

Chronic Rhinitis Is a High-Risk Comorbidity for 30-Day Hospital Readmission of Patients with Asthma and Chronic Obstructive Pulmonary Disease



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What is already known about this topic? Early readmission with a primary diagnosis of asthma and chronic obstructive pulmonary disease (COPD) is a major health care burden. Among clinical factors, different comorbid conditions (eg, diabetes, obesity) significantly influence readmission.

What does this article add to our knowledge? Besides other comorbidities, chronic rhinitis (CR) also is a significant comorbidity for early readmission with asthma or COPD. Despite significant clinical association between these conditions, the influence of this comorbidity in early asthma/COPD-related readmissions has not been previously investigated.

How does this study impact current management guidelines? Asthma or COPD patients with allergic rhinitis or nonallergic rhinitis as a comorbidity should be properly diagnosed and treated for the appropriate CR subtype in the outpatient setting in an effort to reduce early readmissions and health care burden.

BACKGROUND: Early hospital readmissions for asthma and chronic obstructive pulmonary disease (COPD), measured as hospital readmission within 30 days from the last discharge, is a major economic burden to our health care system. The association of this measure with comorbid chronic rhinitis (CR) has not been investigated before despite significant clinical association between CR and asthma or COPD.

OBJECTIVE: To investigate the association of CR with the risk of asthma or COPD-related early hospital readmission rates.

METHODS: This retrospective cohort study was performed using the asthma- and COPD-related hospital encounter and patient comorbidity data between June 15, 2012, and July 19, 2017, from a large hospital care system in Cincinnati, Ohio. Patients (any sex, race or socioeconomic status, and of all ages) with a primary discharge diagnosis of asthma (n = 4754 patients, 10,111 encounters) and COPD (n = 2176 patients, 4748

encounters) based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes were included. Relevant comorbidities, including comorbid allergic rhinitis (AR) or nonallergic rhinitis (NAR), in such patients were identified using ICD-10-CM codes. The association between 30-day asthma or COPD-related hospital readmission (1670 such encounters for asthma and 736 for COPD) and comorbid CR in the affected patients were determined using Cox proportional hazards models. Multivariate-adjusted hazard ratios (HRs), adjusted for relevant patient comorbidities, compared 30-day asthma- and COPD-related readmissions of patients with CR with those patients without a CR diagnosis.

RESULTS: Analysis was performed on 4754 patients with asthma and 2176 patients with COPD. The median follow-up period (+interquartile range) for asthma was 980 (+760) days and for COPD was 553 (+827) days. The HRs for 30-day asthma- or COPD-related readmission rates were significantly higher in patients with AR (HR = 4.4 [3.9, 5.0] and 2.4 [1.7, 3.2], respectively) or NAR (HR = 3.7 [2.9, 4.9] and 2.6 [1.8, 3.7], respectively) compared with patients without rhinitis. For asthma, both AR and NAR had higher HRs compared with all other comorbidities analyzed. For COPD, both AR and NAR had HRs to the magnitude as obesity and hypertension.

CONCLUSIONS: Comorbid CR is significantly associated with 30-day asthma- and COPD-related readmissions. These findings are useful for guiding health care professionals to focus on outpatient management of both the upper and lower respiratory tracts to reduce early readmission of patients with asthma and COPD. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:279-85)

Key words: Asthma; COPD; 30-day readmissions; Chronic rhinitis; Chronic sinusitis; Adjusted hazard ratio; Censored regression analysis

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Abbreviations used*AIC- Akaike information criterion**AR- Allergic rhinitis**COPD- Chronic obstructive pulmonary disease**CR- Chronic rhinitis**CS- Chronic sinusitis**EHR- Electronic health records**HR- Hazard ratio**ICD-10-CM- International Classification of Diseases, Tenth Revision, Clinical Modification**NAR- Nonallergic rhinitis**NP- Nasal polyps**UCH- University of Cincinnati Hospitals (Medical Center)*

Unplanned hospital readmissions are a major health care burden accounting for as much as approximately 58% of total costs in Medicare insured populations (65+ years).¹ Nearly 20% of all Medicare discharges are readmitted within 30 days.² Twelve percent of these discharges are potentially avoidable with better outpatient management of the primary and comorbid conditions that could save billions of dollars in Medicare expenditures.² Among all discharge diagnoses, asthma and chronic obstructive pulmonary disease (COPD) are a major cause of unplanned hospital readmissions.^{3,4} The nationwide 30-day readmission rate for patients with asthma has been between 14% and 39%.^{5,6} As the asthma prevalence continues to rise,⁷ asthma-related readmissions become a significant economic concern for health care cost-reduction strategies. Unplanned early hospital readmissions can quickly and significantly overwhelm health care resource utilization while further diminishing the patient's disability and quality of life. One approach to easing the health care burden of 30-day readmission rates is to better control acute exacerbations. Therefore, concerted efforts to understand factors contributing to acute exacerbations resulting in unplanned readmissions are critical.

Asthma and COPD exacerbations and early readmissions are impacted by patient comorbidities, the quality of health care provided, easy access to outpatient follow-up after discharge, and socioeconomic and psychosocial issues.⁸ For any of these categories, development and validation of readmission risk-prediction models can identify which factors trigger early readmissions that can have practical implications for prioritization of transitional care interventions for preventing early readmissions.⁹ In this study, a risk-prediction model was developed focusing on which comorbidities affected 30-day readmission rates for asthma and COPD. For asthma and COPD, examples of specific comorbidities that are modifiable risk factors previously targeted for prevention of acute exacerbations include tobacco use, diabetes mellitus, infections, and obesity.^{10,11} One additional important comorbidity that is frequently overlooked as being trivial by clinicians is allergic rhinitis (AR) and/or nonallergic rhinitis (NAR).¹² Although the knowledge on exact pathogenesis of asthma continues to evolve, previous studies have described significant associations between asthma and chronic rhinitis (CR).¹³⁻¹⁵ Asthma, COPD, and CR frequently have very similar triggers for exacerbation, inflammatory cell profiles, and biomarkers.^{16,17} However, CR as a comorbid predictor of unplanned early asthma- and COPD-related hospital readmission remains poorly defined and therefore warrants further investigation given their close interaction. This study investigated

if comorbid CR (ie, AR or NAR) is significantly associated with 30-day asthma- and COPD-related readmissions using standard methodologies for a risk-prediction model.

METHODS**Study cohort**

This retrospective cohort study was performed by chart review and analysis of hospital encounter records for patients discharged from University of Cincinnati Hospitals (UCH) with the diagnosis of asthma or COPD between June 15, 2012, and July 19, 2017.

Demographic data

Hospital encounter data were extracted from the hospital practice and deidentified by an experienced reviewer at UCH. For each patient, information on hospital encounter(s), demographics, pre-existing comorbidities (eg, CR [AR or NAR], cardiac arrhythmia, diabetes mellitus, hypertension, obesity, and tobacco use), relevant clinical parameters at admission, and medications was obtained. Patients who were alive until the end of the study period were only included in the estimation of hazard ratios (HRs) for 30-day asthma- and COPD-related readmission. Measures of disease severity, such as forced expiratory volume in the first second, were not available.

Inclusion criteria and determination of comorbidities

Patients of all ages were included in the study cohort if they had a primary discharge diagnosis at each hospital encounter for asthma or COPD (based on International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] diagnosis codes in the electronic health records [EHR]) first recorded in their EHR between the start and end dates and were alive by the end date. Previously or currently treated chronic medical conditions or comorbidities (recognized by the ICD-10-CM codes) were used as determinants for the 30-day readmission model. The prevalence of these determinants in the early readmitted patients was compared with those never readmitted within the study period.

Exclusion criteria

Data from patients who left against medical advice but had a primary diagnosis of asthma or COPD were not included.

Outcome

The outcome for the study analysis was 30-day asthma- and COPD-related hospital readmission and defined as any unplanned consecutive admission within 30 days after being discharged alive from a hospital stay where asthma or COPD was a principal diagnosis during the study period. The index admission was defined as the first occurrence of the patient's hospital encounter for asthma or COPD within the study period. For the regression analysis, readmission within 30 days was classified as an "event" and no readmissions as "censored."

Statistical analyses

Univariate analysis. Relations between the outcome and patient comorbidities or demographics were determined using exploratory model analysis. Results on demographic characteristics between comparison groups, that is, patients readmitted ≤ 30 days versus not readmitted, were determined by analysis of variance for continuous variables and χ^2 tests of association for categorical variables. The latter included age groups, sex, race, and percentage of patients with AR/NAR, cardiac arrhythmia, diabetes mellitus, hypertension, obesity, and tobacco use between the comparison groups. These analyses determined the likely explanatory variables

TABLE I. Demographic and descriptive characteristics of patients with asthma readmitted (≤ 30 d) vs not readmitted (total $n = 4754$)

Variable	Comparison groups (n, %)	
	Not readmitted (n = 3897, 82%)	Readmitted (≤ 30 d) (n = 857, 18%)
Sex		
Female	2453 (82.3%)	529 (17.7%)
Male	1457 (81.6%)	329 (18.4%)
	χ^2 statistic = 0.35; $P = .6$	
Race*		
Black	1663 (80.1%)	413 (19.9%)
White	2063 (83.5%)	408 (16.5%)
Others	184 (83.3%)	37 (16.7%)
	χ^2 statistic = 9.0; $P = .01$	
Age (mean $\pm$ SD, y)	49 (± 17.8)	53 (± 16.4)
	$P < .0001$	
Length of stay (mean, d)	0.67	0.66 (index) 1.1 (readmission ≤ 30 d) 0.84 (readmission > 30 d)

SD, standard deviation.

*Statistically significant differences.

for inclusion in the multivariate models. All variables with P values $\leq .15$ in the exploratory analysis were regarded as possible covariates and were included in the multivariate analysis.

Multivariate modeling approach for multiple hospitalization analysis and 30-day readmission model for asthma.

The analytical dataset for regression analysis was limited to 1 observation per patient in patients with multiple admissions to avoid biased estimates of standard errors in the regression model. A time to readmission analysis using Cox proportional hazards regression analysis for single- and multiple-event time data was used in this study to model time to readmission events. This permitted the investigation of differences in 30-day asthma- and COPD-related readmission between patients with and without CR while adjusting for other influential covariates and also allowing for delayed entry and time censoring.

Analysis was adjusted for previously or currently treated other comorbidities and number ("counts") of previous readmissions. Univariate and multivariate adjusted HRs between comparison groups were determined. Multivariate analysis was started with a saturated model and analysis was run through a backward stepwise model building approach. A final model was created with statistically significant effects of explanatory variables on readmission interval. In addition, the best subset selection method was performed to confirm the stepwise backward selection method.

Addressing multicollinearity in multivariate analyses.

A test for collinearity among predictor variables was performed using the χ^2 test for association. Comorbidities and patient characteristics significantly associated with AR were removed from the multivariate model and analysis was rerun to derive the final model.

TABLE II. Demographic and descriptive characteristics of patients with COPD readmitted vs not readmitted ($N = 2176$)

Variable	Comparison groups (n, %)	
	Not readmitted (n = 1771, 81.4%)	Readmitted (≤ 30 d) (n = 405, 18.6%)
Sex		
Female (57%)	1006 (81.5%)	229 (18.5%)
Male (43%)	765 (81.3%)	176 (18.7%)
	χ^2 statistic = 0.01; $P = .92$	
Race*		
Black	528 (78.0%)	149 (22.0%)
White	1207 (83.3%)	242 (16.7%)
Others	36 (72%)	14 (28%)
	χ^2 statistic = 12.5; $P = .002$	
Age (mean $\pm$ CL), y	64.2 (63.6, 64.8)	63.8 (62.7, 64.9)
	$P = .60$	
Length of stay (mean, d)	2.2	2.0
	F value = 1.2; $P = .27$	

Total number of unique patients with COPD not readmitted and readmitted within 30 d = 2176.

CL, confidence limit; COPD, chronic obstructive pulmonary disease.

*Statistically significant differences.

Cumulative hazard and cumulative incidence function plots (an example for asthma and AR only).

Cumulative hazard and incidence of 30-day asthma-related readmissions were determined for patients with or without AR. The final regression analysis result identifying the significant variables associated with 30-day readmission for the proportional hazard model was used to generate predicted cumulative hazard and incidence risk curves, using the options for cumulative hazard and cumulative incidence functions, for any patient not in the study. The corresponding plots visualized the adjusted HR and cumulative probability of 30-day asthma-related readmission given a patient has all of the significant risk factors versus no risk factor or given a patient has all of the risk factors versus a patient having all of the risk factors except AR.

RESULTS

Patient demographics

The demographic characteristics of patients readmitted ≤ 30 days versus those not readmitted for asthma- and COPD-related hospital encounters are shown in Tables I and II. The median amount of time (+interquartile range) contributed by each patient to the study (ie, follow-up time) was 980 (+760) days for patients with asthma and 553 (+827) days for patients with COPD.

Age. The mean age (± 95 confidence limit [CL]) at the start of the study for patients with asthma not readmitted was slightly less than those readmitted ≤ 30 days, that is, 49 (48.5-49.5) versus 53 (52-54) years ($P < .0001$).

Race. Black patients represented 43.5% ($n = 2076$) of the asthmatics in the study population with 19.9% ($n = 413$) being readmitted within 30 days, and whites represented 51.8% ($n = 2471$), 16.5% ($n = 408$) of whom were readmitted within 30

TABLE III. Adjusted hazard ratios (HRs) for 30-d asthma-related readmission (number of patients readmitted ≤ 30 d = 857; number of patients never readmitted = 3897)

Comorbidity	Comparison groups	HR	95% HR CL		P value
Chronic rhinitis					
Allergic	Yes vs no	4.4	3.9	5.0	<.0001
Nonallergic		3.7	2.9	4.9	
Tobacco use	Yes vs no	1.5	1.3	1.6	<.0001
Sex	Female vs male	0.7	0.7	0.8	.0007
Age	Increase per year	1.012	1.009	1.016	.02
Race	Black vs white	1.5	1.3	1.6	<.0001
	Others vs white	0.9	0.7	1.3	.95

CL, confidence limit.

days. This difference in percentage of black versus white asthmatics and COPD patients readmitted within 30 days was statistically significant (asthmatics, 19.9% vs 16.5%, $P = .01$; COPD patients, 22% vs 16.7%, $P = .002$). The average age of black patients with asthma was significantly less than the white asthmatics, both for readmitted and not readmitted cohorts (Table E6, available in this article's Online Repository at www.jaci-inpractice.org). The ages of early readmitted patients, of either race, were significantly higher than the ages of patients not readmitted (age difference in years = 3.7 for blacks, 5.0 for whites; Table E6).

Index and 30-day readmission events

A total of 858 (ie, 18%) of 4768 unique patients with asthma and 405 (ie, 18.6%) of 2176 patients with COPD were readmitted at least once within 30 days. For these patients, 1670 (16.5%) of 10,111 asthma-related hospital encounters and 736 (15.5%) of 4748 COPD-related hospital encounters were readmission encounters within 30 days. Correspondingly, 3897 (38.6%) encounters were index asthma admissions and 1771 (37.6%) were index COPD admission for patients who were not readmitted until the end of the study.

Comorbidities

Specific comorbidities that independently had a high risk for 30-day asthma- and COPD-related readmissions are summarized in Tables E1, E2 and E7 (available in this article's Online Repository at www.jaci-inpractice.org), respectively. AR, NAR, cardiac arrhythmia, diabetes mellitus, hypertension, obesity, tobacco use, and the number of previous readmissions independently determine significant risks for the 30-day asthma- and COPD-related readmissions. Of interest, the average number of asthma-related hospital admissions, within the study duration, for patients with AR versus patients without rhinitis was approximately 5.4 versus 1.4 ($P < .0001$) and for patients with NAR versus patients without rhinitis 5.7 versus 1.4 ($P < .0001$). Similarly, the average number of COPD-related admissions for patients with AR versus patients without rhinitis and patients with NAR versus patients without rhinitis were 2.6 versus 1.5 ($P = .004$) and 3.3 versus 1.5 ($P = .0005$), respectively. Thus, readmission frequencies for either asthma or COPD were significantly higher with CR as a comorbidity compared with patients without rhinitis.

TABLE IV. Adjusted hazard ratios (HRs) for 30-d COPD-related readmission (number of patients readmitted ≤ 30 d = 405; number of patients never readmitted = 1771)

Comorbidity	Comparison groups	HR	95% HR CL		P value
Chronic rhinitis					
Allergic	Yes vs no	2.4	1.7	3.2	<.0001
Nonallergic		2.6	1.8	3.7	
Arrhythmia	Yes vs no	1.4	1.2	1.7	.0003
Hypertension	Yes vs no	2.2	1.8	2.5	<.0001
Obesity	Yes vs no	2.1	1.5	2.4	<.0001
Tobacco	Yes vs no	1.3	1.2	1.5	.0003
Sex	Male vs female	1.2	1.1	1.4	.03
Race	Black vs white	1.7	1.4	2.0	<.0001
	Other vs white	1.7	1.1	2.6	.02

CL, confidence limit.

Multicollinearity with AR or NAR

The prevalence of other comorbidities in patients with AR or NAR is summarized in Table E3 (available in this article's Online Repository at www.jaci-inpractice.org). Within the asthma subset, cardiac arrhythmia, diabetes mellitus, hypertension, obesity, and the number of previous readmissions were highly associated with either AR or NAR. Tobacco use, sex, age, and race were less significantly associated. Within the COPD subset, none of these variables were significantly associated with AR or NAR. Accordingly, the less significantly associated or unassociated variables were included in the final multivariate regression model to determine the adjusted HRs.

Adjusted HR for 30-day asthma- and COPD-related readmissions

The adjusted HRs for 30-day asthma- and COPD-related readmissions are summarized in Tables III and IV, respectively. The significant risk between CR and 30-day asthma- or COPD-related readmission persisted after adjusting for other comorbidities and accounting for multicollinearity. Selection of AR or NAR over other comorbidities significantly associated ($P < .01$) with AR or NAR was decided on the basis of model comparison using lower Akaike information criterion (AIC) (Tables E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org, for asthma and COPD, respectively) as well as the best subset selection method. Tables E4 and E5 in this article's Online Repository at www.jaci-inpractice.org summarize the best subset selection models for risk of 30-day asthma and COPD-related readmission. The number of explanatory variables in a model is indicated in the first column and the variable names on the right. These models are sorted in descending order of their score χ^2 values within each model size. Retaining AR or NAR in the regression models provided a lower AIC or higher global score χ^2 value. In the final model, the adjusted HRs for 30-day readmission with asthma and COPD were significantly higher in patients with AR or NAR versus patients without rhinitis. For both patients with AR and patients with NAR, the adjusted HRs for 30-day asthma-related readmission were 4.4 or 3.7, respectively ($P < .0001$ for AR and NAR) and for COPD-related readmission 2.4 or 2.6, respectively ($P < .0001$ for AR and NAR). A decision tree analysis determined AR as the most

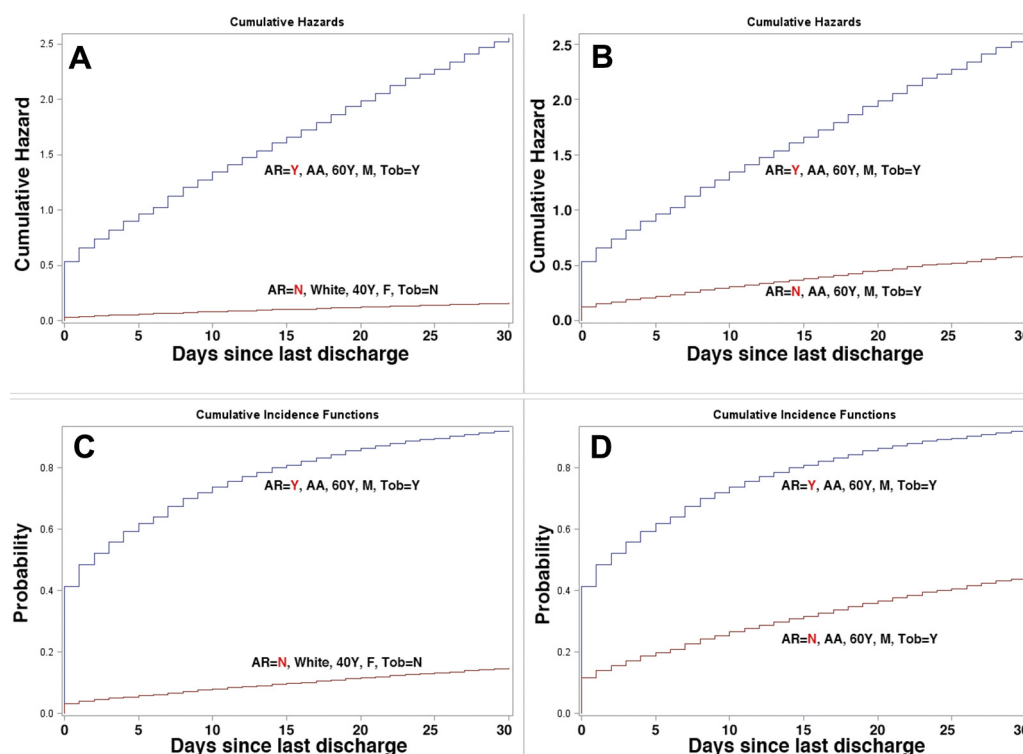


FIGURE 1. A and C, Cumulative hazard and cumulative incidence probability for 30-day asthma-related readmission in patients with all of the significant predictors as comorbidities (blue) versus no comorbidities (red). B and D, Similar plots for patients with all of significant comorbidities (blue) versus patients with all comorbidities except AR (red), thus implying the relative importance of AR as a comorbidity on 30-day asthma-related readmissions. AA, African American (black); AR, allergic rhinitis; Tob, tobacco use.

significant contributor to the probability of asthma-related readmission (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). A sensitivity analysis using logistic regression (ie, via odds ratios rather than HRs) provided similar results (Table E8, available in this article's Online Repository at www.jaci-inpractice.org). In addition, in asthmatics the risk for 30-day readmission was 50% higher for tobacco users (HR = 1.5, $P < .0001$) and 30% lower for females (HR = 0.7, $P = .0007$) compared with nonusers. Finally, aging increased the risk of 30-day asthma-related readmission by approximately 1% every year ($P = .02$) and black patients had a 50% higher risk of readmission compared with whites (HR = 1.5, $P < .0001$) (Table III).

For 30-day COPD-related readmission, significant other covariates besides CR were cardiac arrhythmia (HR = 1.4, $P = .0003$), hypertension (HR = 2.2, $P < .0001$), obesity (HR = 2.1, $P < .0001$), tobacco use (HR = 1.3, $P = .0003$), male sex (HR = 1.2, $P = .03$), and race (black/other vs white: HR = 1.7, $P < .05$) (Table IV). Table E5 in this article's Online Repository at www.jaci-inpractice.org shows the best subset selection models for risk of COPD readmission. AR or NAR along with obesity and hypertension were significant predictors in the 3-variable model.

Cumulative hazard and incidence function for 30-day asthma-related readmissions

Figure 1 displays the cumulative hazard and cumulative incidence for 30-day asthma-related hospital encounters against

the time since last discharge for specific patients compared against each other. Panel A represent the cumulative hazard for a black, 60-year-old male patient with a history of tobacco use and AR compared with a white, 40-year-old female patient nonsmoker without AR. Panel B compares the same male patient as in panel A to a similar patient but without AR. Panels C and D show cumulative incidence for 30-day asthma-related readmission for the same patients as in panels A and B. These plots highlight the significance of AR as a comorbidity in 30-day asthma-related readmissions. In panels B and D, it may be noted that just AR as a comorbidity significantly increases the cumulative hazard and probability of 30-day readmission compared with patients not having AR despite having similar other significant comorbidity predictors for 30-day readmission.

DISCUSSION

This study highlights 2 important aspects of present-day effective health care strategies specifically applicable to management of chronic obstructive airways diseases. First, the analytical techniques used in this study determine the risk of rehospitalization in patients with asthma and COPD attributable to relevant comorbidities. Cox's semiparametric model explains the effect of various comorbidities including CR on the hazard rates for 30-day asthma- and COPD-related readmission and thus validates hospital readmission risk prediction tools from other studies^{18,19} but it adds CR as a significant comorbidity not investigated in those studies. Such a predictive model offers clinically applicable stratification of readmission risk and provides

pre-emptive information during the index hospitalization to prompt a transitional care intervention (eg, expert management of CR) during discharge planning.

Secondly, there is enormous interest in using readmission rates, attributable to chronic obstructive airways diseases, as a health care quality metric. Preventing hospital readmissions is a vital intervention for reduction in health care expenditures. Based on such strategies, the current health policies emphasize shifting the balance of care for long-term conditions from secondary to primary care. The major goal of this policy shift is reduction in hospital admission rates for “ambulatory care sensitive” conditions, such as COPD. In 2012, the Centers for Medicare and Medicaid Services launched the Hospital Readmissions Reduction Program to reduce the risk of hospital readmissions for acute myocardial infarction, pneumonia, and heart failure. In 2013, the program was expanded to include rehospitalizations for COPD exacerbations. To accomplish these goals, it is necessary for primary care physicians to recognize and treat comorbidities that have a significant impact on asthma- and COPD-related readmissions. Pharmacotherapeutic studies have shown that the treatment of CR can improve asthma.¹⁶ Thus, identification of CR in patients with asthma or COPD is important because of its role in highlighting transitional care interventions that may decrease asthma- and COPD-related 30-day readmissions.

The significant association of CR in asthma- or COPD-related early readmission, as determined in this study, can be validated on data from other care providers in different geographical regions. Our study investigated whether CR is associated with a significantly increased risk of 30-day asthma- and COPD-related readmission after adjustment for applicable covariates such as age, cardiac arrhythmia, diabetes mellitus, hypertension, obesity, tobacco use, and the amount of time each study subject contributes to the study period. Adjusted HR from the Cox model indicates that patients with CR experience more than twice the number of 30-day asthma- or COPD-related readmissions than subjects without rhinitis. The model adjusted for the fixed-value predictors such as race and sex, and time-varying predictors (ie, age, the length of stay, and a count of prior readmissions). Previous studies have determined a high prevalence of asthma and COPD in patients with CR.²⁰⁻²⁵ Other studies have also determined significant correlation of high nasal symptom scores, representative of CR, with high sputum production²⁶ that is typically observed during acute exacerbations in COPD.²⁷ Consequently, frequent severe exacerbations impose frequent early readmissions.²⁸ These mechanisms substantiate our study results that CR in patients with asthma or COPD increases the risk for early readmission.

CR can be associated with other comorbidities including chronic sinusitis (CS), nasal polyps (NP), and blood eosinophilia.^{29,30} This association may be relevant in causing acute exacerbations of asthma that need hospitalization.³¹ Additional analyses were performed on the aggregated data available at the TriNetX cloud-based platform for all the patients on network ($n = 1,016,960$) at the UCH. This analysis determined the additional risk of acute exacerbations of asthma/COPD with and without CS (including NP using the ICD-10-CM code J32) in patients with comorbid CR (Table E9, available in this article's Online Repository at www.jaci-inpractice.org). Analysis shows that the risk ratio of acute exacerbation in CR with CS (including NP) is 0.18, but it is 0.13 in CR without CS. The relative risk of an acute exacerbation of asthma/COPD in the presence of CS as an additional comorbidity with CR is 1.39 and the attributable

risk percent is 28%. Thus, it implies that there is a 1.4-fold greater probability of acute exacerbation of asthma/COPD in CR with CS (including NP) than without CS. In addition, approximately 28% occurrences of acute asthma/COPD exacerbations (in the specified time) may be preventable by treating CS (including NP) in patients with CR. Additional analysis on patients within this network concludes that peripheral eosinophilia in patients with CR increases the risk of acute exacerbations 2.56-fold. Thus, CR with peripheral eosinophilia is more significantly associated with acute asthma/COPD exacerbations than CR without peripheral eosinophilia. Peripheral blood eosinophil count is significantly associated with eosinophilia of the respiratory tract.³² This blood biomarker reflects submucosal eosinophilia of the airways.³³ The eosinophilic COPD patients are more responsive to therapeutic interventions.³⁴ Accordingly, an emphasis on the treatment of comorbid CR with eosinophilia in patients with asthma/COPD with either oral or inhaled corticosteroids is expected to improve lung function and thereby prevent exacerbations, by as much as 61% as determined in our study (Table E10, available in this article's Online Repository at www.jaci-inpractice.org).

Limitations

As this study was conducted using data for only 1 hospital system, it is not generalizable until the prediction model is applied and validated on data from other health care systems in different geographical locations. In addition, the potential for misdiagnosis of comorbidities, or unmatched diagnosis codes, can influence the study results and their interpretation. HRs described in this study characterize model performance at the patient level, not at the hospital level. Quality of care for treating patients was an unmeasured factor that can affect the predictive model at the hospital level. The regression model did not include factors indicative of general health status, disease severity, socioeconomic factors, and psychiatric comorbidity (eg, chronic mental illnesses) that may have an impact on readmission rates. The significant comorbidities, described in this study, may partially explain the readmission risk model. To develop a better model, other explanatory variables such as socioeconomic barriers, access to affordable care, patient health education, patient motivation as a shared responsibility towards better health, medication reconciliation and adherence, early post-discharge follow-up, are factors that may be equally important.

CONCLUSIONS

Both AR and NAR were significantly associated with an increased risk of 30-day asthma- and COPD-related readmission. These findings emphasize the subcellular interactions between the upper and lower airways that need to be better elucidated to improve asthma and COPD outcomes. Longitudinal studies are needed to assess whether the treatment of CR in hospitalized patients with asthma and COPD has a significant impact on 30-day readmission rates. Until then, patients with these comorbidities should be properly diagnosed and treated for the appropriate CR subtype in the outpatient setting in an effort to reduce early hospital readmissions.

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U. Singh conceptualized and designed the study; designed, analyzed, and interpreted the data; drafted the manuscript; and approved the version of the manuscript to be published. V. Wangia-Anderson provided expert interpretation and feedback, revised the manuscript critically for important intellectual content, and approved the version of the manuscript to be published. J. A. Bernstein designed the study, provided expert interpretation and feedback, revised the manuscript critically for important intellectual content, and approved the version of the manuscript to be published. The hospital encounter and patient demographic data were extracted, deidentified, and provided by Pete Baker, PhD, database administrator, data warehouse analyst at the Center for Health Informatics, Department of Biomedical Informatics, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

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ONLINE REPOSITORY**METHODS****Details of the statistical methods for multivariate regression model and determination of adjusted hazard ratio**

The likelihood of 30-day readmission was modeled using the “phreg” procedure (SAS system). Important assumptions for the regression model were independence of readmission intervals between distinct patients and a multiplicative relationship between predictors and the hazard. The regression model is as follows:

$$h(t) = h_0(t) \exp(b_1X_1 + b_2X_2 + \dots + b_pX_p)$$

where $h(t)$ is the expected hazard at time t , and $h_0(t)$ is the baseline hazard and represents the hazard when all the predictors, ($X_1, X_2, \dots, X_p$), that is, comorbidities or patient characteristics, are equal to zero. The expected hazard ($h(t)$), or rate of readmission, is the product of baseline hazard ($h_0(t)$) and the exponential function of a linear combination of the predictors. Cox regression was used to model time to readmission events to investigate differences in 30-day asthma- and chronic obstructive pulmonary disease (COPD)-related readmission between patients with specific comorbidities while adjusting for influential covariates and also allowing for delayed entry and time censoring. The hazard function describes the risk of a readmission within 30 days or being readmission free, conditional on patient survival up to the end of the study. This approach enables inclusion of readmission events and time-varying covariates (eg, length of stay) that change values with each hospitalization. After ordering the admission dates in

chronological order for each subject, follow-up time periods for multiple hospitalization time modeling were calculated from the start of follow-up, and subsequent hospital admission dates. Patients experiencing multiple readmissions contributed fully to the analysis and determined whether asthma or COPD patients with chronic rhinitis (CR) were readmitted within 30 days more often than such patients without CR.

The best subset selection method determined the definite number of best models comprising 1, 2, or 3 variables, and continued up to the single model having all of the explanatory variables. The global score χ^2 statistic was the criterion for determining the best subset. For models having the same number of explanatory variables, the model with higher global score χ^2 statistic was preferred over the other.

Addressing multicollinearity in multivariate analyses

High degree of collinearity of independent variables inflates the standard errors of regression coefficients in multivariate regression analyses. Elimination of multicollinearity determines the truly significant variables. Test for collinearity among predictor variables (ie, allergic rhinitis [AR] vs cardiac arrhythmia, diabetes mellitus, hypertension, obesity, tobacco use, sex, race, and age group) was performed using the χ^2 test for association. Comorbidities and patient characteristics significantly associated with AR were removed from the multivariate model and analysis was rerun to derive the final model. Retention of covariates in the final model was based on lowest Akaike information criterion values of the resultant model as well as the best subset selection by score criterion (Tables E4 and E5).

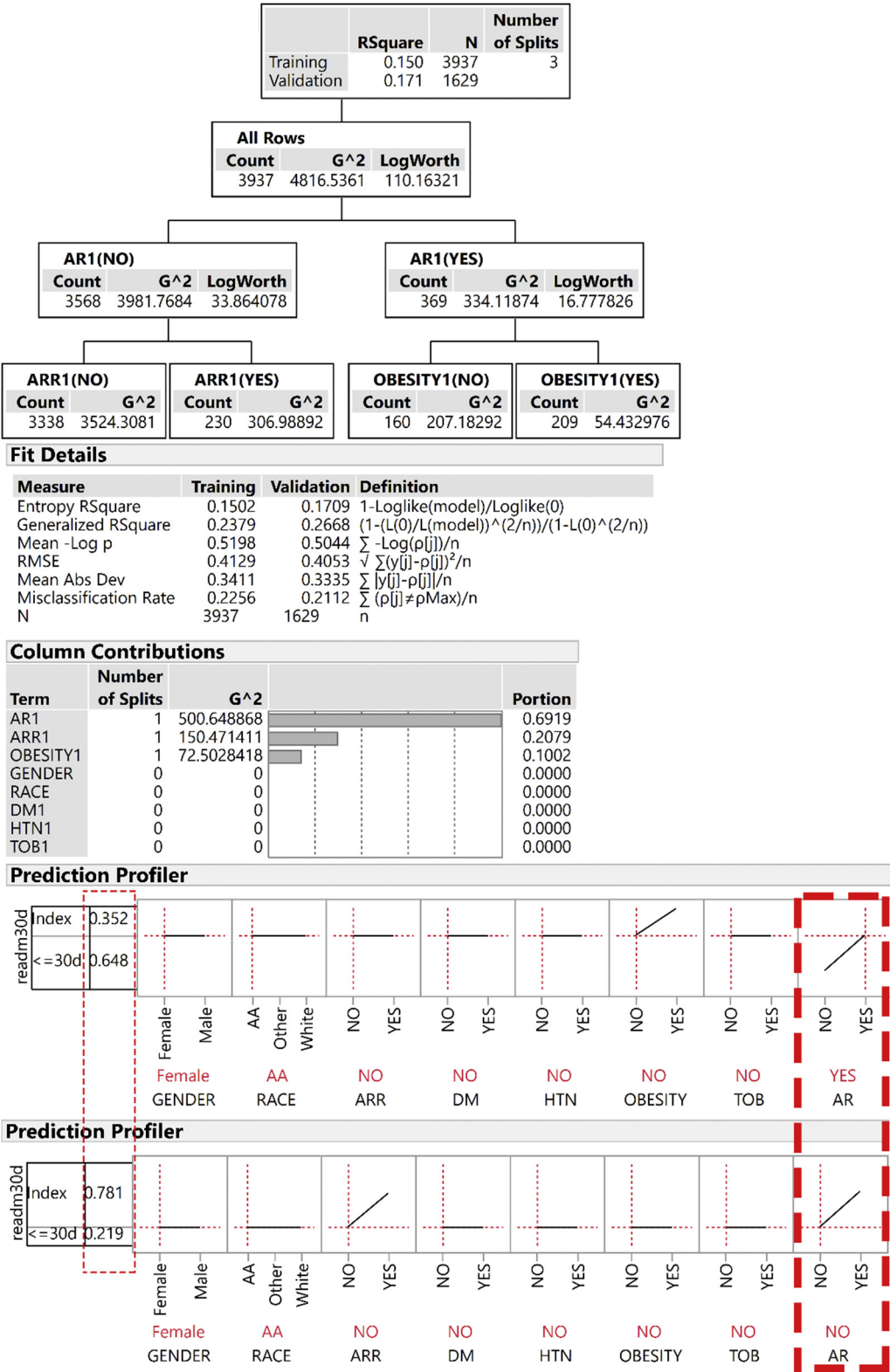


FIGURE E1. Decision tree to determine significant contributors of early (≤ 30 days) asthma-related readmission (comorbidities included in the exploratory analysis included allergic rhinitis, diabetes mellitus, hypertension, cardiac arrhythmia, obesity, tobacco use, and age). Allergic rhinitis is the most significant contribution of the decision tree in the prediction model. The prediction profiler in the lower panel shows that probability of 30-day readmission in a female African American patient without allergic rhinitis (AR) (and without diabetes, hypertension, obesity, or history of tobacco use) as a comorbidity is 21.9% but increases to 64.8% in the same patient with only AR as the only other comorbidity. (Training dataset included data from 3937 patients.) AA, African American (black); AR, allergic rhinitis; ARR, cardiac arrhythmia; DM, diabetes mellitus; HTN, hypertension; RMSE, root-mean-square error; TOB, tobacco use.

TABLE E1. Univariate analysis of comorbidities in 30-d asthma-related readmission

Comorbid condition	Percentage of patients with vs without the comorbidity readmitted ≤ 30 d	Readmission hazard ratio (CI) for 30-d readmission	P value
Allergic rhinitis	50.6% vs 16.9%*	5.1 (4.6, 5.7)	<.0001
Nonallergic rhinitis	56.9% vs 17.1%	4.8 (4.3, 5.5)	<.0001
Cardiac arrhythmia	42.9% vs 16.9%	4.1 (3.7, 4.6)	<.0001
Diabetes mellitus	26.7% vs 17.1%	2.8 (2.6, 3.2)	<.0001
Hypertension	26.5% vs 15.8%	2.6 (2.3, 2.8)	<.0001
Obesity	37.7% vs 16.3%	3.6 (3.2, 4.0)	<.0001
Tobacco use	20.0% vs 17.2%	1.7 (1.6, 1.9)	<.0001

Comparison of prevalence of specific comorbidities in patients with asthma who were readmitted within 30 d (total patients = 4754; no. of patients readmitted with primary discharge diagnosis of asthma ≤ 30 d = 857). Number of previous readmissions also was an independent risk factor for subsequent readmissions ($P < .001$). Every readmission increased the risk of subsequent 30-d readmission by approximately 3%.

AR, Allergic rhinitis; CI, confidence interval.

*A total of 50.6% (ie, 79/156) of all patients with AR as opposed to 16.9% (ie, 779/4612) of all patients without AR were readmitted with asthma in ≤ 30 d.

TABLE E2. Univariate (independent) analysis of comorbidities in 30-d COPD-related readmission

Comorbid condition	percentage of patients with vs without comorbidity	Readmission hazard ratio ($\pm$ CI) for 30-d readmission	P value
Allergic rhinitis	35% vs 18.3%*	2.3 (1.7, 3.2)	.004
Nonallergic rhinitis	35% vs 18.5%	2.5 (1.0, 6.3)	.04
Cardiac arrhythmia	24.0% vs 16.9%	1.8 (1.5, 2.1)	.003
Diabetes mellitus	20.6% vs 17.0%	1.6 (1.4, 1.9)	.06
Hypertension	22.3% vs 13.8%	2.5 (2.2, 3.0)	<.0001
Obesity	31.7% vs 16.2%	2.6 (2.2, 3.1)	<.0001
Tobacco use	19.4% vs 16.6%	1.6 (1.4, 1.8)	.08

Comparison of prevalence and hazard ratios of specific comorbidities in patients with 30-d COPD-related readmissions vs those not readmitted (total no. of patients = 2176; no. of patients readmitted within 30 d = 405). Number of previous readmissions was also an independent risk factor for subsequent COPD-related readmission ($P < .001$). Every readmission increased the risk of subsequent 30-d readmission by approximately 7%.

AR, Allergic rhinitis; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

*Interpretation: 35% (14/40) of all patients with AR as opposed to 18.3% (391/2136) of patients without AR were readmitted with COPD in ≤ 30 d.

TABLE E3. Association of specific comorbidities with AR or NAR

Comorbidity	Patients with asthma		Patients with COPD	
	AR vs Nonrhinitis	NAR vs Nonrhinitis	AR vs Nonrhinitis	NAR vs Nonrhinitis
Cardiac arrhythmia	13% vs 3%; $P < .0001$	16% vs 4%; $P < .0001$	15% vs 14%; $P = .80$	20% vs 14%; $P = .41$
Diabetes mellitus	21% vs 8%; $P < .0001$	26% vs 9%; $P < .0001$	30% vs 24%; $P = .36$	30% vs 24%; $P = .52$
Hypertension	43% vs 20%; $P < .0001$	47% vs 20%; $P < .0001$	55% vs 48%; $P = .38$	55% vs 48%; $P = .53$
Obesity	26% vs 7%; $P < .0001$	32% vs 7%; $P < .0001$	13% vs 11%; $P = .75$	15% vs 11%; $P = .56$
Tobacco use	31% vs 27%; $P = .24$	36% vs 27%; $P = .05$	55% vs 46%; $P = .25$	55% vs 46%; $P = .41$
Sex (% females)	71% vs 62%; $P = .04$	75% vs 62%; $P = .006$	72% vs 57%; $P = .04$	65% vs 56.7%; $P = .46$
Age (y)	46.5 vs 49.9; $P = .02$	49.5 vs 49.7; $P = .9$	65.3 vs 64.1; $P = .57$	65.6 vs 64.1; $P = .62$
Race				
Black	58% vs 43% $P = .02$	54% vs 43% $P = .08$	48% vs 31%; $P = .06$	50% vs 31%; $P = .17$
White	38% vs 52%	41% vs 52%	53% vs 67%;	50% vs 67%;
Others	4% vs 5%	5% vs 5%	0% vs 2%;	0% vs 2%;
Count of readmissions	5.3 vs 1.4; $P < .0001$	5.7 vs 1.4; $P < .0001$	2.6 vs 1.5; $P = .004$	3.3 vs 1.5; $P = .0005$

AR, allergic rhinitis; COPD, chronic obstructive pulmonary disease; NAR, nonallergic rhinitis.

TABLE E4. Regression models for 30-d asthma-related readmission selected by score criterion (best subset selection)

No. of variables	Score χ^2	Variables included in model
1	1016.4	AR
1	686.0	ARR
1	642.0	Obesity
2	1352.2	AR, ARR
2	1241.0	AR, obesity
2	1188.4	AR, HTN
3	1472.5	AR, ARR, obesity
3	1434.9	AR, ARR, HTN
3	1416.2	AR, ARR, DM
4	1525.3	AR, ARR, obesity, TOB
4	1524.6	AR, ARR, obesity, sex
4	1511.1	AR, ARR, HTN, obesity
5	1568.8	AR, ARR, obesity, TOB, sex
5	1566.7	AR, ARR, HTN, obesity, sex
5	1555.1	AR, ARR, HTN, obesity, TOB
6	1602.2	AR, ARR, HTN, obesity, TOB, sex
6	1590.4	AR, ARR, DM, obesity, TOB, sex
6	1586.5	AR, ARR, obesity, TOB, race, sex
7	1614.3	AR, ARR, HTN, obesity, TOB, race, sex
7	1610.1	AR, ARR, HTN, obesity, TOB, age, sex
7	1609.3	AR, ARR, DM, HTN, obesity, TOB, sex
8	1626.9	AR, ARR, HTN, obesity, TOB, race, age, sex
8	1623.0	AR, ARR, DM, obesity, TOB, race, age, sex
8	1621.0	AR, ARR, DM, HTN, obesity, TOB, race, sex
9	1632.6	AR, ARR, DM, HTN, obesity, TOB, race, age, sex

AR, Allergic rhinitis; ARR, cardiac arrhythmia; DM, diabetes mellitus; HTN, hypertension; TOB, tobacco use.

TABLE E5. Regression models for 30-d COPD-related readmission selected by score criterion (best subset selection)

No. of variables	Score χ^2	Variables included in model
1	145.547	Obesity
1	135.546	HTN
1	95.8903	Race
2	244.1929	HTN, obesity
2	224.2153	Obesity, race
2	206.1101	HTN, race
3	304.7024	HTN, obesity, race
3	271.2195	NAR, HTN, obesity
3	269.4539	HTN, obesity, TOB
4	326.9226	ARR, HTN, obesity, race
4	326.5055	NAR, HTN, obesity, race
4	324.0012	HTN, obesity, TOB, race
5	348.9402	NAR, ARR, HTN, obesity, race
5	348.1942	ARR, HTN, obesity, TOB, race
5	343.5452	NAR, HTN, obesity, TOB, race
6	367.8345	NAR, ARR, HTN, obesity, TOB, race
6	356.0618	NAR, ARR, HTN, obesity, race, sex
6	352.7419	ARR, HTN, obesity, TOB, race, sex
7	373.6031	NAR, ARR, HTN, obesity, TOB, race, sex
7	368.2283	NAR, ARR, HTN, obesity, TOB, race, age
7	368.0554	NAR, ARR, DM, HTN, obesity, TOB, race
8	373.9106	NAR, ARR, HTN, obesity, TOB, race, age, sex
8	373.7291	NAR, ARR, DM, HTN, obesity, TOB, race, sex
8	368.4163	NAR, ARR, DM, HTN, obesity, TOB, race, age
9	374.0152	NAR, ARR, DM, HTN, obesity, TOB, race, age, sex

ARR, Cardiac arrhythmia; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; NAR, nonallergic rhinitis; TOB, tobacco use.

TABLE E6. Subgroup analysis of age differences in 30-d asthma-related readmission vs no readmission between races

Comparison groups	Estimates of age difference	Standard error	Adjusted <i>P</i> value
Blacks readmitted ≤ 30 d vs whites readmitted ≤ 30 d	−8.0	1.2	<.0001
Whites readmitted ≤ 30 d vs whites not readmitted	5.0	0.9	<.0001
Blacks readmitted ≤ 30 d vs blacks not readmitted	3.7	0.9	.0014
Blacks readmitted ≤ 30 d vs whites not readmitted	−3.0	0.9	.0172
Blacks not readmitted vs whites readmitted ≤ 30 d	−11.6	0.9	<.0001
Blacks not readmitted vs whites not readmitted	−6.6	0.6	<.0001

TABLE E7. Demographic characteristics and differences in comorbidity rates between the comparison groups

Comorbidity	Comorbidity category	Comparison groups	
		Readmitted ≤ 30 d (n = 857)	Never readmitted (n = 3,897)
Allergic rhinitis	Yes	79 (9%)	77 (2%)
	No	778.00	3820.00
Nonallergic rhinitis	Yes	62 (7%)	47 (1%)
	No	795	3850.00
Cardiac arrhythmia	Yes	85 (10%)	113 (3%)
	No	772	3784
Diabetes mellitus	Yes	117 (14%)	322 (8%)
	No	740	3575
Hypertension	Yes	258 (30%)	717 (18%)
	No	599	3180
Obesity	Yes	142 (17%)	235 (6%)
	No	715	3662
Tobacco use	Yes	260 (30%)	1039 (27%)
	No	597	2858
Other characteristics			
Average age (y)		52.9 (16.3)	49.0 (17.8)
No. of admissions (average)		3.9 (6.0)	1
Average length of stay		0.76 (2.3)	0.6 (12.9)

TABLE E8. Odds ratio estimates for the statistically significant comorbidities in the logistic regression model for asthma-related 30-d readmission

Effect	Estimate	95% CL	
AR (yes vs no)	5.3	3.8	7.3
NAR (yes vs no)	6.4	4.3	9.5
TOB (yes vs no)	1.3	1.06	1.5
Sex (male vs female)	1.09	0.93	1.3
Race (black vs white)	1.3	1.1	1.5
Race (other vs white)	1.2	0.8	1.7
Age	1.017	1.012	1.021

AR, allergic rhinitis; CL, confidence limit; NAR, nonallergic rhinitis; TOB, tobacco use.

TABLE E9. Risk analysis for acute exacerbations of asthma/COPD in chronic rhinitis patients with and without chronic sinusitis and nasal polyps*

Comorbidity	No. of patients with Asthma/COPD		Row total	Risk of exacerbation	Relative risk	Attributable risk percent
	Acute exacerbation	No exacerbation				
CR+(CS+NP)+NP [†]	1380	6090	7470	18%	1.4	28%
CR only	4490	29,240	33,730	13%		
Clinical diagnosis			ICD-10-CM codes used in analysis			
CR			J31.0, J30, J30.9, J30.0, J30.9, J30.2, J31			
CS (includes NP)			J32			
Asthma			J45.32, J45.52, J45.901, J45.51, J45.22, J45.21, J45.31			
COPD			J44.1, J45.41, J44, J45.902, J45.42, J45.990, J44.0			
NP only			J33			

COPD, Chronic obstructive pulmonary disease; *CR*, chronic rhinitis; *CS*, chronic sinusitis; *ICD-10-CM*, International Classification of Diseases, Tenth Revision, Clinical Modification; *NP*, nasal polyposis.

*Only a few patients (approximately 30) met the criteria for CR with NP but without CS.

[†]Using the data available at TriNetX platform for patients in network at University of Cincinnati Medical Center.

TABLE E10. Risk analysis for acute exacerbations of asthma/COPD in chronic rhinitis patients with and without eosinophilia*

Comorbidity	No. of patients with asthma/COPD		Row total	Risk of exacerbation	Relative risk	Attributable risk percent
	Acute exacerbation	No exacerbation				
CR with eosinophilia [†]	1160	2700	3860	0.30	2.56	61%
CR without eosinophilia	4680	35,190	39,870	0.12		
Clinical diagnosis			ICD-10-CM codes used in analyses			
CR			J31.0, J30, J30.9, J30.0, J30.9, J30.2, J31			
Asthma			J45.32, J45.52, J45.901, J45.51, J45.22, J45.21, J45.31			
COPD			J44.1, J45.41, J44, J45.902, J45.42, J45.990, J44.0			

COPD, Chronic obstructive pulmonary disease; *CR*, chronic rhinitis; *ICD-10-CM*, International Classification of Diseases, Tenth Revision, Clinical Modification.

*Using the data available at TriNetX platform for patients in network at University of Cincinnati Medical Center.

[†]Peripheral eosinophilia (blood eosinophil % >6%).