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ORIGINAL RESEARCH

Association Between Medication Adherence and Risk of COPD in Adult Asthma Patients: A Retrospective Cohort Study in Canada

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Background: Poor adherence to prescribed asthma medications and risk of severe asthma exacerbations have been well established. However, the effects of changes in asthma medication compliance levels and subsequent risk of COPD is unknown and yet to be investigated. This study investigated the independent effect of medication adherence (MA) and asthma severity levels on the risk of COPD.

Methods: We used four linked administrative health databases from the Population data BC to identify asthma patients aged 18 years and older between January 1, 1998 and December 31, 1999 without diagnosis of COPD. The primary event was time-to-COPD diagnosis during the follow-up period (January 1, 2000 to December 31, 2018). The proportion of days covered (PDC) – was used as a surrogate measure for medication adherence (MA) assessed at optimal-level (≥ 0.80), Intermediate-level (0.50–0.79), and low-level (< 0.5) of adherence. A propensity adjusted analysis with Marginal Structural Cox (MSC) model was employed to estimate the adjusted hazard ratios (aHR) and 95% confidence intervals (95% CI) for the effect of medication adherence and asthma severity over time.

Results: At cohort entry, the sample included 68,211 asthma patients with an overall mean age of 48.2 years. The 18-year incidence of COPD in asthma patients was 9.8 per 1000-persons year. In an inverse weighted propensity adjusted analysis of the MSC model, higher MA levels were significantly associated with decreased risk of COPD as follows: optimal-level (aHR: 0.19, 95% CI: 0.17–0.24); Intermediate-level (aHR: 0.20, 95% CI: 0.18, 0.23) compared to the low-level adherence group. A significant increase in COPD risk was observed in severe asthma patients with low medication adherence (aHR: 1.72, 95% CI: 1.52–1.93), independent of other patient factors.

Conclusion: Optimal (≥ 0.80) and intermediate adherence (0.5 to 0.79) levels were associated with reduced risk of COPD incidence over time. Interventions aimed at improving adherence to prescribed medications in adult asthma patients should be intensified to reduce their risk of COPD.

Keywords: asthma, COPD, medication adherence, severe asthma, propensity analysis

Introduction

Asthma is highly prevalent disease with substantial health and economic burden. In Canada, appreciable number of the population (12 years and older) are burdened with the condition with a growing prevalence rate of 8.1%.[1] Moderate to severe asthma may result in increased morbidity,[2,3] and hospitalizations.[3–5] Fortunately, good asthma control through optimal medication adherence may help avoid costly asthma complications and exacerbations. To minimize asthma complications and exacerbations, treatment should be adjusted stepwise as recommended by the Global Initiative for asthma (GINA) and other guidelines.[6,7] Adhering to the recommended treatment is important to optimize the benefit of the drug. Treatment adherence has been recognized as an important determinant influencing the effectiveness of the medications. Current clinical practice guidelines including the 2022 GINA guideline recommend the use of low-dose inhaled corticosteroids (ICS)-Long acting beta-2 agonist [LABA] (formoterol) use as needed and for maintenance

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therapy.[6] Despite the known benefits of asthma medications, adherence remains suboptimal among adults, with rates ranging from 30–50%.[8,9]

Poor adherence is linked to several clinical events including poor asthma control, asthma exacerbation, asthma-related emergency visits and hospitalizations, persistent eosinophilic inflammation, and oral corticosteroids (OCS) use.[10] In a meta-analysis by Engelkes et al,[11] poor adherence to asthma medications was significantly associated with severe asthma exacerbations. Several researchers have also documented similar findings[9,12–14]. Also, approximately 5% of severe asthmatics are not optimally controlled with standard therapy and are classified as "difficult to control"[15,16] and subsequently develop airway remodeling that causes chronic irreversible airflow obstruction.[17,18] A recent meta-analysis has identified a positive association between early history of asthma and later risk of COPD. (odds ratio= 7.9; 95% Confidence Interval: 5.4–11.5).[19]

Although there exists a strong positive association between prior history of asthma and COPD diagnosis, the factors linking progression from asthma diagnosis to COPD over time remain largely unresolved. Currently, factors determining COPD incidence in asthma patients have not been well addressed, especially using a large population cohort study. Poor adherence to the various prescribed asthma and concomitant medications could be a contributing factor to this phenomenon. This important factor could play a mediating role in reducing the number of asthma patients who develop COPD.

Sub-optimal use of asthma medication and non-adherence to the various prescribed asthma medications could be a contributing factor to later development of COPD. There exists a significant gap in current research assessing the role of this important factor. Since achieving optimal asthma medication adherence (MA) has the potential of minimizing asthma exacerbations,[11,20] our study investigated the effect of MA levels on the risk of developing COPD in later life. We hypothesize that improved adherence to asthma medications over time is likely to reduce asthma patients' risk of developing COPD in later life. The unique contribution of this study is based on investigating the long-term effects of asthma medication adherence levels over time and subsequent risk of COPD using a large population-based cohort with long-term follow-up.

Methods

Study Design and Data Sources

We employed a retrospective cohort study that utilized four linked administrative claims databases obtained from the Population Data BC in British Columbia (PopData BC), Canada. The PopData BC captures health records of all BC residents registered in the province's universal insurance program.[21] The PopData BC includes longitudinal de-identified electronic medical data from primary care visits, general practitioners, and specialist consultants. These data are linkable both to each other and to other externally managed datasets.[22] This study was approved by the Health Research Ethics Board (HREB) at Memorial University in Newfoundland, Canada (REF #: 2019.216). The data accessed complied with relevant data protection and privacy regulations of the province of British Columbia in Canada. The data custodians of PopData BC approved the following four patient databases to be assessed for this study:

i) The *Discharge Abstract Databases* (DAD)[23] for hospital separations, which captures data on discharges and hospitalizations of in-patients and day surgery patients from acute care hospitals in BC;

ii) The *Medical Service Plan* (MSP) database,[24] which captures records of physician visits;

iii) the *PharmaNet database*,[25] which contains records of all medications prescribed and medical supplies dispensed from community pharmacies in BC; and

iv) the *registration and demographic* (consolidation file) database, which provided data on the demographic and longitudinal registration status of patients in the healthcare system of BC.[26]

We obtained all health records captured in the four databases from January 1, 1998 to December 31, 2018. We defined the index period (January 1, 1998 to December 31, 1999) as the date in which patients were first identified in the database with a diagnosis of asthma. Thus, the 2-year index period was used as the "wash-in" period to allow sufficient time for prevalent asthma to be identified. The follow-up period for this study spanned from January 1, 2000 to December 31, 2018.

Case Identification – Index Cohort at Baseline

We selected patients with a physician diagnosis of asthma (January 1, 1998 to December 31, 1999) using a validated case definition.[21,27] Based on the case definition, the asthma patients were identified from three databases (DAD, MSP, and PharmaNet) based on at least one of the following criteria:

i) Patients having one or more asthma-related hospitalizations 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 with two or more records of physician visits with asthma diagnostic codes (ICD-9 codes: 493.x).

Patients identified with either criteria 1, 2, or both, were also checked for records of filled prescriptions for at least four asthma-related medications within 1 year in the PharmaNet database (See Table S1 for medication lists). We applied the case definition criteria to identify asthma patients 18 years and older with no prior diagnosis of COPD from January 1, 1998 to December 31, 1999 (two-year index period). We further excluded incident cases of COPD among the identified asthma patients at baseline during cohort identification. The identified cohort were followed from January 1, 2000, to December 31, 2018, for the diagnostic outcome of COPD.

Primary Exposure Variable of Interest – Medication Adherence

The primary exposure variable was medication adherence (MA). We employed the proportion of days covered (PDC) as a proxy for estimating the rate of adherence to prescribed medications within a 12-month period for each patient in each of the respective study duration.[28–30] We used the PDC method to calculate the MA rates at baseline (between January 1, 1998 to December 31, 1999) and time varying MA rates during the follow-up (January 1, 2000 to December 31, 2018). The PDC was calculated as the ratio of the number of days of medication covered, or drug-on-hand, to the sum of days within the treatment period (12-month period).[28–31] The PDC was estimated from the PharmaNet database using the "days of medication supply", "fill/refill date", and "drug identification number" variables. Using the "SAS Macro" developed by Chang et al,[32] we calculated the PDC rates and adjusted for inpatient stays by censoring the number of hospitalized days during the measurement period. The study estimated medication adherence for all prescribed single and multiple controller medications [prescribed inhaled corticosteroids (ICS) only, separate ICS and Long-acting beta-2 agonist (LABA) prescribed together for a patient, ICS/LABA combination, and Leukotriene receptor antagonist (LTRA)]. Additionally, we calculated patient's adherence to all prescribed short-acting beta-2 agonist (SABA). Choudhry et al[33] outlined three proposals for computing adherence among patients with concomitant medication prescriptions. Based on the first approach by Choudhry et al,[33] we averaged the estimated adherence rates for each medication class at the patient level. That is, if more than one medication was prescribed for a patient, mean adherence was calculated at the patient level. The adherence rates were categorized into the optimal-adherence ($\geq$ 0.80), intermediate-adherence (0.50–0.799), and low-adherence ($<$ 0.5) levels. We used the 0.80 cut-off value for assessing the optimal adherence, as it has been documented as the optimal threshold for achieving important clinical outcomes in adult asthma patients.[11,13,34,35]

Secondary Exposure -Asthma Severity

Asthma severity level was defined based on the criteria specified in the Canadian Asthma Consensus Guidelines for assessing the severity and control of patients with asthma. Based on the algorithm developed by Firoozi et al,[36] we defined asthma severity levels based on the intensity of prescribed ICS/other controller medications, prescription of short-acting-beta 2 agonist, and whether there is an indication of markers of moderate-to-severe asthma exacerbations (asthma-related hospitalization or emergency department visits due to asthma) or not. Thus, asthma severity levels were defined as follows: a) mild asthma group corresponds to having a prescription of 0–500µg/day doses of inhaled corticosteroids (ICS) [including budesonide, fluticasone, beclometasone, and ciclesonide] and not receiving additional controller therapy or having ICS doses of 0–250µg/day for patients receiving additional controller therapy. Also, patients were classified into the mild asthma category if they did not have a marker for a moderate to severe exacerbation or had taken at least an average of three short-acting beta-2 agonists (SABA) doses per week for a 12-month period. Patients were classified into the moderate asthma category if they were prescribed with >500µg/day doses of ICS with no

additional usage of controller therapy or had a prescription of >250μg/day doses of additional controller therapy, except for those with high SABA usage and moderate to severe asthma exacerbations. Severe asthma patients were defined as individuals who had prescription records of ">1000μg/day ICS doses", except for patients with markers of uncontrolled asthma (ie having 10 doses of SABA per week).

Study Outcome: Time-to-Incidence of COPD

The primary study outcome was the time-to risk of COPD diagnosis in asthma patients. We defined COPD from the database during the follow-up period (January 1, 2000 to December 31, 2018). We adopted Chen et al[37] and Gershon et al[38] case definition, which has been validated against chart reviews with high (85%) sensitivity. Thus, COPD was defined based on the presence of at least one hospitalization or two or more outpatient visits on different dates with COPD as the most responsible diagnosis (using ICD-9 codes: 491.xx, 492.xx, 493.2x, 496.xx; and ICD-10-codes: J43.xx, J43.xx, J44.xx). An individual was censored if they did not develop COPD during the follow-up, left any of the four linked databases, or died or lost on the last day of follow-up.

Propensity Adjusted Covariates

At baseline, several covariates were identified based on the literature and the availability of complete information on variables in the database to be controlled for as confounders. The limited extant literature, although mixed, listed variables such as obesity, history of cigarette smoking, air pollution, particulate matter, and sex as potential risk factors for incidence of COPD in the Canadian population.[39,40] Additionally, various demographic characteristics, such as patient sex and age, were selected for analysis. We scanned the diagnosis codes in medical claims during the baseline and the post-index period (follow-up) to identify various comorbidities. Using the identified comorbid conditions, we estimated the Charlson comorbidity index (CCI) as a marker for the comorbidity burden of patients by excluding asthma from the score.[41] Comorbidity burden was classified into three categories based on a documented cut-off point by Nunez et al[42]: - CCI score 0; CCI score 1; CCI score ≥ 2; where higher score accounted for greater comorbidity burden in the adjusted analysis. Asthma-related comorbidities, such as sinusitis and upper respiratory diseases, were also identified at baseline and examined. Asthma exacerbations were considered as one of the covariates and defined as either oral corticosteroid (OCS) claims, emergency room visits, and/or asthma hospitalizations.[14,43,44] We further scanned the medical claims database to identify patients' use of tobacco and nicotine dependence, categorized as presence =1 or absence=0. A study by Wiley et al[45] supports the use of ICD-codes for identifying smokers or smoking status in a clinical population. Also, we included obesity (coded as 1 for body mass index (BMI)>30kg/m^2 and 0 otherwise) as one of the risk factors extracted from the database. In addition, emergency hospital admission and length of hospital stay were considered as possible risk factors.

Statistical Methods

Standard descriptive statistics were used to describe the baseline characteristics. We performed all the statistical analyses in both SAS version 9.4 and STATA version 16. We estimated the mean, median, standard deviation, and interquartile range (IQR) for the continuous variables, and constructed frequency and relative frequency tables for categorical variables. We employed the Pearson chi-square test to test the association between categorical covariates and adherence levels at baseline. Also, the authors performed the one-way analysis of variance (ANOVA) and Kruskal–Wallis test to test significant differences between the means and medians of the continuous variables among the three MA levels.

Propensity-Score Derivation

Using multinomial logistic regression, propensity scores, estimated as the probability of adherence conditional on baseline covariates associated with COPD, were generated and adjusted for in the primary analysis. The model included the predicted probability of predefined levels of MA; that is, optimal, intermediate, and low levels of medication adherence. Significant covariates for COPD included in the propensity score included the patient's age, sex, Charlson comorbidity index, asthma-related comorbidities (such as upper respiratory diseases and sinusitis), asthma-related hospitalizations, emergency department visits, asthma exacerbation, length of hospital stay, tobacco use/nicotine

dependence, and asthma severity at baseline. These factors were independently and significantly associated with COPD outcome in a bivariate logistic regression model. Obesity was not significantly related to the risk of COPD, but was included in the propensity score model since earlier studies have documented obesity as a risk factor for COPD in asthma patients.[39]

Primary Analysis-Assessment of MA to All Prescribed Medications

The primary analysis was to assess the independent effects of medication adherence (MA) and asthma severity (physician-diagnosed) on the risk of COPD, adjusting for other relevant patient covariates and confounders using the inverse probability treatment weighted (IPTW) estimates and propensity scores generated.

We used multivariate marginal structural Cox's (MSC) model with Inverse Probability Treatment Weighting (IPTW) that included time-varying medication adherence level, asthma exacerbation, and asthma severity, in addition to all baseline covariates adjusted for potential confounders using propensity scores. Due to the presence of time-varying exposure (medication adherence), time-varying asthma exacerbation, and asthma severity, using any of the forms of standard Cox proportional hazard models (ie, standard Cox and time-dependent Cox models) could lead to biased estimates. Also, the longitudinal nature of the database with the inclusion of repeated measurements in the presence of time-dependent covariates violates the proportional hazard assumption and makes the standard Cox's model inappropriate for the analysis of this dataset. Moreover, the time-dependent Cox model is unlikely to properly adjust for time-varying confounders, resulting in biased estimates. The Marginal Structural Cox model addresses the limitations of both the standard Cox's proportional and time-dependent Cox's models by employing inverse probability of exposure weighting to provide consistent and unbiased estimates of the effect of the main exposure of interest.[46,47] Time-varying/dependent confounders and covariates included in the multivariate structural Cox's model were time-dependent medication adherence levels (low, intermediate, and optimal), asthma severity levels (mild, moderate, severe), and asthma exacerbations over time. Each analysis was evaluated at 5-year, 10-year, and 18-year (overall) follow-up periods.

Secondary Analysis-Assessment of MA to Specific Medication Classes

The secondary analysis was performed to assess the specific effect of adherence to various individual and combined asthma medications, including short-acting beta-2 agonist (SABA), long-acting beta-2 agonist (LABA), and inhaled corticosteroids (ICS), adjusting for other relevant patient covariates and confounders using the propensity scores generated. Effect modification using interaction terms was performed for both primary and secondary analysis to assess the differential effect of medication adherence by the severity of asthma.

Results

Baseline Characteristics

A total of 68,211 adult asthma patients were identified from the four linked-databases obtained from the PopData BC for data analysis (see Figure S1 in the Supplementary Material). Overall, the distribution of the sample by medication adherence levels at baseline were low-level (n=46, 666, 68.4%), moderate-level (9557, 14.0%), and optimal-level (11,988, 17.6%). At the cohort entry, there were 49,155(72.06%) patients diagnosed with mild asthma, 15,595 (22.87%) moderate, and 3461(5.07%) severe with an overall mean age of 48.2 years. The patients' baseline characteristics are presented in Table 1 stratified by medication adherence (MA) levels.

The prevalence of patients' clinical variables at baseline included asthma hospitalizations (n=2701, 3.96%); emergency department visits (n=3158, 4.63%); median (interquartile range) length of hospital stay as 3.00 (2–6) days. The patients collected a number of prescribed asthma-related medications. Prevalence of prescription medication includes inhaled corticosteroids (ICS) only (n=5842, 20.58%); short-acting beta-2 agonist or SABA only (n=14,037, 20.58%), ICS/LABA combinations (n=90, 0.13%). The fewer number of ICS/LABA combination during the index period (January, 11998 and December 31, 1999) was due to the fact that the guidelines recommending prescription of the combined inhalers containing ICS and LABA were not updated. However, a substantial number of patients used separate ICS and LABA inhalers

Table 1 Cohort Characteristics by Asthma Medication Adherence Levels for the Patient at Baseline

Variables	Overall	Medication Adherence (MA) levels			
		Low-Level (PDC<0.50)	Intermediate (PDC=0.5–0.79)	Optimal (PDC: ≥80%)	P-value
N	68,211	46,666 (68.4%)	9557 (14.0%)	11,988 (17.6%)	
Socio-demographic					
Mean age, (SD in years)	48.20 (18.63)	46.50 ±18.12	50.89 ±18.09	52.71 ±19.29	<0.0001
Male Sex	27,756(40.69)	18,306(39.23)	4136(43.28)	5314(44.33)	<0.0001
Obesity (BMI>30kg/m^2)	205(0.30)	134(0.29)	25(0.30)	46(0.40)	0.171
Tobacco/nicotine use	96(0.14)	59(0.10)	18(0.20)	19(0.20)	0.288
Charlson comorbidity index					
Score=0	66,766 (97.90)	45,906(98.37)	9277(97.07)	11,583(96.62)	<0.0001
Score=1	1226 (1.80)	615(1.32)	251(2.63)	360(3.00)	
Score ≥2	219(0.30)	145(0.31)	29(0.30)	45(0.38)	
Clinical variables/outcomes					
Sinusitis	108(0.16)	74(0.16)	15(0.16)	19(0.16)	0.999
URI	284(0.42)	174(0.37)	42(0.44)	68(0.57)	0.012
Asthma hospitalization	2701(3.96)	1760(3.77)	389(4.07)	552(4.60)	<0.0001
Emergency department visit	3158(4.63)	2295(4.92)	354(3.7)	509(4.25)	<0.0001
Asthma exacerbation	5585(8.19)	3871(8.30)	705(7.4)	1009(8.42)	0.007
Hospital stay [median (IQR)]	3.0(2–6)	3.0(2–6)	4(2–7))	4(2–7)	0.009
Asthma severity at baseline					
Mild asthma	49,155(72.06)	33,730(72.28)	7205(75.39)	8220(68.57)	<0.0001
Moderate asthma	15,595(22.87)	10,776(23.09)	1851(19.37)	2968(24.76)	
Severe asthma	3461(5.07)	2160(4.63)	501(5.24)	800(6.67)	
Asthma medications prescribed					
SABA only	14,037(20.58)	10,718(22.97)	1464(15.32)	1855(15.47)	<0.0001
ICS only	5842(20.58)	4220(9.04)	751(7.86)	871(7.27)	<0.0001
ICS/LABA combination	90(0.13)	57(0.12)	12(0.13)	21(0.18)	0.355
ICS+SABA only	39,451(57.84)	26,354(56.47)	5870(61.42)	7227(60.29)	<0.0001
ICS+LABA only	6639(9.73)	4003(8.58)	1148(12.01)	1488(12.41)	<0.0001
Others	2152(3.15)	1281(2.75)	324(3.39)	547(4.56)	<0.0001

Abbreviations: BMI, body mass index; URI, upper respiratory infections; SABA, short acting beta-2 agonist; LABA, long-acting beta-2 agonist; ICS/LABA, inhaled corticosteroids/long-acting beta-2 agonist; other medications included leukotriene receptor antagonists (LTRA) and theophylline; IQR, interquartile range; SD, standard deviation.

prescribed together during same the index period. For instance, a total of (6639, 9.73%) were prescribed with both ICS and LABA separately at the same time, 39,451(57.84%) prescribed with ICS and SABA separately at the same time.

Analysis of Survival Trend Within the 18-Year Follow-Up Period

The 18-year incidence of COPD in the overall cohort was 9.81 per 1000-persons year. Figures 1 and 2 present the survival curves for the overall 18-year follow-up for COPD stratified by medication adherence and severity of asthma. Asthma patients with sub-optimal (or low) levels (MA< 0.5) and a history of severe asthma are at increased risk of COPD diagnosis later in life.

Bivariate Analysis of Baseline Factors and Risk of COPD

Table 2 presents the bivariate association between the various baseline factors and risk of COPD in asthma patients. All significant covariates presented at baseline were included in the derivation of the propensity score used in the multivariate analysis for assessment of the effect of medication adherence and severity of asthma over time. Obesity was not significantly related to the risk of COPD but was included in the propensity model since earlier studies have documented obesity as a risk factor for COPD in asthma patients.[46]

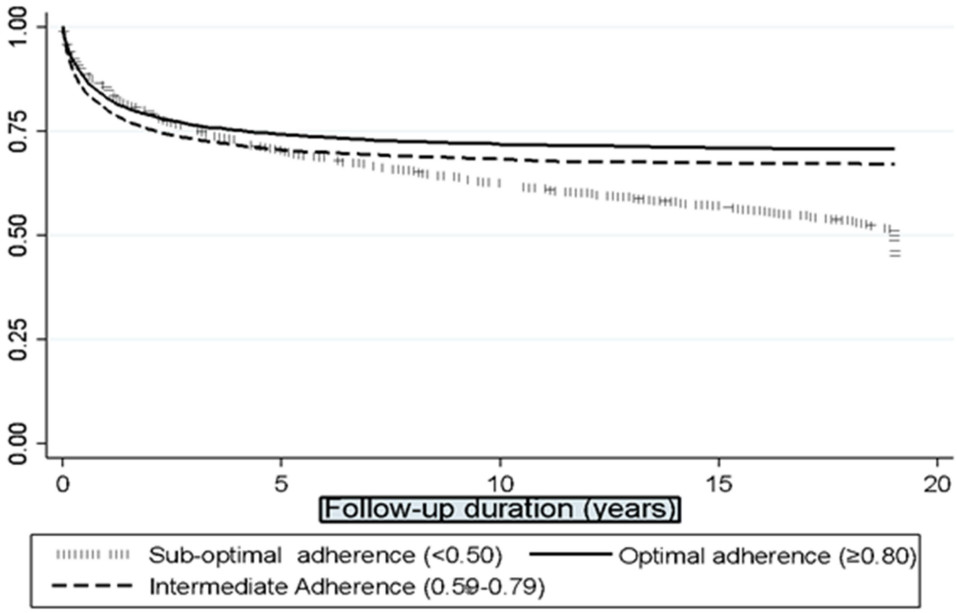

Figure 1 Adjusted survival curves for time-to incidence of COPD stratified by medication adherence (p<0.001).

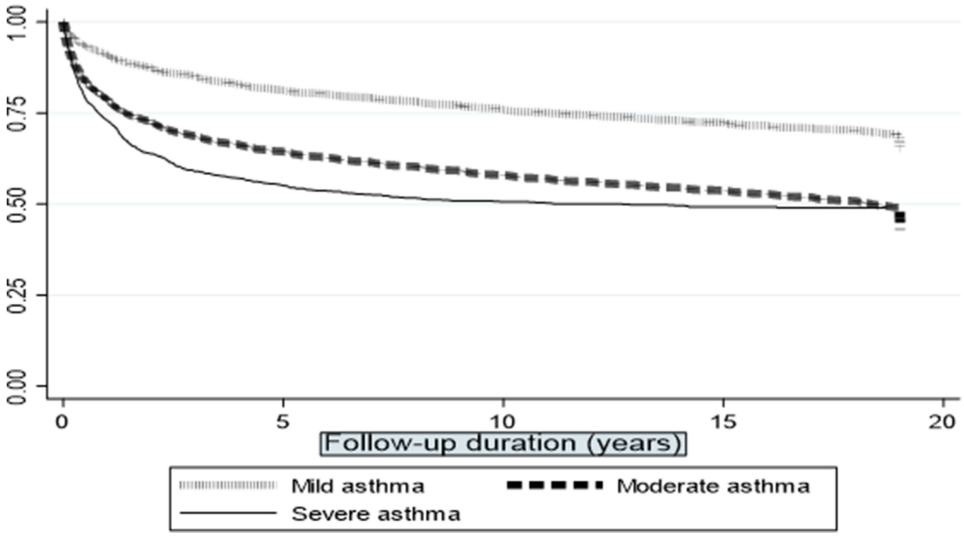

Figure 2 Survival curves for time-to incidence of COPD stratified by asthma severity (p<0.001).

Adjusted Inverse Propensity Weighted Analysis of MA Effect on COPD

From Table 3, the adjusted hazard ratios (aHR) for each of the primary and secondary analyses were estimated, comparing the effect of MA on COPD incidence at 5-year, 10-year, and 18-year (overall) follow-up.

Compared to the low (or sub-optimal) adherent patients, individuals who attained intermediate and optimal adherence levels in the 18-year follow-up period were 80% (aHR: 0.20, 95% CI: 0.18–0.23) and 81% (aHR: 0.19, 95% CI: 0.17–0.24) less likely to develop COPD respectively after adjusting for asthma severity levels and the potential confounders in the propensity score for all prescribed asthma-related drugs. Similar trends were observed at 5-year and 10 years follow-up period in the primary analysis.

Further, when compared to the mild asthma patients, severe and moderate asthma patients were at an increased risk of developing COPD with (aHR: 3.73, 95% CI: 2.74, 5.09) and (aHR: 1.68, 95% CI: 1.49, 1.89), respectively. The risk of

Table 2 Patient Baseline Factors Associated with the Risk of COPD in Bivariate Analysis (18-Year Follow-Up)

Patient Factors	Hazard Ratio	95% CI	*p*-value
Age (years)	1.03	(1.031, 1.04)	<0.0001
Male Sex	1.27	(1.23, 1.33)	<0.0001
Charlson Comorbidity Index	1.45	(1.37, 1.54)	<0.0001
Asthma-related comorbidity			
Sinusitis	0.53	(0.30, 0.94)	0.029
Upper respiratory diseases	1.41	(1.16, 1.73)	0.001
Asthma related hospitalization	1.18	(1.09, 1.28)	<0.0001
Emergency department visit	0.94	(0.85, 1.03)	0.203
Asthma exacerbation	1.08	(1.01, 1.15)	0.019
Length of stay (days)	1.38	(1.35, 1.40)	<0.0001
Tobacco use/nicotine dependence	1.78	(1.28, 2.46)	0.001
Obesity (BMI>30)	0.97	(0.75, 1.27)	0.846
Asthma severity			
Mild	Ref		
Moderate	1.52	(1.46, 1.58)	<0.0001
Severe	2.60	(1.54, 4.39)	<0.0001

Table 3 Propensity-Adjusted Association Between Medication Adherence, the Severity of Asthma and Incidence of COPD

Study Factors	5-Year		10-Year		Overall (18-Year)	
	aHR(95% CI)	*p*-value	aHR(95% CI)	*p*-value	aHR(95% CI)	*p*-value
(A) Primary analysis: Adherence levels to all prescribed asthma medications combined						
Adherence measured by PDC						
Optimal-level	0.33(0.31, 0.35)	<0.0001	0.25(0.23, 0.28)	<0.0001	0.19(0.17, 0.24)	<0.0001
Intermediate	0.35(0.33, 0.37)	<0.0001	0.27(0.25, 0.30)	<0.0001	0.20(0.18, 0.23)	<0.0001
Low-level (or suboptimal)	Ref	n/a	Ref	n/a	Ref	n/a
Asthma Status						
Severe	3.07(2.81, 3.35)	<0.0001	3.10(2.81, 3.44)	<0.0001	3.73(2.74, 5.09)	<0.0001
Moderate	1.65(1.57, 1.74)	<0.0001	1.53(1.43, 1.63)	<0.0001	1.68(1.49, 1.89)	<0.0001
Mild	Ref	n/a	Ref	n/a	Ref	n/a
(B) Secondary analysis*: Adherence asthma specific-medications						
Adherence to ICS only						
Optimal-level	0.32(0.29, 0.37)	<0.0001	0.32(0.28, 0.37)	<0.0001	0.33(0.27, 0.41)	<0.0001
Intermediate	0.39(0.35, 0.44)	<0.0001	0.39(0.35, 0.44)	<0.0001	0.39(0.32, 0.47)	<0.0001
Low-level	Ref	n/a	Ref	n/a	Ref	n/a
Adherence to combinations (ICS/LABA)						
Optimal-level	0.29(0.25, 0.32)	<0.0001	0.26(0.22, 0.30)	<0.0001	0.25(0.20, 0.31)	<0.0001
Intermediate	0.40(0.35, 0.45)	<0.0001	0.37(0.33, 0.42)	<0.0001	0.30(0.26, 0.35)	<0.0001
Low-level	Ref	n/a	Ref	n/a	Ref	n/a

Notes: Table include *adjusted hazard ratios* (aHR) and 95% *Confidence Interval* (95% CI). Propensity adjusted analysis using Marginal Structural Cox model (inverse probability weighted cox model) which adjusted for both baseline covariates and time varying covariates and confounders. *Optimal level* = [PDC ≥ 0.80], *Intermediate level*= [0.50 ≤ PDC ≤ 0.79], *low-level (or suboptimal)* = [PDC <0.5]; ref=reference group; n/a= not applicable. *Analysis are adjusted for severity of asthma.

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; MA, medication adherence; PDC, proportion of days covered.

COPD in severe asthma patients increased by more than 3 folds while that of the moderate asthma group increased by a factor of 1.68.

Drug Specific Effect in Secondary Analysis

Adherence to specific asthma medications such as ICS and ICS/LABA combinations and risk of COPD over 5-year, 10-year, and 18-year follow-up periods were also assessed. From Table 3, patients who attained optimal adherence to their prescribed ICS over time were at a reduced risk of developing COPD [aHR: 0.33, 95% CI: 0.27, 0.41] using inverse probability weighted estimates (stabilized weights) and after adjusting for propensity scores at baseline and asthma severity compared to the sub-optimal (low) ICS users. Similarly, optimal adherence to prescribed combined ICS/LABA over the 18-year follow-up period were 75% less likely to develop COPD, 74% less likely to develop COPD in the 10-year follow-up and 71% less likely to develop COPD in the 5-year follow-up compared to the non-adherent patients.

Effect Modification of MA by the Severity of Asthma

Figure 3 presents an additional subgroup analysis or effect-modification of MA by asthma severity levels on COPD diagnosis in asthma patients. There was a significant effect modification of MA by asthma severity over time. For instance, individuals who attained optimal adherence in the mild asthma group compared to low adherence patients achieved the greatest protection from COPD risk with an adjusted hazard ratio and 95% confidence interval of (0.18, 0.14–0.80). Also, severe asthma patients who achieved optimal adherence (that is, PDC≥ 0.80) over time compared to low adherence in mild asthma patients were not protected to a greater extent with a 14% reduced risk of developing COPD (aHR: 0.86, 95% CI: 0.76–0.98). However, patients with low adherence (<0.5) and a history of severe asthma were 1.72 times more likely to be diagnosed with COPD.

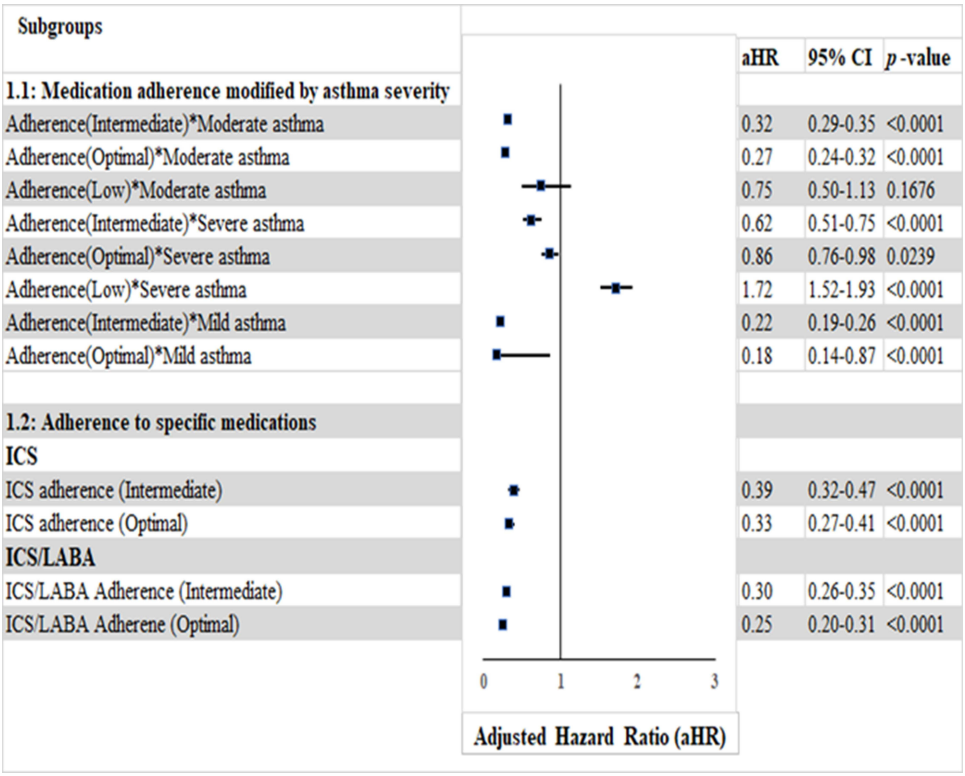

Figure 3 Association between medication adherence and risk of COPD modified by asthma severity levels. aHR: adjusted hazard ratio; 95% CI: 95% confidence interval; Reference category for subgroup 1.1 is "low adherence*mild asthma"; *Reference category for subgroup 1.2 is "low adherence".

Discussion

Medication adherence (MA) has been recognized as an important determinant influencing treatment outcomes of asthma patients. Previous studies have shown significant association between sub-optimal asthma medication adherence and several clinical events including poor control, increased exacerbation with related emergency visits and hospitalizations, persistent eosinophilic inflammation, increased oral corticosteroids use[10,48] and mortality[49] among asthma patients.[9,11–13,50,51] The current study built on the previous academic and clinical literature and added global evidence for the association between medication adherence and incidence of COPD among asthma patients and followed up for 18-years. This study assessed the independent effect of asthma medication adherence levels on risk of COPD using a population-based administrative health database from PopData BC in Canada.

This study provides important clinical insight into the risk profile of suboptimal adherence to asthma medications and subsequent disease exacerbations. In this large observational cohort of asthma patients, the 18-year incidence of COPD in the overall cohort of asthma patients (n=68,211) was 9.8 per 1000-persons year. The incidence rate recorded in our study is similar to incidence rates of COPD in other jurisdictions. For instance, data from the Rotterdam study found overall incidence of COPD as 8.9 per 1000-person years.[52] Similarly, a study by Antoniou et al[38] estimated incidence of COPD among individuals with HIV versus HIV-negative in Ontario as 10.4 versus 9.0 cases per 1000 person-years. Baseline results showed a high rate of poor adherence (PDC <0.5) of 68%. The high non-adherence rate in this cohort could be linked to several adverse asthma-related outcomes which may contribute to increased risk of irreversible airway obstruction or COPD. Following adjustment for potential confounding factors using propensity analysis in the MSC model, we found a significant association between asthma medication non-adherence and risk of COPD. Suboptimal level of medication adherence (MA) was associated with increased risk of COPD incidence as early as 5-years of follow-up after asthma diagnosis. Sensitivity analyses using asthma-specific medications (ICS alone and ICS/LABA combinations) demonstrated consistent findings of increased risk of COPD diagnosis associated with low/poor adherence to medications in asthma patients, even after adjusting for time-dependent asthma severity. Severe asthma patients were at 3-fold times more likely to be diagnosed with COPD later in life, independent of other confounding factors that were controlled for in the model. However, the association of MA with COPD incidence was modified by asthma severity levels, with poor adherent severe asthma patients bearing the greatest burden of early diagnosis of COPD. That is, poorly adherent severe asthma patients were 1.72 times more likely to develop COPD over the 18-year follow-up period compared to mild asthma patients.

Also, the results of the present study is consistent but adds to previously conducted studies that investigated optimal adherence and reduced risk of asthma exacerbations.[18,20–23] However, the previous studies did not investigate further association between optimal, intermediate, or low adherence levels of MA and the risk of COPD diagnosis in a long-term follow-up. In addition, previous works did not evaluate the impact of time-varying adherence to asthma medications on risk of COPD. More so, the long-term effect of compliance and non-compliance to the various treatment regimens and risk of developing COPD in asthma patients have not been fully investigated in a large population-based study. This current study fills in the gap in the literature through the use of a large administrative database with an 18-year follow-up period. Since asthma is a chronic disease with no cure, it is important to understand the long-term effects of the changes in medication adherence levels on risk of COPD over time.

Our study also adds to the evidence in the current literature that improved adherence to asthma medications over a long period is associated with reduced risk of COPD diagnosis. This observational population-based analysis contributes to the growing body of knowledge that provides evidence for the role of MA in an asthma patient. The major strength of this study is that we have examined the association between changes in medication adherence levels, asthma severity over time, and risk of COPD among asthma patients. The implication of the results indicates that mild, moderate, and severe asthma patients who achieved optimal adherence or mostly comply with the guideline-directed treatments are less susceptible to asthma exacerbations and COPD diagnosis.

While optimal adherence to prescribed asthma medications improves important clinical events, barriers (including patient, clinician and treatment related) that minimizes the achievement of satisfactory adherence levels should be well addressed. For instance, the long-term drug usage and the complex regimens requiring numerous medications with

varying dosing intervals is likely to contribute to low adherence. Patient and clinician related barriers including "low motivation to change behaviour", "psychological problems", "low confidence in clinician or medicine" and "treatment by different caregivers" affects asthma medication adherence over time. To maximize and improve adherence levels, there is the need for a thorough patient and clinician or healthcare providers [HCPs] (including physicians, nurses and pharmacists) education on the disease. HCPs would need to discuss with the patients the rationale for achieving optimal adherence, and the benefits of regular (ie monthly) asthma education with patients. The regular clinician-patient partnership will enable patients to ask relevant questions concerning the disease process and treatment. Also, encouraging more frequent physician visit of asthma patients will enhance monitoring of patient's adherence over time and contribute to effective treatment of asthma.

Additionally, HCPs should adopt an innovative and cost-effective interventions to achieve optimal medication adherence in patients with severe asthma. Several interventions have been documented for improving medication adherence in asthma patients. For instance, an effective multi-component mobile health intervention significantly improves patients overall adherence to asthma medications.[53] Also, "adherence education interventional programmes" such as one-to-one and group face-face adherence education sessions, motivational interviewing, nurse-led psychoeducation, and interactive voice recognition systems significantly improve patient's adherence to asthma medications. Evidence indicates that the pooled effect of the educational interventions shows a better benefit of 20 percentage points over the control group (no education).[54] In addition, HCPs can help improve inhaler techniques as one of the possible solutions to nonadherence to asthma inhaler medications. This could be done through both HCP and patient education on inhaler technique to help the proper usage of inhalers to achieve optimal adherence.[55]

Limitations

The use of an administrative claim database for population-based studies presents some limitations that might have affected the study. First and foremost, the PDC measure used as a proxy for medication adherence was calculated based on filled/refilled claims and the sum of days covered which does not guarantee whether patients ingested the medications or not. Measuring medication adherence using pharmacy databases provides an objective measure of adherence and it is a simple tool to use in clinical setting. Administrative pharmacy claim database adherence rates have been documented to demonstrate concordance with adherence rates estimated from some objective methods such as pill counting and electronic monitoring.[56,57] Also, we adjusted for inpatient stays or days hospitalized from the calculation of the medication adherence, and thus, the estimates derived reflected actual medication use.

Furthermore, the linked databases used for this research did not capture other important covariates including physical examination variables, laboratory tests, air pollution, income approximations with postal codes and other environmental factors. Thus, some of these unmeasured variables in the data could have possibly resulted in residual confounding in the model. Also, there were limited records on history of tobacco use and obesity in the administrative database used. However, these limitations were accounted for to a larger extent since we included and adjusted for some important baseline and time-varying confounders and covariates such as obesity, asthma severity levels, tobacco use history, and asthma exacerbation using the Marginal Structural Cox model, which provides a robust adjusted estimate for making inferences. Although the data used lacked detailed clinical information, the use of a large administrative population database added relevant information which reflected the real-world setting. Thus, the results of this study can be generalized to other populations with similar demographics in other provinces or territories in Canada and North America at large.

Conclusion

The study investigated the association between changes in medication adherence levels (optimal, Intermediate, and low/poor) and risk of COPD diagnosis among patients in an 18-year follow-up period that spanned from January 1, 2000, to December 31, 2018. From the Marginal Structural Cox model, optimal adherence to medication in adult asthma patients over time was associated with reduced risk of COPD diagnosis in later life. Specifically, patients who optimally adhered to asthma controller medications such as ICS and ICS/LABA were protected from risk of COPD onset after adjusting for important patient factors. Additionally, severe and moderate asthma patients were at an increased risk of COPD incidence

compared to mild asthma patients over time, with severe asthma patients having the greatest risk. However, the association was modified by asthma severity levels as poorly adherent severe asthma patients were 1.72 times more likely to develop COPD over the 18-year follow-up period compared to mild asthma patients. Strategies aimed at improving compliance to prescribed asthma medications for long-term treatment of asthma should be intensified especially in severe asthma patients to minimize their risk of COPD diagnosis.

Disclaimer

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) or PopData, BC.

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Disclosure

The authors declare no competing interests.

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