equation (GEE) logistic regression adjusted for patient covariates, the outcome of “asthma exacerbation” was modeled against varying MA cutoffs; *excellent* ‘ ≥ 0.90 ’; *very good* ‘0.80–0.89’; *good* ‘0.70–0.799’; *moderate* ‘0.6–0.699’; *mild* ‘0.50–0.599’ compared to *poor* ‘ < 0.50 ’ for both PDC and MPR.

Results: The sample included 68,211 physician-diagnosed asthma patients with a mean age of 48.2 years and 59.3% females. The adjusted odds ratios (OR) and 95% confidence interval (CI) at the various cutoff for PDC-levels predicting asthma exacerbation events were: *Excellent* MA [OR = 0.84, 95% (0.82–0.86), *very good* MA [OR: 0.86, (0.83, 0.89), *good* MA [0.91, (0.88–0.94)]; *moderate* MA [0.93, (0.90–0.96)]; *mild* MA [0.95, (0.92–0.98)]; compared to *poor* MA level. Threshold levels for both the PDC and MPR measure greater than 0.80 provided optimal threshold associated with over 15% reduced likelihood of experiencing asthma exacerbations.

Conclusion: Intervention aimed at improving asthma exacerbation events in adult asthma patients should encourage increased medication adherence threshold level greater than 0.80.

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Introduction

The primary purpose of asthma management is to achieve good asthma control and minimize future disease exacerbations. Recent evidence documents poor asthma control among all age groups and is linked to decreased quality of life (1), increased use of bronchodilators (2), increased healthcare utilization (3), and cost (4). To achieve optimal control of asthma, adherence to prescribed medications is essential to improve the health outcomes of patients (3,5,6). Increased medication adherence (MA) among patients is known to be associated with improved clinical outcomes and patient prognosis. Administrative claim databases represent a vital source of information for

assessing asthma medication adherence among community patients with physician-diagnosed asthma (7). Currently, there is no standardized or ideal threshold for measuring optimal MA for asthma patients.

Recently, pharmacy administrative databases have emerged as an essential resource for calculating MA (8). Measuring MA in a pharmacy claim database presents several benefits, including identifying a substantial number of asthma medication users promptly in the community; and providing access to data on prescription claims and quantity of dispensed medications over time (7,9).

Several measures of asthma MA have been reported for measuring adherence to single and multiple prescribed asthma medications in pharmacy claim

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databases (10–12). The Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) were the two commonly reported methods for measuring medication adherence in adolescent and adult asthma patients (10,12,13). These two adherence metrics were valid, sensitive, and reflected the real-life situation of medication usage (14).

While MPR and PDC have been widely applied, medical researchers and clinicians face a dilemma concerning the optimum degree of adherence expected to achieve significant clinical outcomes among asthma patients. Engelkes et al. (10) have reported varying adherence thresholds (MPR or PDC < 0.5, ≥ 0.75 , ≥ 0.80 , 75 percentile, and median) for classifying adherent and non-adherent asthma groups. Notable among them was adopting the ' ≥ 0.80 ' thresholds for classifying adherent and non-adherent patients, which has been conventionally used regardless of the clinical contexts (15). The choice of ' ≥ 0.80 ' adherence thresholds has been suggested in most studies as the optimum adherence level (10,13,16,17). However, the threshold may differ across medication therapeutic classes or disease conditions (8,18). While previous works have estimated disease specific adherence cut-offs, a number of gaps still remain. First, existing studies used healthcare utilization, such as hospitalization (11,19), as surrogate outcome measures rather than clinical outcomes that reflect disease control. Clinical outcomes that reflect disease control, such as; asthma exacerbation, would more accurately reflect medication adherence for adult patients with asthma.

In addition, some researchers have raised concerns about this cutoff point for lack of clinical rationale underlying decision for the chosen threshold value (3,10). Also, the actual impact of varying adherence thresholds on asthma control remains unclear. The nonexistence of a gold standard threshold for assessing the 0.80 cutoff presents us with an opportunity to investigate this vital research area with a particular focus on determining the optimal threshold to achieve significant clinical endpoints such as asthma exacerbation (asthma hospitalization; emergency department visits, and oral corticosteroids (OC) claims).

We believe that attaining a certain adherence level will positively improve important clinical outcomes in adult asthma patients. To our knowledge, very few studies have investigated the association between using varying MA thresholds and the risk of asthma exacerbations. This study adds to the literature from the Canadian point of view. The primary objective of this study was to investigate the association between varying adherence thresholds of the PDC and MPR

methods among asthma patients and risk of asthma exacerbation to determine the optimal adherence cut-off value.

Method

Study design and setting

We conducted an observational cohort study using Canadian administrative population based-health databases from British Columbia (BC), Canada. The Population Data BC (PopData BC) includes health records of all BC residents registered in the province's publicly funded universal insurance program (20). The PopData BC is a multi-university, data, and education resource that facilitates interdisciplinary research on the determinants of human health, well-being, and development (21). We obtained the requested data from PopData BC for the fiscal years 1998 to 2018 (a 20-year observational administrative data). We used the first two years, that is, the period between January 1, 1998, to December 31, 1999, as the '*wash-in*' period to allow sufficient time for the prevalent cases of physician-diagnosed asthma to be identified. We defined the index period (1998–1999) as the time a patient was first identified in the database with a diagnosis of asthma. As such, subsequent asthma exacerbation outcomes were determined within 18 years follow-up period spanning from January 1, 2000, to December 31, 2018.

Data source

The PopData BC administrative health databases used included: (i) the *Discharge Abstracts Database* (DAD) for hospital separations from 1998 to 2018 (22); (ii) the *Medical Service Plan* (MSP), which captures records of physician visits from 1998 to 2018 (22); (iii) the PharmaNet database which contains records of all medications dispensed in BC community pharmacies from 1998 to 2018 (23), and (iv) the Demographic and Registration (consolidated) database which provide primary demographic data and longitudinal registration status in the healthcare system of the province (24,25).

Cohort definition

The study employed a validated case definition of asthma to identify all physician-diagnosed asthma patients in three databases (DAD, MSP, PharmaNet) (20,26). According to the validated case definition, patients were considered to have a diagnosis of

asthma based on meeting at least one of the following criteria:

- i. patients having one or more asthma-related hospitalizations in the DAD database (based on International Classification of Diseases-9th edition (ICD-9): 493.x, ICD-10th edition: J45, J46) during a 12-month rolling window;
- ii. Patients having two or more physician visits for asthma using asthma diagnosis codes (ICD-9 codes: 493.x) in the MSP database. Additionally, asthma patients in the DAD and MSP databases should have records of at least four prescriptions of an asthma-related medication in the PharmaNet database (see asthma-related drug lists in the [supplementary material](#) in [Table S1](#)).

Using these criteria for case definitions, asthma patients 18 years and older with no history of ever diagnosed chronic obstructive pulmonary disease (COPD) were identified between January 1, 1998, to December 31, 1999, and included in the source population. The identified asthma patients were followed from January 1, 2000, to December 31, 2018, to identify subsequent asthma exacerbation outcomes.

Exposure variable: Assessment of medication adherence measure

The primary exposure measure for this study was medication adherence. Adherence was assessed using the Medication Possession Ratio (MPR) (27) and Proportion of Days Covered (PDC) (28) adherence metrics. The authors calculated the PDC adherence measure by dividing the number of days of medication covered (i.e. the number of days with a drug on hand) by the sum of days between the first and the last fill dates. We estimated the MPR measure as the ratio of the sum of days of medication supplied to the sum of days between the first, and the last fill dates (27,28). Using the PDC and the MPR methods, the study calculated medication adherence on all prescribed controller medications over time. Thus, all asthma controller medications listed in [Table S1](#) in the [supplementary material](#) were included in the calculation of the medication adherence over time. Specifically, we estimated medication adherence on prescribed inhaled corticosteroids (ICS), Long-acting beta-2 agonist (LABA), ICS/LABA combination, and Leukotriene receptor antagonists (LTRA). Further, we also calculated patients' adherence to prescribed

short-acting beta-2 agonist (SABA) at baseline/patient identification stage. During the computation of asthma medication adherence, we adjusted for inpatient (IP) stays by censoring the days a patient was hospitalized. We calculated patients' adherence to prescribed concomitant medications based on the first approach of Choudhry's and colleagues' (29) proposal for the definition of concurrent adherence. Based on Choudhry et al. proposal, we first calculated the prescription-based PDC and MPR for each medication class for the individual patients. We later averaged the estimated PDC and MPR at the patient level. The continuous adherence rates were categorized into five different adherence thresholds levels for both PDC and MPR and coded as follows: *poor* MA ('<0.5' = 0, reference); *mild* MA ('0.50–0.59' = 1); *moderate* MA ('0.60–0.69' = 2); *good* MA ('0.70–0.79' = 3); *very good* MA ('0.80–0.89' = 4); and *excellent* MA ('≥0.90' = 5).

Outcome measures

The primary outcome was measured as “*asthma exacerbation*” during the 18-year follow-up/measurement period (2000–2018). We defined asthma exacerbation as the occurrence of at least one of the following three events: (i) asthma episodes that required collection of prescribed oral corticosteroids (OCS), (ii) emergency room visits, and/or (iii) hospitalization due to asthma (13,28,30,31).

Covariates

Demographic information captured for each patient included patients' age and sex (male/female). Charlson's comorbidity index (CCI) was estimated to measure the burden of comorbid conditions associated with asthma patients (32). The various comorbid conditions were identified based on the diagnostic codes (ICD-9 and ICD-10) recorded as part of inpatient and outpatient hospital care. The CCI was calculated at baseline and subsequently measured at follow-up after excluding asthma from the score (32). Other asthma-related comorbidities such as sinusitis and upper respiratory infections were also identified in this study. Other covariates considered in this study included tobacco use and nicotine dependence (yes = 1, vs. no = 0), obesity (body mass index ≥ 30 kg/m²) [obese = 1, vs. normal = 0]. Patients' length of stay in hospital and emergency hospital admissions (asthma and non-asthma related) were also considered important risk factors for asthma exacerbations.

The various categories of asthma severity at diagnosis (mild, moderate, and severe) were identified at baseline (1998–1999) and included in the model. We defined asthma severity based on an algorithm developed by Firoozi and colleagues (2007) (33). The three asthma severity states (mild, moderate, and severe) was defined based on the intensity of prescribed ICS and other controller medications, the use of short-acting beta-2 agonist (SABA) and an indication of markers of moderate-to-severe asthma exacerbations. The *mild asthma* group was identified if they had records of prescription of 0–500 µg/day doses of ICS and not taking any additional controller drugs. *Mild asthma* was also defined as having prescriptions of ICS doses of 0–250 µg/day plus additional controller therapy and must not have had a marker of moderate to severe asthma exacerbation nor has overused SABA (using an average of at least 3 doses of SABA per week within 12 months. Patients prescribed with >500 µg/day doses of ICS with no additional usage of controller therapy or having more than >250 µg/day doses of additional therapy were classified as moderate asthma patients. Finally, *severe asthma* was defined as patients who had a prescription of more than 1000 µg/day of ICS except for patients with markers of uncontrolled asthma who ingested additional prescription of more than 10 doses of SABA per week for patients with uncontrolled asthma.

Statistical methods

We measured “*asthma exacerbation*” during the follow-up period as the study outcome and investigated the association between the five adherence cut-off values (*poor, mild, moderate, good, and excellent*) and the risk of exacerbations over time.

We used SAS version 9.4 and STATA version 16 (SAS Institute Inc. 2013) for data, cleaning, coding, and analyses. Descriptive statistics were presented for baseline characteristics. First, we employed the bivariate generalized estimating equation (GEE) logistic regression to estimate the unadjusted odds ratio, and 95% confidence interval to identify possible risk factors associated with asthma exacerbations (34). This was done to identify the relevant risk factors to be included in the model by estimating adjusted odds ratios (OR).

We further applied the multivariate GEE logistic regression to examine the association between the five varying adherence thresholds and risk of asthma exacerbation after adjusting for significant covariates. The GEE logistic regression model was adopted to account for correlation due to the patient’s repeated set of

measurements on asthma exacerbations and other sets of covariates (34). A p values of 0.05 was used in all tests of statistical significance. Sensitivity and specificity analysis was further performed. Using the Receiver Operating Characteristics (ROC) curve, we determined the ideal cutoff for both PDC and MPR adherence measures to achieve optimal control of asthma exacerbation using the value with the highest sensitivity.

Ethics approval was sought from the Health Research Ethics Board (HREB) at the Memorial University of Newfoundland (REF #: 2019.216).

Results

Patient characteristics at baseline

At baseline, a total of 68 211 patients were identified in the index years spanning January 1, 1998, to December 31, 1999: that is, 58 970 (86.45) asthma patients were identified from January 1, 1998, to December 31, 1998, and 9,241 (13.55) from January 1, 1999, to December 31, 1999. Based on the validated case definition, the study identified 248 086 patients from the PharmaNet database, 101 555 from the MSP database, and 3,666 patients from the DAD database at the initial stage. We linked the three databases together with the consolidated database. After removing duplicate patient records, and incident cases of COPD (asthma-COPD), the study included 68 211 unique adult asthma patients (≥ 18 years) as the study population (see Figure 1).

Table 1 presents the descriptive statistics of the characteristics of the study population at baseline. The mean age was 48 years, with the majority of patients being 40 years and older. More than half of the study population were female (59.25%, $n = 40\,455$). No comorbidity was reported for 97.88% of the patients, and 1.80%, 0.22%, and 0.10 reported 1, 2, and >3 comorbidities, respectively. Additionally, we identified 205 obese patients, 96 patients with a history of tobacco use and nicotine dependence, 49 155 (72.06%) were *mild* asthma patients, 15 595 (22.87%) *moderate* and 3,461 (5.07%) *severe* asthma patients.

Bivariate analysis of patient factors

The study set the statistical significance level at a maximum of 0.20 for examining all bivariate analyses of the association between varying adherence thresholds and “*asthma exacerbations*” outcomes. Table 2 presents the covariates, including the varying

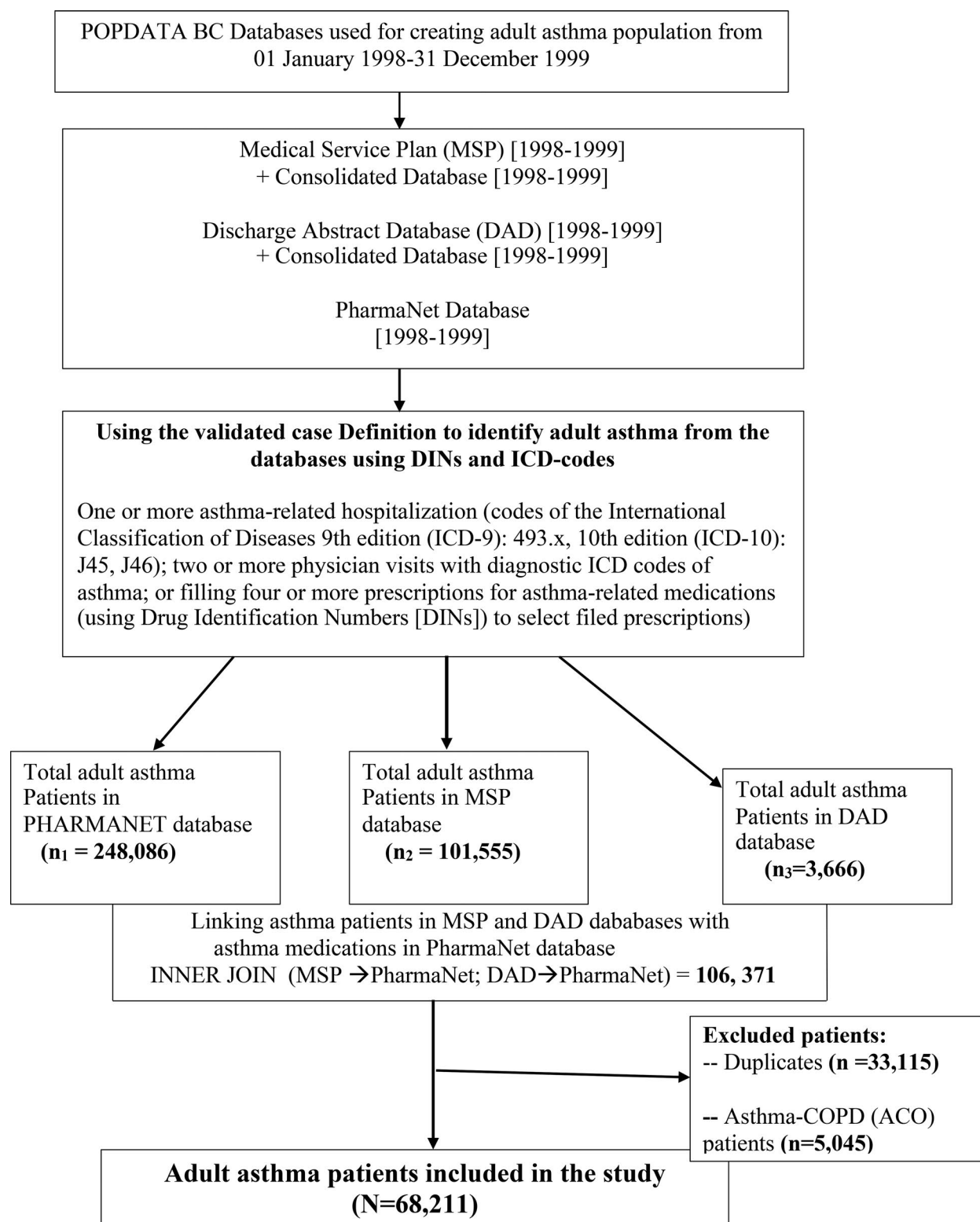


Figure 1. Study flow chart for selecting adult asthma patients from the POPDATA BC databases.

adherence threshold that were significant at 0.20 statistical level of association between varying adherence thresholds and “asthma exacerbations.” For PDC, using the *poor* “<0.5” as the reference category level, the *mild* MA category, that is “0.50–59” was significantly

associated with less likelihood of developing *asthma exacerbations* (OR: 0.93; 95% CI: 0.90, 0.95, $p < 0.0001$). Similarly, the categories of PDC cutoff values at *moderate* MA “0.60–0.69,” *good* MA “0.70–0.79,” *very good* MA “0.80–0.89” and *excellent* “ ≥ 0.90 ” were

Table 1. Sample characteristics by medication adherence thresholds*.

Baseline variables	Overall N = 68,211	Medication adherence thresholds N (%) or Mean $\pm$ SD					P-value
	N (%)	<0.5	0.50–0.59	0.60–0.69	0.70–0.79	≥ 0.80	
PDC, mean (SD)	0.39(0.32)	46,666(68.41)	3,982(5.84)	3,091(4.53)	2,484(3.64)	1,1988(17.54)	0.00
MPR, mean (SD)	0.41(0.34)	45,569(66.81)	3,818(5.60)	2,876(4.22)	2,194(3.22)	13,754(20.16)	0.00
Sex (Male), N (%)	27,756(40.69)	18,306(65.95)	1,686(6.07)	1,346(4.85)	1,104(3.98)	5,314(19.15)	0.00
Sex (Female), N (%)	40,455 (59.25)	28,360(70.10)	2,296(5.68)	1,745(4.31)	1,380(3.41)	6,674(16.50)	
Mean Age (SD, years)	48.20 (18.63)	46.12(17.99)	49.89(18.80)	49.62(18.66)	52.28(19.03)	52.22(19.15)	0.00
Length of hospitalization [days, N (%)]							
0	65,526(96.06)	4,4918(68.54)	3,811(5.82)	2,969(4.53)	2,390(3.65)	11,438(17.46)	0.00
1	1,876(2.75)	1,262(67.27)	119(6.34)	77(4.10)	54(2.89)	364(19.40)	
2	559(0.82)	353(63.15)	34(6.08)	34(6.08)	21(3.76)	117(20.93)	
≥ 3	250(0.37)	133(53.20)	18(7.20)	11(4.4)	19(7.6)	69(27.60)	
Emergency admission (Yes), N (%)	1,023(1.50)	662(64.71)	60(5.87)	49(4.79)	42(4.10)	210(20.53)	0.09
Tobacco use/nicotine dependence (Yes), N (%)	96(0.14)	59(61.46)	6(6.25)	7(7.29)	7(7.29)	18(18.75)	0.33
Obesity (BMI > 30 kg/m ²), N (%)	205(0.30)	134(65.37)	13(6.34)	6(2.93)	6(2.93)	46(22.43)	0.33
Charlson Comorbidity Index (CCI)							
CCI score 0	66,766 (97.88)	45,906(68.76)	3,878(5.81)	3,003(4.49)	2,396(3.59)	11,583(17.35)	0.00
CCI score 1	1,226 (1.80)	615(50.16)	93(7.59)	80(6.53)	78(6.36)	364(29.40)	
CCI score 2	151(0.22)	99(65.56)	11(7.28)	8(5.30)	10(6.62)	23(15.24)	
CCI score ≥ 3	68(0.10)	46(0.10)				22(32.35)	
Asthma related comorbidity							
Sinusitis	108(0.16)	74(68.52)	8(7.40)	6(5.56)		20(18.52)	0.58
Upper respiratory infection	284(0.42)	174(61.27)	15(5.28)	15(5.28)	12(4.23)	68(23.94)	0.05
Asthma severity							
Mild	49,155(72.06)	33,503(68.23)	3,054(6.22)	2,395(4.88)	1,841(3.75)	8,311(16.92)	0.00
Moderate	15,595(22.87)	13,137(68.94)	928(4.87)	696(3.65)	643(3.37)	3,652(19.17)	
Severe	3,461(5.07)	1,754(50.70)	–	17(0.50)	90(2.60)	1,600(46.20)	

Baseline variables indicate a variable is significant at 0.01. PDC=Proportion of Days Covered; MPR=Medication Possession, BMI=Body mass index, SD=Standard deviation.

*Medication adherence thresholds: *Poor* = "<0.5"; *Mild* = "0.50–0.59"; *Moderate* = "0.60–0.69"; *Good* = "0.70–0.79"; *Very good* = "0.80–0.89"; *Excellent* = "0.90–1.00."

significantly associated with less likelihood of asthma exacerbation over time.

A similar trend was observed for the bivariate analysis comparing MPR thresholds with "*asthma exacerbation*" over the study period. Additionally, the following patient covariates were significantly associated with "*asthma exacerbations*." They included patients' sex, age (years), length of stay, tobacco use/nicotine dependence, obesity, CCI, asthma-related comorbidities and asthma severity at baseline.

Multivariate analysis of the association between varying adherence thresholds and asthma exacerbations

In the multivariate analysis presented in Table 3, we examined the association between varying adherence threshold and "*asthma exacerbations*." The significant patient baseline characteristics and variables in the bivariate analysis were adjusted in the GEE model. In Table 3, we obtained the adjusted odds ratio for measuring the strength of the association between PDC thresholds and asthma exacerbations. Compared to the reference category of 'PDC level < 0.5', patients who achieved *mild* MA (PDC level = 0.50–0.60) were significantly less likely to develop asthma exacerbations (OR: 0.95, 95% CI: 0.92–0.98) after controlling

for patients factors at baseline. Similar significance (OR, 95% CI) was achieved for the effect of "*moderate* MA" (OR: 0.93, 95% CI: 0.90–0.96), "*good* MA" (OR: 0.91, 95% CI: 0.88–0.94), "*very good*" MA (OR: 0.86, 95% CI: 0.83–0.89) and "*excellent* MA" OR: 0.84, 95%CI: 0.82, 0.86) categories as after adjusting for important significant covariates. The adjusted relative likelihood of a reduction in asthma exacerbation outcomes using the PDC cutoffs were 5%, 7%, 9%, 14%, and 16% for *mild* MA, *moderate* MA, *good* MA, *very good* MA, and *excellent* MA categories when compared to the *poor* MA category as the reference.

A similar multivariate analysis was performed for the MPR adherence measure presented in Table 4. After we adjusted for the male sex, age, length of stay, history of tobacco use/nicotine dependence, obesity, asthma-related comorbidities, CCI, and asthma severity in the multivariate model, the data was consistent with that observed using the PDC score presented in Table 3. The relative likelihood of a reduction in asthma exacerbation outcomes using the MPR cutoffs were 5%, 6%, 7%, 12%, and 15% for mild, moderate, good, very good, and excellent compared to poor MA category as the reference.

Further, we performed subgroup analysis by investigating the association between varying thresholds of

Table 2. Bivariate association between the patient characteristics and level of medication adherence predicting risk of asthma exacerbations.

Covariates	Unadjusted odds ratio	95% confidence interval	P-value
<i>PDC threshold</i>			
Poor "<0.5"	Ref		
Mild "0.50–0.59"	0.93	(0.90, 0.95)	<0.0001
Moderate "0.60–0.69"	0.93	(0.90, 0.96)	<0.0001
Good "0.70–0.79"	0.92	(0.89, 0.94)	<0.0001
Very good "0.80–0.89"	0.88	(0.86, 0.91)	<0.0001
Excellent "0.90–1.00"	0.87	(0.86, 0.89)	<0.0001
<i>MPR threshold</i>			
Poor "<0.5"	Ref		
Mild "0.50–0.59"	0.93	(0.90, 0.95)	<0.0001
Moderate "0.60–0.69"	0.93	(0.90, 0.96)	<0.0001
Good "0.70–0.79"	0.93	(0.91, 0.97)	<0.0001
Very good "0.80–0.90"	0.90	(0.87, 0.93)	<0.0001
Excellent "0.90–1.00"	0.88	(0.87, 0.90)	<0.0001
Sex (Male)	0.67	(0.66, 0.68)	<0.0001
Age (years)	0.94	(0.94, 0.95)	<0.0001
Length of stay (days)			
0	Ref		
1	4.09	(3.98, 4.17)	<0.0001
2	2.34	(2.28, 2.40)	<0.0001
≥3	1.32	(1.28, 1.36)	<0.0001
Tobacco use/nicotine dependence (yes)	3.05	(2.79, 3.33)	<0.0001
Obesity (yes)	1.46	(1.35, 1.59)	<0.0001
Charlson Comorbidity Index	0.62	(0.60, 0.65)	<0.0001
CCI score 0	Ref		
CCI score 1	0.05	(0.06, 0.07)	<0.0001
CCI score 2	0.01	(0.01, 0.02)	<0.0001
CCI score ≥3	0.01	(0, 0.02)	<0.0001
Asthma related comorbidities			
Sinusitis (yes)	3.49	(3.19, 3.83)	<0.0001
Upper respiratory infection (yes)	4.96	(4.72, 5.22)	<0.0001
Asthma severity			
Mild	Ref		
Moderate	1.08	(1.07, 1.10)	<0.0001
Severe	1.28	(1.24, 1.31)	<0.0001

PDC = Proportion of days covered; MPR = Medication possession ratio.

Table 3. Multivariate analysis of the association between varying PDC adherence thresholds and risk of asthma exacerbation.

	Asthma hospitalization	Emergency department visit	Asthma exacerbation (Combined asthma hospitalization, & ED visits)
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
PDC thresholds			
Poor "<0.5"	Ref	Ref	Ref
Mild "0.50–0.59"	0.96(0.92, 1.00)	0.96(0.93, 1.01)	0.95(0.92, 0.98)***
Moderate "0.60–0.69"	0.96(0.93, 1.01)	0.93(0.90, 0.98)	0.93(0.90, 0.96)***
Good "0.70–0.79"	0.93(0.90, 0.97)***	0.90(0.86, 0.94)***	0.91(0.88, 0.94)***
Very good "0.80–0.89"	0.90(0.87, 0.94)***	0.86(0.83, 0.89)***	0.86(0.83, 0.89)***
Excellent "0.90–1.00"	0.89(0.87, 0.92)***	0.85(0.83, 0.88)***	0.84(0.82, 0.86)***

Adjusted for patient sex, age(years), length of hospital stays, tobacco use, Charlson comorbidity index (CCI), asthma-related comorbidities (sinusitis, upper respiratory diseases), obesity, and asthma severity; *** indicates a variable is significant at 0.05.

PDC and MPR and asthma exacerbation over time among users of ICS and ICS/LABA controller medications. Figure 2 summarizes the effects of varying ICS and ICS/LABA adherence thresholds and the risk of asthma exacerbation. From Figure 2, the optimal PDC and MPR adherence thresholds '0.80–1.00' reduced asthma exacerbation by 21% among users of ICS medication. Using the PDC adherence thresholds, patients who achieved an adherence thresholds of at least 0.90 among ICS/LABA users improved their asthma control

by 30%, while those who attained adherence within 0.80–0.90 reduced their exacerbations by 17%. Similarly, higher levels of MPR adherence (>0.90) among ICS/LABA users were significantly associated with reduced burden of the disease over time.

Sensitivity analysis

Figures S1 and S2 present Receiver Operating Curve (ROC) curve analysis for PDC and MPR. This was

Table 4. Multivariate analysis of the association between varying MPR adherence thresholds and asthma exacerbation.

MPR thresholds	Asthma hospitalization	Emergency department visit	Asthma exacerbation (Combined asthma hospitalization, ED visits)
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Poor "<0.5"	Ref	Ref	Ref
Mild "0.50–0.59"	0.94(0.90, 1.00)	0.98(0.93, 1.03)	0.95 (0.92, 0.98)***
Moderate "0.60–0.69"	0.94(0.89, 1.00)	0.96(0.92, 1.00)	0.94 (0.91, 0.97)***
Good "0.70–0.79"	0.94(0.89, 1.01)	0.92(0.89, 0.97)***	0.93 (0.90, 0.96)***
Very good "0.80–0.89"	0.91(0.87, 0.95)***	0.88(0.84, 0.92)***	0.88 (0.85, 0.92)***
Excellent "0.90–1.00"	0.90(0.88, 0.93)***	0.86(0.84, 0.88)***	0.85 (0.84, 0.87)***

Adjusted for patient sex, age(years), length of hospital stays, tobacco use, Charlson comorbidity index (CCI), asthma-related comorbidities (sinusitis, upper respiratory diseases), obesity, and asthma severity; *** indicates a variable is significant at 0.05.

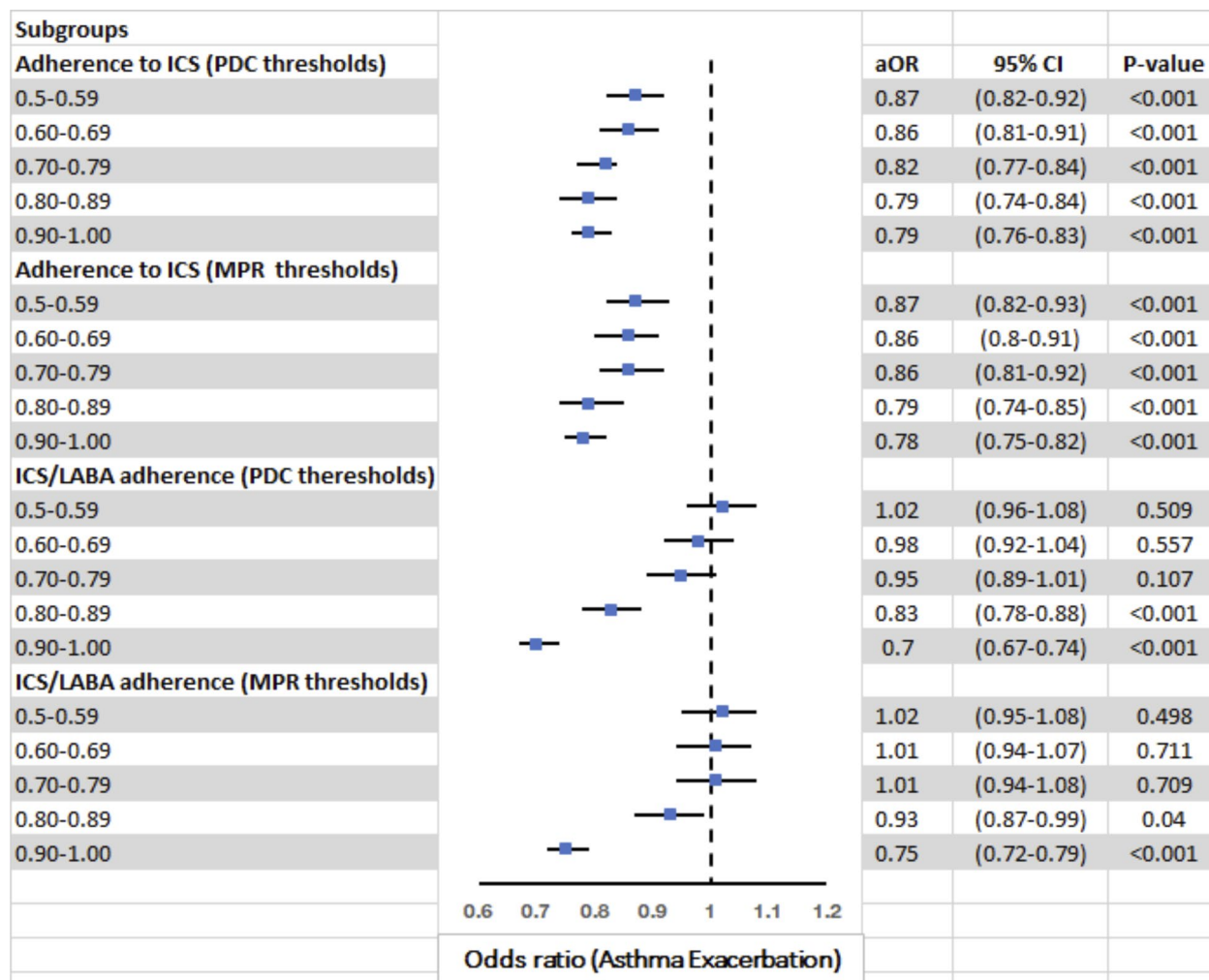


Figure 2. Forest plot of association between varying PDC and MPR thresholds among patients with ICS and ICS/LABA usage and risk of asthma exacerbation over time. ICS=Inhaled corticosteroids; ICS/LABA=Inhaled corticosteroids/Long-acting beta-2 agonist; aOR=Adjusted odds ratio; PDC=Proportion of days covered; MPR=Medication Possession Ratio. The model was adjusted for sex, age, comorbidity burden (CCI), asthma related comorbidities, history of tobacco smoking/nicotine dependence, obesity, and length of hospital stay.

performed to investigate the overall predictive ability of the estimated adherence rates for each of the PDC and MPR adherence cutoff values. The *Area under the curves* (AUC) were 0.7697 and 0.7684 for the PDC and MPR variables, respectively, which were

statistically greater than the chance (0.50). From [Table S2](#) in the [supplementary material](#), the higher PDC and the MPR adherence scores (≥ 0.70 ; ≥ 0.80) were highly sensitive in predicting the risk of exacerbation among adult asthma patients.

Discussion

In this study, we conducted an observational cohort study to determine the optimal adherence threshold for classifying adherent and non-adherent asthma groups. To the best of our knowledge, very few studies have examined varying PDC and MPR adherence thresholds and their association with clinical outcomes in the adult asthma population. This study aimed at determining an optimal adherence threshold for achieving important clinical outcomes such as reduced asthma exacerbations outcomes including asthma hospitalization, emergency department (ED) visits, and oral corticosteroids claims.

Our results show that patients who attained a PDC or MPR adherence rate of at least 0.5 were significantly less likely to experience asthma exacerbation compared to the MA cutoff value of less than 0.5. The selection of the most predictive adherence cutoff value was based on the strength of the odds ratio (i.e. the higher the adherence scores, the lower the odds ratio in predicting exacerbations). Six adherence thresholds were adopted and were subsequently examined for the risk of asthma exacerbations. Compared to PDC or MPR values <0.5 , all the remaining adherence thresholds (*mild* MA '0.5–0.59'; *moderate* MA '0.60–0.69'; *good* MA '0.70–0.79' *very good* MA '0.80–0.89' and, *excellent* MA ' ≥ 0.90 ') were significantly associated with reduced asthma exacerbations over time.

However, higher compliance rates such as *excellent*, *very good*, and *good* MA levels significantly reduced the risk of asthma exacerbation to a larger extent than the *moderate* and *mild* adherence rates. In particular, patients who achieved an *excellent adherence* (PDC ≥ 0.90) demonstrated a better asthma control with a greater reduction in asthma exacerbations (16%). In contrast, patients who achieved a cutoff higher than 0.50 demonstrated some improvement in their clinical events. For instance, patients who attained a *mild adherence* (PDC: 0.50–0.59) compared to *poor adherence* (PDC < 0.5) reduced their future exacerbations by 5%. That is, higher levels of adherence scores were significantly more effective in improving asthma exacerbations than the moderate compliance scores. These findings have significant implications in managing patients with a diagnosis of asthma. Given that poor/sub-optimal medication adherence contributes to increased asthma exacerbations, it is expedient for healthcare providers to distinguish between poorly adherent asthma patients from those who needs additional therapies as stipulated in the GINA guidelines to achieve maximum symptom control.

Our study generally corroborates with existing studies that found reduced asthma exacerbations among adherent patients (10,13,19,31,35,36). For instance, in a study by Ismaila et al. (13), patients who achieved an MPR adherence threshold of ≥ 0.80 among users of fluticasone-propionate/salmeterol were significantly associated with 52% reduction in exacerbation. Guo and colleagues (19) found an achievement of ICS-and-LABA MPR ≥ 0.80 associated with 29% reduced likelihood of emergency department visits (OR: 0.81 95% CI:0.79–0.84) but higher risk of asthma related hospitalization (OR: 1.56, 1.50–1.62). Similarly, high ICS adherence (MPR ≥ 0.50) compared to low (MPR <0.20) was significantly associated with less likelihood of asthma exacerbation (adjusted OR: 0.828, 95% CI: 0.707 to 0.971) (31). Our study, therefore, suggests that a greater achievement of adherence (>0.90) combined with treatment persistence reduces the likelihood of relevant clinical events (such as asthma-related hospitalization and emergency department visits) and subsequently reduces future complications.

Of note, the findings in the literature partially corroborate our current study with regards to the effects of specific categories of adherence cutoff values and reduced risk of asthma exacerbation. However, previous studies did not provide a broader threshold categorization to determine the cutoff that ensures that patients are fully compliant with their medications. Our study shows that a higher threshold of over 0.90 provides better asthma control than the conventional 0.80 thresholds. This suggests that it would be valuable for healthcare providers who treat patients with asthma to incorporate routine assessment and optimization of adherence to prescribed treatments. Thus, it would be important for clinicians to improve on ongoing education of asthma patients on the importance of adherence to prescribed medications and asthma control at every physician visits. Further, the introduction of effective interventions aimed at facilitating and improving asthma medication adherence may be beneficial in minimizing asthma morbidity and subsequent exacerbations.

Also, the assessment of the long-term effect of changes in adherence with treatments using specific thresholds has not been fully addressed. This current study was built on these existing studies and further addressed the knowledge gaps. We investigated the association between six varying adherence thresholds and asthma exacerbation to provide a clinical basis for the choice of a threshold. This study adds further evidence to the literature with regards to the selection of appropriate threshold capable of achieving

important clinical outcomes. Further, whereas both MPR and PDC have been widely documented for assessing medication adherence in asthma administrative databases, our study recommend the use of the PDC over the MPR method. This is because the PDC provides a more conservative estimate of the medication adherence compared to MPR and it is appropriate for calculating adherence on prescribed multiple medications. The PDC avoids double counting of medication coverage when there is an overlap of two refills. Also, the Pharmacy Quality Alliance recommends PDC to be used to calculate medication adherence on prescribed multiple therapies. Despite the fact that the PDC adherence measure is highly recommended for measuring adult asthma patients, the estimation of adherence could have been affected by certain factors. For instance, incorrect inhaler techniques might have influenced the optimal delivery of therapies since certain inhalers require different approaches in their administration. Other factors that might have affected optimal adherence rates included fear of side effects, and unintentional patient-centered barriers such as forgetfulness.

Strength and limitations

In this study, a large population cohort of physician-diagnosed asthma patients was used to determine the association between six varying scores of medication adherence and risk of asthma exacerbation. Due to the longitudinal nature of the data, we employed the GEE logistic regression model to account for possible correlation due to the patient's repeated set of measurements on asthma exacerbations and other covariates (34). This study was limited to incomplete patient records on clinical and laboratory data such as pulmonary function test (PFT), laboratory findings, systolic and diastolic blood pressures. However, despite the omission of these variables in the administrative databases, the variables used provided robust estimates of the model parameters after adjusting for relevant confounders and covariates such as the changes in asthma severities over time, tobacco use, and nicotine dependence, obesity, and asthma-related comorbidities.

Conclusion

This study aimed at determining optimal adherence threshold(s) capable of improving important clinical endpoints in adult asthma patients. Our result suggests that attaining compliance of '0.80–0.89' reduced

patients' risk of asthma exacerbations by 12% compared to compliance < 0.50. Further, a higher compliance rate of ≥ 0.90 reduced patients' exacerbation by over 15%. Also, patients who adhered to their prescribed ICS and ICS/LABA based on the PDC improved their asthma control by 21% and 30%, respectively. We noted that achieving ' ≥ 0.80 ' adherence is optimal in improving asthma control and characterizing adherent and non-adherent adult asthma patients. This information could serve as the basis for selecting an appropriate adherence threshold with clinical rationale for assessing patient compliance. Additionally, the findings provide policymakers with information to effect change within the healthcare system to ultimately improve patient outcomes.

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Declaration of interest

The authors declare no competing interests and that this study has not been published previously in a similar form. All inferences, opinions, and conclusions drawn in this study are those of the authors and do not reflect the opinions or policies of the Data Steward(s) of population data BC.

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