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Respiratory tract infection-induced asthma exacerbations in adults with asthma: assessing predictors and outcomes

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ABSTRACT

Objective: To evaluate clinical and economic burden associated with respiratory tract infection (RTI)-induced asthma exacerbations and to identify risk factors associated with these exacerbations. Factors associated with these exacerbations are understudied and little information is available about consequent expenditures. **Methods:** In this retrospective case-control study, medical records and pharmacy data in King Abdullah University Hospital in Northern Jordan were reviewed for adults with asthma aged 40 years and older, over the period 2013–2016. Cases of RTI-induced asthma exacerbations were identified, and controls were selected randomly from asthmatic adults who did not experience any RTI-induced asthma exacerbation during the same period. Independent-samples t-tests and chi-square tests were conducted to compare patient characteristics of cases and controls. Predictors of RTI-induced asthma exacerbations and the resultant complications were evaluated using multivariable logistic regression. Multivariable regression on log-transformed charges was used to predict expenditures of these exacerbations. **Results:** A total of 137 cases and 548 controls were identified. Using inhaled corticosteroid + long-acting beta-agonists (ICS + LABA) was significantly associated with lower odds of RTI-induced asthma exacerbations (OR = 0.4; 95% CI, 0.21–0.77; $p = 0.006$), and lower odds of resultant serious complications (OR = 0.23; 95% CI, 0.07–0.69; $p = 0.009$), compared to being untreated with any asthma maintenance treatment. Asthma severity and co-morbidities were associated with increased susceptibility to these exacerbations. The average charges of RTI-induced asthma admissions and outpatient exacerbations were 1042.9 JD (\$1471.0) and 81.1 JD (\$114.4), respectively. **Conclusions:** ICS + LABA, asthma severity and co-morbidities appeared to affect the clinical and economic burden associated with RTI-induced asthma exacerbations. Efforts to prevent these exacerbations in patients with risk factors are warranted.

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Asthma control; RTI; inpatient admission; outpatient exacerbation; expenditure; ICS + LABA

Introduction

Asthma is a chronic disease with significant clinical and economic burden [1–3]. The global prevalence of asthma was estimated to be 4.5%, and has increased in recent years among adults [4]. In 2015, asthma was ranked among the top 20 diseases causing disability globally, and the 23rd in causing morbidity as measured by disability-adjusted life years (DALYs) [3]. According to the Centers for Disease Control and Prevention (CDC), morbidity and mortality are increasing in middle-aged and older adults with asthma [5]. Emergency care, hospitalization, permanent disability, marked limitations of life, and even premature death have all been associated with uncontrolled asthma [6–8]. Similarly in Jordan, the

World Health Organization (WHO) reported that asthma was among the most common health problems treated at hospitals [9] and asthma has been reported to affect approximately 10% of older adults in Jordan [10]. However, the exact burden of asthma in Jordanian adults is still understudied [11].

Even though asthma is often considered a disease of younger patients, recent morbidity and mortality statistics showed that the majority of asthma-related deaths were among those aged over 55 years old [12,13]. Medical expenditures attributable to asthma are especially high in older adults with uncontrolled asthma [14,15].

To prevent asthma-related morbidity and mortality, the primary goal of asthma management is to prevent

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acute exacerbations and minimize asthma symptoms [16]. Respiratory tract infections (RTIs) are common precipitants of acute asthma exacerbations in adults, playing a role in an estimated 45% to 80% of exacerbations [17,18]. Adults with asthma were found to have increased frequency, duration and severity of RTIs compared to adults without asthma [19]. Certain comorbid conditions, such as heart failure (HF) and chronic obstructive pulmonary diseases (COPD) have been suggested in previous literature to complicate asthma control [20–22]. However, their influence on susceptibility and response to RTI, and the resultant asthma exacerbations, are still unclear [23]. Although RTIs are major contributors to asthma exacerbations, little information is available on the cost of RTIs in adults with asthma. Host factors associated with the susceptibility of an adult with asthma to infection-induced asthma exacerbations are still understudied [23]. Clearly, preventing RTIs in patients at risk is essential to decrease asthma exacerbations and resulting morbidity and mortality in adults with asthma [12]. The purpose of this study was to evaluate clinical and economic burden associated with RTI-induced asthma exacerbations, and to identify risk factors associated with these exacerbations in adults with asthma.

Method

Study design and population

In this retrospective case-control study, cases were defined as adults with asthma who had at least one asthma exacerbation induced by RTIs as documented in physician notes during the period of January 2014 to December 2016. When more than one RTI-induced asthma exacerbation was identified in this time frame for the same patient, the most recent exacerbation was selected as the index case. All time-dependent variables were obtained from the year prior to the index asthma exacerbation (e.g., for index cases identified in 2014, 2013 data were used). Controls were defined as adults with asthma who did not experience any RTI-induced asthma exacerbation during the pre-specified study period (2013–2016).

Medical records and pharmacy data of patients attending King Abdullah University Hospital (KAUH), Northern Jordan, during the years of 2013–2016 were used to identify eligible patients and all relevant data. The computerized medical records at KAUH were searched by a specialized information technology personnel to identify all patients with asthma diagnosis, as detected in their medical records, and aged 40 years and older. Medical records for all

identified patients were then reviewed manually by the research team to confirm asthma diagnosis and to evaluate for study eligibility. Patients were excluded if they had any of the following conditions: other respiratory problems such as lung bronchiectasis and cystic fibrosis, psychiatric disorders, end stage organ damage, autoimmune diseases, anatomical heart disorders, cancer, Alzheimer's disease, or respiratory failure preceding the occurrence of the index RTI induced asthma exacerbation. Control patients were excluded if they died before the end of the study period. Accordingly, all included patients had the full chance of having RTI-induced asthma exacerbation.

Among the eligible controls, an exact number of four times the cases were randomly selected [24]. Patient flow through the selection criteria is documented in Figure 1.

This research was approved by the Institutional Review Board (IRB) Committee at KAUH (Ref number: 7/101/2016).

Study outcomes

RTI-induced asthma exacerbations

Inpatient asthma hospitalizations were first identified with ICD10 codes related to RTIs and asthma exacerbations (J00–J22 and J40–J47). Medical records were then reviewed to confirm the presence of RTI-induced asthma exacerbations. RTI-induced asthma exacerbations that were treated in the outpatient setting (outpatient clinic or emergency department) were

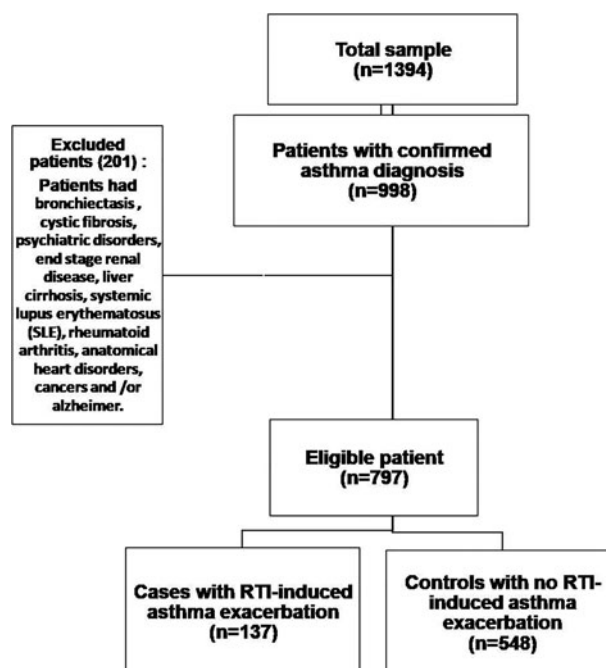


Figure 1. Sample selection flowchart.

identified by reviewing patient medical records for all eligible patients.

Complications of RTI-induced asthma exacerbations

Complications of RTI-induced asthma exacerbations including death, respiratory failure, intensive care unit admission, and mechanical ventilation were identified using patient medical records.

Length of hospital stay for RTI-induced hospitalizations

Length of hospital stay for RTI-induced hospitalizations was calculated (in days) as the time from the admission date to the discharge date.

Inpatient and outpatient charges

The billing system at KAUH was used to extract hospitalization charges in total and by service components. For each inpatient admission, charge per day was calculated by dividing total charge by the length of hospital stay in days. Charges of RTI-induced asthma exacerbations treated in the outpatient setting were also extracted.

Covariates

Medical records were used to capture patient information, including demographics (age, gender, weight, and height), co-morbidities, smoking status, and asthma maintenance treatments. All chronic co-morbid conditions were extracted, including COPD, cardiovascular conditions (HF, ischemic heart disease (IHD), hypertension, and arrhythmia), and others. Asthma maintenance treatments included inhaled corticosteroids (ICSs), long-acting beta-adrenoreceptor agonists (LABAs), and long acting anti-cholinergic agents, and were categorized as none, ICS + LABA combinations, and others (long acting anti-cholinergic, ICS, or LABA monotherapies).

Forced expiratory volume in one second (FEV1)% was used to categorize the severity of lung function impairment as normal ($FEV1 \geq 80\%$), mild to moderately severe ($FEV1$ 50–79%) and severe to very severe ($FEV1 < 50\%$) [25]. An indicator of asthma severity/control was categorized as the following: Severe asthma if $FEV1 < 50\%$ or if the patient had one or more asthma exacerbation in the year before the index case and the FEV1 value is missing, and mild-moderate asthma if the $FEV1 \geq 50\%$ or if the patient had no asthma exacerbations in the year before the index case and the FEV1 value is missing.

Secondary analysis

Factors associated with receiving asthma maintenance treatments (ICS, LABA, and/or long acting anti-cholinergic) versus not receiving any of the maintenance treatments were evaluated, regardless of the initiation time of these medications.

Statistical analysis

Simple descriptive statistics, such as percentages and arithmetic means with standard deviations, were calculated to describe patient characteristics for the total sample and by case-control status. Patient characteristics of the cases and controls were compared using unadjusted bivariable tests (chi-square for categorical variables, t-test for continuous variables). All reported p values were 2-sided with a 0.05 significance level.

Multivariable logistic regression models were performed to identify risk factors associated with RTI-induced asthma exacerbations and complications among cases. Odds ratios (ORs) with 95% confidence intervals were estimated, adjusting for demographics and clinical characteristics. Multivariable linear regression was performed to identify predictors of hospital length of stay (in days; from the admission day to the discharge day). Charges related to RTI-induced asthma exacerbations (in total and per inpatient day) were summarized using descriptive statistics. Total charges were aggregated by services provided and calculated as percentages of the total amount of all admission charges. To evaluate the association between inpatient per day charges and patient characteristics, charge amounts were log-transformed and analyzed using multivariable regression. Factors associated with receiving asthma maintenance treatments were evaluated using multivariable logistic regression.

Variables included in all of the mentioned regression models were selected using backward stepwise process, and included if $p < 0.2$. All reported p values in final models were 2-sided with a 0.05 significance level. All data analyses were conducted using STATA version 14 (StataCorp. 2015. Stata. Statistical Software: Release 14. College Station, TX: StataCorp LP.).

Results

Patient characteristics

In total, 685 adults with asthma were included in this study, including 137 index cases (97 inpatient and 40 outpatient exacerbations) and 548 controls. Table 1 describes characteristics of study sample in total and by case-control status. For the total sample, average

Table 1. Demographics and clinical characteristics in adults with asthma who experienced RTI-induced asthma exacerbations (cases) versus those without RTI-induced asthma exacerbations (controls).

Variable	Total n = 685	Cases n = 137	Controls n = 548	p value ^a
Age, y				
40–64	467 (68.2)	87 (63.5)	380 (69.3)	0.189
≥65	218 (31.8)	50 (36.5)	168 (30.7)	
Gender				
Male	234 (34.2)	42 (30.7)	192 (35.0)	0.334
Female	451 (65.8)	95 (69.3)	356 (65.0)	
BMI				
<25	88 (14.9)	18 (14.3)	70 (15.0)	0.602
25–29.9	198 (33.5)	38 (30.2)	160 (34.3)	
≥30	306 (51.7)	70 (55.6)	236 (50.6)	
Smoking status				
Smoker or ex-smoker	158 (24.7)	42 (30.7)	116 (23.0)	0.066
Non-smoker	483 (75.4)	95 (69.3)	388 (77.0)	
Number of comorbidities	1.5 ± 1.4 ^b	1.9 ± 1.5 ^b	1.4 ± 1.4 ^b	0.003
COPD	37 (5.4)	12 (8.9)	25 (4.6)	0.047
HF	31 (4.5)	13 (9.5)	18 (3.3)	0.002
DM	230 (33.6)	57 (41.9)	173 (31.6)	0.022
Cardiovascular comorbidities ^c	382 (55.9)	87 (64.0)	295 (53.8)	0.033
FEV1 %				
≥80	166 (53.9)	20 (38.5)	146 (57.0)	0.002
50–79	103 (33.4)	18 (34.6)	85 (33.2)	
<50	39 (12.7)	14 (26.9)	25 (9.8)	
Asthma maintenance treatments used				
No maintenance treatments	84 (12.3)	14 (22.6)	53 (9.7)	<0.001
ICS+LABA	558 (81.5)	97 (70.8)	461 (84.1)	
Other maintenance treatments (Anticholinergic, ICS or LABA)	43 (6.3)	9 (6.6)	34 (6.2)	
Statin use	282 (42.2)	64 (47.1)	218 (40.9)	0.194
NSAID use	139 (20.8)	24 (17.7)	115 (21.6)	0.313
Theophylline use	47 (7.2)	17 (12.7)	30 (5.8)	0.006

Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; FEV1: forced expiratory volume in one second; HF: heart failure; ICS: inhaled corticosteroid; LABA: long-acting beta-adrenoreceptor agonist; NSAID: nonsteroidal anti-inflammatory drug; RTI: respiratory tract infection.

Data are presented as n (%) unless otherwise indicated.

^aStatistical significance was set at a 2-sided $p < 0.05$. Bivariable analyses (two-sample t-tests and Wald chi-square tests) were used.

^bData are presented as mean ± standard deviation.

^cCV comorbidities include: ischemic heart disease, hypertension, heart failure, and arrhythmia.

age was 59 ± 12.5 years old, 65.8% were females and 51.7% were obese. Cases had significantly greater number of comorbidities compared to controls (1.9 ± 1.5 versus 1.4 ± 1.4 , p values = 0.003). Specifically, compared to controls, cases had higher prevalence of the following comorbidities: COPD (8.9% versus 4.6%, p values = 0.047), DM (41.9% versus 31.6%, p values = 0.022) and HF (9.5% versus 3.3%, p values = 0.002). The number of patients with severe lung function impairment were significantly higher in cases compared to controls (26.9% versus 9.8%, p values = 0.002). Interestingly, compared to 9.7% in controls, 22.6% of cases were not receiving any asthma maintenance treatment. Finally, 73% of cases were lower RTIs.

Predictors of RTI-induced asthma exacerbations

Using ICS + LABA was significantly associated with lower odds of RTI-induced asthma exacerbations compared to being untreated with any asthma maintenance treatments (OR = 0.40; 95% CI, 0.21–0.77; p values = 0.006). Each additional comorbid condition

was associated with 23% higher odds of RTI-induced asthma exacerbations, adjusting for other potential confounders (OR = 1.23; 95% CI, 1.03–1.47; p values = 0.024). In addition, having severe asthma (i.e., FEV1 < 50% or one or more asthma exacerbation in the prior year) increased the odds of RTI-induced asthma exacerbations by 5.20 times compared to having mild to moderate asthma (OR = 5.20; 95% CI, 2.85–9.35; p values ≤ 0.001; Table 2).

Complications of RTI-induced asthma exacerbations

Out of 137 cases, around 15% had complications including death, respiratory failure, ICU admission, and/or mechanical ventilation. Although the overall occurrence of complications as a group was not significantly different by age group, all inpatient deaths were among older adults (five inpatient deaths; 10% case fatality risk for older adult cases and 12.2% for older adult inpatient cases). The number of inpatient asthma exacerbations in the previous year was a significant predictor of complications (OR = 1.60; 95%

Table 2. Predictors of RTI-induced asthma exacerbations in adults with asthma.

Variable	Odds ratio	CI (95%)	<i>p</i> value ^a
Age ≥ 65	0.99	(0.57–1.73)	0.983
Male gender	0.64	(0.38–1.07)	0.094
HF	1.88	(0.67–5.28)	0.228
Number of comorbidities	1.23	(1.03–1.47)	0.024
Smoking status	1.60	(0.92–2.78)	0.095
Indicator of severe asthma ^b	5.20	(2.85–9.35)	<0.001
Asthma maintenance treatments used			
ICS+LABA	0.40	(0.21–0.77)	0.006
Other maintenance treatments (Anticholinergic, ICS, or LABA)	0.67	(0.22–2.02)	0.473

Abbreviations: CI: confidence interval; HF: heart failure; ICS: inhaled corticosteroid; LABA: long-acting beta-adrenoreceptor agonist; RTI: respiratory tract infection.

Odds ratios were estimated using multivariable logistic regression. Variables included in the model were selected using backward stepwise process with *p* values < 0.2. In addition, age was added to the model because of its clinical importance.

^aStatistical significance was set at a 2-sided *p* < 0.05.

^bHaving FEV1% <50 or if the patient had one or more asthma exacerbation in the year before the index case.

CI, 1.02–2.5; *p* values = 0.043). In addition, receiving ICS + LABA maintenance treatment was associated with lower odds of complications (OR = 0.23; 95% CI, 0.07–0.69; *p* values = 0.009).

Among the 97 inpatients with RTI-induced asthma exacerbations, the presence of HF and having one more inpatient asthma exacerbation in the year before were associated with increased hospital stay by 3.91 and 0.83 days, respectively (Table 3).

Charges related to RTI-induced hospital admissions and outpatient exacerbations

A total of 140 RTI-induced hospital admissions and 68 outpatient exacerbations were identified during the study period. The average of total admission charges was 1,042.9 JD (\$1471.0) [median = 668.0 JD, interquartile range (IQR) = 438.0–1126.0 JD] with 6.4 ± 4.8 days average length of stay per admission. Average charge per inpatient day was 160.0 JD (\$225.7) [median = 132.0 JD, IQR = 109.0–168.0]. The average of total visit charges was 81.1 JD (\$114.4) [median = 62.4 JD, interquartile range (IQR) = 35.2–107.8 JD].

Geometric mean charge per inpatient day was higher for older adults versus younger adults (a ratio of 1.30; 95% CI, 1.12–1.51; *p* values = 0.001). The ratios of the geometric means were also statistically significant for patients with COPD and for obese patients over non-COPD and normal weight patients, respectively and adjusting for other potential confounders (Table 4). In total, laboratory services and drugs contributed to 26.5% and 23.5% of the total of admission charges, respectively (Figure 2). Both older age and COPD were also significant predictors of outpatient exacerbation charges (Table 4). Drugs

contributed to around 70% of the total of outpatient exacerbation charges.

Predictors of receiving asthma maintenance treatments

Having CV co-morbidities including ischemic heart disease, hypertension, heart failure, and arrhythmia was associated with lower odds of receiving maintenance asthma treatments (OR of 0.38; 95% CI, 0.19–0.76; *p* values = 0.006). Being a smoker or ex-smoker was associated with lower likelihood of receiving asthma maintenance treatments (OR was 0.44; 95% CI, 0.22–0.87; *p* values = 0.021), Table 5.

Discussion

This study evaluated predictors of RTI-induced asthma exacerbations and their clinical and economic burden. Our results suggest several key findings regarding RTI-induced asthma exacerbations. First, the use of ICS + LABA controllers, having severe asthma, and the presence of comorbid conditions, especially HF, appeared to affect the clinical burden associated with these exacerbations. Second, RTI-induced asthma exacerbations were associated with considerable economic burden. Older age, obesity, and COPD comorbidity were the major predictors of inpatient economic burden associated with these exacerbations. Laboratory services and drugs contributed to around half of inpatient total charges.

Asthma maintenance treatment (ICS + LABA) was associated with decreased likelihood of RTI-induced asthma exacerbations and serious complications, compared to not using any maintenance treatment. On the other hand, no superior effect was shown with using any of the ICS, LABA, or long acting

Table 3. Predictors of complications/length of hospital stay in RTI-induced asthma exacerbations.

Complications	Odds ratio	(CI) 95%	<i>p</i> value ^a
Age ≥ 65	1.60	(0.57–4.60)	0.354
HF	1.90	(0.46–8.30)	0.360
Number of inpatient exacerbations in the year before Asthma maintenance treatments used	1.60	(1.02–2.50)	0.043
ICS+LABA	0.23	(0.07–0.69)	0.009
Other maintenance treatments (Anticholinergic, ICS, or LABA)	0.31	(0.03–2.90)	0.309
Length of hospital stay	Coefficient	(CI) 95%	<i>p</i> value ^a
Age ≥ 65	1.30	(−0.53–3.07)	0.156
HF	3.91	(1.26–6.70)	0.005
Number of inpatient exacerbations in the year before	0.83	(0.05–1.60)	0.038
Number of comorbidities	0.47	(−0.12–1.07)	0.116

Odds ratios were estimated using multivariable logistic regression. Variables were selected by backward stepwise process with $p < 0.2$.

Coefficients were estimated using multivariable linear regression. Variables were selected by backward stepwise process with $p < 0.2$.

FEV1% variable was not included in the stepwise model due to high number of missing values. Instead, number of asthma inpatient exacerbations in the prior year was used as an indicator of asthma severity.

Abbreviations: CI: confidence interval; COPD: chronic obstructive pulmonary disease; HF: heart failure; ICS: inhaled corticosteroid; LABA: long-acting beta-adrenoreceptor agonist; RTI: respiratory tract infection.

^aStatistical significance was set at a 2-sided $p < 0.05$.

Table 4. Predictors of charges associated with RTI-induced asthma exacerbations.

Variable	Coefficients	Exp (coefficients)	<i>p</i> value ^a
Inpatient charges per day			
Asthma maintenance treatments used			
ICS+LABA	−0.07	0.93	0.458
Other maintenance treatments (Anticholinergic, ICS or LABA)	−0.01	0.99	0.963
COPD	0.27	1.30	0.030
HF	0.18	1.20	0.168
BMI			
25–29.9	0.10	1.12	0.438
≥30	0.26	1.29	0.038
Age ≥ 65	0.26	1.30	0.001
Outpatient charges			
Age ≥ 65	0.58	1.79	0.030
COPD	0.76	2.14	0.017

Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; HF: heart failure process; RTI: respiratory tract infection.

Multivariable regression on log transformed charges. Variables were selected by backward stepwise.

FEV1% variable was not included in the stepwise process because of between-term co-linearity with HF for this sample.

^aStatistical significance was set at a 2-sided $p < 0.05$.

anticholinergic monotherapies. Consistent with our results, Lee et al. found that using ICS + LABA was significantly associated with a decreased risk of pneumonia-related hospital admissions or emergency room visits among adults with asthma (OR = 0.63) [26]. Prazma et al. found that fewer upper RTI-induced asthma exacerbations were reported by adults with asthma treated with fluticasone propionate plus salmeterol compared to those treated with fluticasone propionate only (12.4% versus 8.3% respectively, $p = 0.006$) [27]. LABA and ICS have been suggested to act synergistically to prevent and mitigate the damage associated with the inflammatory process in asthma; this effect is primarily through protection against the disruption of epithelial integrity and reduction in ciliary beat function induced by RTIs [28–32].

Asthma severity, as indicated by lower FEV1 scores and previous exacerbations, was associated with the

occurrence of RTI-induced exacerbations as well as complications and prolonged hospital stays. Asthma severity was consistently shown to be associated with asthma exacerbations in previous literature [33,34]. Among all asthma exacerbations, RTIs were shown to account for up to 80% of asthma exacerbations [17,18]. Reddel et al. suggested that, even in the presence of controlled asthma, adults with asthma are still vulnerable to asthma exacerbations in association with RTIs [35]. In comparison, findings of the current study emphasize the importance of asthma control in preventing RTI-induced exacerbations. Accordingly, patients with severe or uncontrolled asthma are at high risk for RTI-induced asthma exacerbations and should be targeted in terms of protective strategies as well as asthma progression amelioration strategies.

Beside asthma control and severity, the presence of comorbidities was associated with higher susceptibility

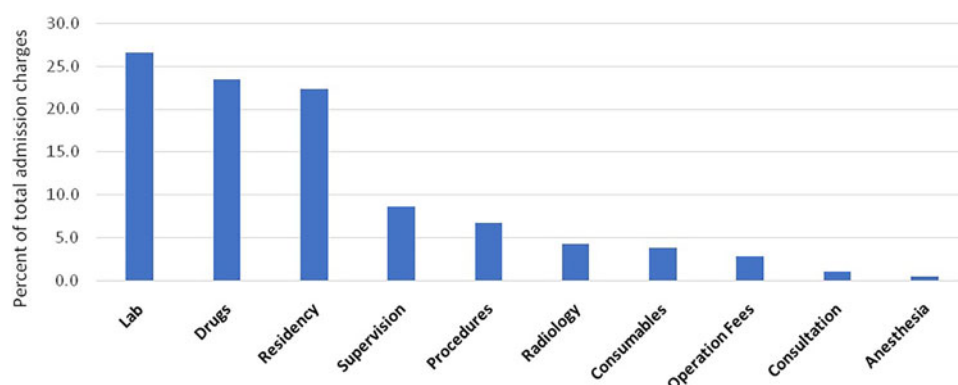


Figure 2. Contribution of inpatient services to the total of admission charges. Charges were aggregated by inpatient services for all admissions and then calculated as percentages of the total of admission charges.

Table 5. Potential factors associated with receiving asthma maintenance treatments (ICS + LABA, anticholinergic, ICS, or LABA).

Variable	Odds Ratio	(CI) 95%	<i>p</i> value ^a
Age ≥ 65	0.91	(0.47–1.77)	0.786
Male gender	1.94	(0.94–4.00)	0.074
Smoker or ex-smoker	0.44	(0.22–0.87)	0.021
Cardiovascular comorbidities ^b	0.38	(0.19–0.76)	0.006
Indicator of severe asthma ^c	0.98	(0.46–2.12)	0.975
COPD	1.12	(0.33–3.79)	0.860

Abbreviations: COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume per second; HF: heart failure; ICS: inhaled corticosteroid; LABA: long-acting beta-adrenoreceptor agonist.

^aStatistical significance was set at a 2-sided $p < 0.05$; Multivariable logistic regression. In addition to variables selected by backward stepwise process, asthma severity, age, and COPD were included.

^bCV comorbidities include: Ischemic heart disease, hypertension, heart failure, and arrhythmia.

^cHaving FEV1% <50 or if the patient had one or more asthma exacerbation in the year before the index case.

to RTI-induced asthma exacerbations, and resultant severe complications in adults with asthma. In agreement with our findings, Perez et al. found that adults with asthma with three or more comorbid conditions were significantly prone to uncontrolled asthma ($p = 0.01$) [36]. Furthermore, a study showed that the risk of asthma in-hospital mortality was significantly associated with patient comorbidity [37]. Disease management education and ongoing follow-up could be helpful in decreasing the clinical burden in patients with multiple comorbidities.

Even though older adults and COPD patients did not exhibit higher frequency of RTI-induced asthma exacerbations in this study, they did demonstrate higher economic burden associated with these exacerbations compared to younger patients and non-COPD patients, respectively. In fact, expenditures were higher in both inpatient and outpatient exacerbations. Inpatient expenditures were higher for older adults and COPD patients after adjusting to inpatient days, indicating the need to a more intensive care in these

patients. In prior research, older adults with asthma were consistently shown to have higher asthma related expenditures compared to younger patients [15,38,39]. Similarly, patients with concomitant asthma and COPD incurred increased medical costs compared to patients with asthma alone [40]. Our results suggest that greater attention to preventing RTIs in these patients is warranted and can be valuable in term of cost saving. As per our results, the contribution of drug costs to total expenses was substantial. Accordingly, looking further into the cost effectiveness of treatment strategies applied in RTI-induced exacerbations is highly recommended, especially concerning the heavy use of antibiotics in these exacerbations.

Body mass index (BMI) equal to 30 kg/m² or more was also associated with high inpatient charges in this study. Similarly, Shah et al. found that obesity was a significant predictor of asthma-related costs and total healthcare cost among older adults with asthma adjusting for socio-demographics and comorbidities [41]. In fact, increased body weight was suggested to alter the immune system and to increase inflammation in the body, which in turn can affect asthma severity and response to infections [42,43].

Our study findings further support the previous evidence that undertreatment of asthma is a significant problem that needs further attention [44]. For patients with CV comorbid conditions, the tendency to not receiving asthma maintenance treatments could be explained by intolerance due to the pathophysiologic interaction between asthma medications and CV diseases [45–47]. Intolerance of asthma treatments in patients with CV comorbidities is an issue that needs further evaluation in light of benefits and risks in this population. Smoking status was another factor that was associated with asthma under-treatment in the current study. Consistent with our results, previous research showed that asthma subjects with

persistent symptoms who reported cigarette smoking were at least twice as likely to have undertreated asthma [48]. Patients' perceptions of their overall asthma control could largely be affected by their acceptability of symptoms. Adults with asthma who smoke have been shown to overlook or neglect asthma symptoms, resulting in being undertreated [49].

Limitations

Our study has some limitations, most of them inherent to the retrospective study design. First, patients' information was obtained from medical records and pharmacy data. Accordingly, we were challenged by some missing information, mainly the FEV1 values for a considerable portion of patients. Consequently, potential confounding by asthma severity was our major limitation. However, extensive efforts were taken to capture all available pulmonary function tests and to compensate for missing values with other asthma severity indicators, such as asthma exacerbations in the year before the index exacerbation. Employing the presence of asthma exacerbation(s) over a one year period to determine asthma severity using retrospective data has been validated in previous literature [50,51]. In addition, insufficient information about educational level was found in medical records. Second, misdiagnosis of asthma and COPD is a concern especially in older adults [52]. Therefore, we were only as accurate as the documented physician notes in medical records. Third, receiving treatment in unaffiliated institutions could not be completely ruled out, an issue that may have affected the accuracy with which we measured asthma treatment in this study. In addressing this limitation, we have checked medication received not only using pharmacy prescription data at KAUH, but also by searching patients' medical notes to verify the treatment received as taken in their medical history. Fourth, we were limited by a relatively small number of identified cases, that may have limited statistical power in detecting the effect of age and other factors on complications and hospital stays (as only cases were included in these analyses). Future research to identify cases prospectively may capture potential cases more effectively. Finally, we were not able to evaluate the etiology of these exacerbations or the appropriateness of treatment strategies used in the cases identified in the current study due to its retrospective nature. Accordingly, future prospective research is needed to reliably investigate the etiology and treatment strategies of RTI-induced asthma exacerbations in both

inpatient and outpatient settings. Specifically, research in which adults with asthma are recruited and followed over a reasonable period of time prospectively is needed to effectively capture all subsequent asthma related exacerbations, whether due to RTIs or not. This would be valuable to characterize predictors as well as the relative burden associated with exacerbations due to RTIs, compared to other reasons in patients whose asthma is poorly controlled. In addition to enhancing the completeness of data collected, a prospective design would be employed to apply a true time event history model with a pre-specified time origin to better describe how aging, changes in health status, and changes in asthma controller use dynamically affect the risk of exacerbations.

Conclusion

Overall, findings from this study shed light on which adults with asthma are at higher risk of developing RTI-induced asthma exacerbations and the associated clinical and economic burden. Targeting undertreated patients, and those with obesity and comorbid conditions, is warranted to prevent and mitigate the impact of these exacerbations. Therefore, by identifying these patients, this study sets the stage for future research and efforts to reduce risks and to optimize preventive and treatment strategies efficiently for patients with asthma.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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