Progression to Uncontrolled Severe Asthma: A Novel Risk Equation

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ABSTRACT

BACKGROUND: Recently published asthma guidelines by the European Respiratory Society and the American Thoracic Society (ERS-ATS) define severe disease based on medication use and control level. These guidelines also emphasize that asthma severity involves certain biomarker phenotypes, one of them being eosinophilic phenotype. The quantification of the influence of eosinophil level toward predicting disease severity can help decision makers manage therapy better earlier.

OBJECTIVE: To develop a risk-scoring algorithm to identify patients at greater risk of developing uncontrolled severe asthma as defined by ERS-ATS guidelines.

METHODS: Data on asthma patients were extracted from the EMRClaims+ database from January 2004 to July 2011. Patients with continuous enrollment 12 months before and after the date of the first encounter with a diagnosis of asthma (index date) with at least 1 blood eosinophil test result in the 12 months after the index date, but before the development of uncontrolled severe asthma or the study end date, were included. Uncontrolled severe asthma was defined as the first date on which all criteria of the ERS-ATS definition were first satisfied in the 12 months after the index date. Age (≥50 years vs. <50 years), race, and sex were measured at index, and the Charlson Comorbidity Index (CCI) score (>0 vs. 0) was measured in the pre-index period. Elevated eosinophil level was defined as a test result with ≥400 cells/μL. The study cohort was randomly split 50-50 into derivation and validation samples. Cox proportional hazards regression was used to develop the risk score for uncontrolled severe asthma using the derivation cohort with independent variables of eosinophil level, age, sex, race, and CCI. A bootstrapping procedure was used to generate 1,000 samples from the derivation cohort. Variables significant in ≥50% of the samples were retained in the final regression model. A risk score was then calculated based on the coefficient estimates of the final model. C-statistic was used to test the model's discrimination power.

RESULTS: The study included 2,405 patients, 147 (6%) of whom developed uncontrolled severe asthma. Higher eosinophil level and CCI score >0 were significantly and independently associated with an increased risk of uncontrolled severe asthma in the derivation cohort (HR=1.90, 95% CI=1.17-3.08 and HR=2.00, 95% CI=1.28-3.13, respectively); findings were similar in the validation cohort. Total risk score was categorized as 0, 2, and 4. All models showed good C-statistics (0.79-0.80), indicating favorable model discrimination. There was a significantly greater number of patients with uncontrolled severe asthma in the risk score segments of 2 and 4 compared with 0 (each $P<0.0001$).

CONCLUSIONS: A risk stratification tool using peripheral eosinophil counts and CCI can be used to predict the development of uncontrolled severe asthma.

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What is already known about this subject

- European Respiratory Society and American Thoracic Society guidelines provide a definition for uncontrolled severe asthma based on medication use and control status.
- Eosinophilic asthma is included as a phenotype of severe and uncontrolled asthma.

What this study adds

- Elevation in peripheral blood eosinophil count is an independent predictor of uncontrolled severe asthma.
- This study adds a severity prediction tool that can be used in population health management by various payers and provider networks to make better recommendations, earlier, in therapy management.

Asthma severity and control are associated with increased cost and health care resource utilization.[1-5] The National Institutes of Health reported several clinical measures of patients with asthma that have been shown to correlate with severity of disease and disease control, including forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV), elevated eosinophils, Immunoglobulin E (IgE), exhaled nitric oxide, and urinary leukotriene levels.[6,7] Studies have consistently shown an association between blood eosinophil elevation and asthma exacerbations, severity, or difficulty in achieving control.[8-10] As this clinical measure has been shown to correlate with asthma control, it follows that predictive models can be developed to help clinicians and payers identify patients at greatest risk for poor health outcomes and higher costs. These models, in turn, would help identify patients in need of further intervention, define medical policy for new treatments, and advance current treatment guidelines.[11]

Currently available risk equations or indices found in the literature address the needs of certain types of asthma patients; e.g., patients in the emergency room (ER), patients with acute bronchial asthma. Rodrigo and Rodrigo (1998) developed an index for early differentiation between patients with poor and good therapeutic response in the ER.[12] Becker et al. (1984) developed the Pulmonary Index (PI) to assess children with acute asthma in the ER.[13] The PI was derived from respiratory rate, wheezing, inspiratory-expiratory ratio, and use of

accessory muscles. Fischl et al. (1981)[14] developed an index to predict relapse and need for hospitalization with acute bronchial asthma. This index used a pulse rate >120 beats per minute, a respiratory rate >30 breaths per minute, a pulsus paradoxus >18 mm Hg, a peak expiratory flow rate <120 liters per minute, moderate to severe dyspnea, accessory-muscle use, and wheezing.

The use of these risk equations is limited to point-of-care settings, and none have considered elevated eosinophils in adults, which our study, along with other studies, has found to be associated with asthma severity and control as well as with greater health care resource use.[15,16] Castro-Rodriquez et al. (2000) developed 2 indices to define risk of asthma in young children with recurrent wheezing, which used eosinophilia in their index.[17] Their indices included frequent wheezing during the first 3 years of life and either 1 major risk factor (parental history of asthma or eczema) or 2 of 3 minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis).

Here, we set out to empirically derive a risk equation to identify asthma patients at greatest risk of developing severe asthma and therefore greater morbidity and costs, using retrospective data. For this purpose, operational definitions were clearly defined for development of the model and to ensure development of a practical tool metric. Recently published 2014 European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines for the evaluation and management of severe asthma represent important guidance for this purpose.[6] Developing a validated risk index that incorporates important and readily available biomarkers such as peripheral blood eosinophils represents an important contribution that may help clinicians better identify patients in routine practice who may benefit from more aggressive intervention.

The objective of this study was to develop a validated risk index to predict the likelihood of developing uncontrolled severe asthma.

Methods

Data Source

The EMRClaims+ database was used for this study. This database includes administrative managed care insurance claims covering approximately 690,000 lives linked to an overlapping health care provider database of electronic medical records (EMR) data, including laboratory values and provider billing files. The database contains more than 20 million electronic records available for access. This integrated database facilitates patient care and research by readily providing access to timely information related to all clinical aspects of patient care. The database contains encounters from 1988 with more than 3.1 million ambulatory care (outpatient and ER) encounters added each year. The database also tracks commercially insured lives through provider-aligned patient panels, managed care membership files, and a master patient index. A unique medical record number serves as a lifetime patient identifier. Standard longitudinal claims data, including pharmacy data (all filled prescriptions), are available for managed care members, providing a comprehensive account of medical care for that population.

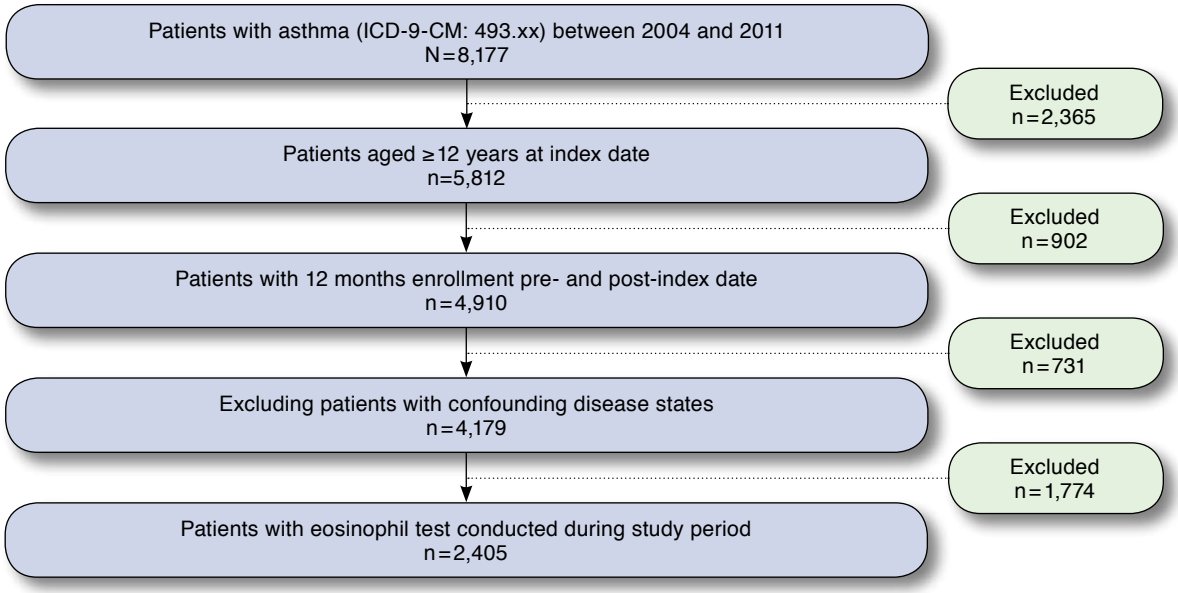
Study Design and Measures

Patients aged ≥12 years were included in the analysis. The date of the first encounter with an asthma diagnosis between January 2004 and July 2011 defined the index asthma date. Patients were required to have continuous enrollment of 12 months before and after the index asthma date. The start date of the pre-index period was defined as the pre-index date. Patients were followed after the index asthma diagnosis up to the date of developing uncontrolled severe asthma, or the end of follow-up. Uncontrolled severe asthma was defined as asthma that remains uncontrolled despite being prescribed ERS/ATS recommended therapy.[6] This definition of uncontrolled severe asthma is a conservative approach, as it does not include individuals who may have severe asthma but who were controlled on their medication regimen. The date of uncontrolled severe asthma was defined as the date at which the following measures were met:

1. Use of high-dose inhaled corticosteroids plus a second controller—long-acting beta-agonist or leukotriene modifier/theophylline, OR systemic corticosteroids for up to or more than 50% of the time (assessment period of 12 months), AND
2. At least 1 of the following (to define uncontrolled asthma):
   a. Frequent severe exacerbations, defined as 2 or more bursts of systemic corticosteroids (>3 days each)
   b. Serious exacerbations, defined as the following:
      - At least 1 hospitalization with a diagnosis of asthma as the primary discharge diagnosis, or
      - an intensive care unit stay (asthma related), or
      - asthma-related mechanical ventilation.
   c. Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted.

Days between index date and date of uncontrolled severe asthma development were measured. Demographics (age, sex, race) were recorded at index. Comorbidities from the Charlson Comorbidity Index (CCI) were identified during the 12-month pre-index period to calculate a composite CCI score.[18] Patients with confounding diseases during the pre-index period such as chronic obstructive pulmonary disease, emphysema, Churg-Strauss syndrome, Wegener's granulomatosis, eosinophilia, pulmonary fibrosis, allergic bronchopulmonary aspergillosis, and lung cancer (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes: 491.xx-492.xx, 494.xx-496.xx, 277.x, 162.x, 446.4, 288.3, 516.31, 515, 518.6) were excluded. Patients were required to have at least 1 blood eosinophil test result before the date of meeting criteria for uncontrolled severe asthma.

FIGURE 1 Study Sample Attrition



ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

The independent variables for risk prediction were selected based on existing literature and clinical advice. Chung et al. (2014) characterize uncontrolled severe asthma as a condition of different biomarker phenotypes,[6] and Szefler et al. (2012) describe biomarkers that should be considered in asthma-related research studies.[7] These biomarkers include clinical measures such as elevated blood eosinophils, sputum eosinophils, exhaled nitric oxide, urinary leukotrienes, and blood IgE levels.[6,7] Previous studies demonstrate an association between eosinophil elevation at ≥400 cells/μL and asthma severity and exacerbations.[8-10,15] This association diminishes at lower eosinophil cut-off levels (≥300 cells/μL, (≥200 cells/μL, ≥140 cells/μL).[8,19] Eosinophil level was defined as a binary variable as ≥400 cells/μL and <400 cells/μL. CCI score (0 and >0) along with age (≥50 years and <50 years) was also defined as a binary variable. Our sample was approximately evenly split at a cut-off age of 50 years (44% ≥ 50 years and 56% < 50 years).

Data Analysis

Initial Candidate Variable Screening. The frequency of factors identified in the study was recorded, and when fewer than 30 cases with a particular factor were identified, the risk factor was removed as a candidate variable from further analysis.

Model Development and Validation. We adopted a split sample technique and Cox proportional hazard (PH) modeling analysis widely used in published literature.[20,21] The total sample of patients was split into 2 cohorts: 50% to a derivation cohort and 50% to a validation cohort.

Fifty percent of the patients from the entire sample were randomly selected to be included in the derivation cohort. Time to development of uncontrolled severe asthma (or study follow-up end date) starting from the index date was the dependent variable in the Cox PH regression analysis. The demographic, comorbidity, and clinical measures described above were the independent variables included. We generated a Cox PH model on the derivation sample using backward elimination to identify the variables that were significantly associated with the risk of asthma-related events ($P < 0.05$).

To stabilize the regression results, we conducted a bootstrapping procedure that included the generation of 1,000 samples from the derivation cohort on which the Cox PH models were run. From this analysis, variables that were significant in at least 50% of bootstrap runs were included in the final derivation model. Therefore, if a variable was entered in the model after the initial derivation but was not significant in at least 500 (50%) of bootstrapped subsamples, this variable was considered for removal. The final model was then run on the derivation sample and C-statistics were computed. C-index is a measure of the probability that a subject from the event group has a higher predicted probability of having an event than a subject from the nonevent group.[22] A C-index value of 0.5 represents no discriminating ability, and a value of 1.0 represents perfect discrimination.[23]

TABLE 1 Demographic and Comorbidity Comparison

	Uncontrolled Severe Asthma, n = 147		Nonsevere Asthma n = 2,258		
	n	%	n	%	*P* Value
Sex					
Female	112	76	1,571	70	0.089
Age groups (years)					<0.001
<50	61	41	1,282	57	
≥50	86	59	976	43	
Race					0.042
White	77	52	999	44	
African American	12	8	334	15	
Other/unknown	58	39	925	41	
CCI score					<0.001
0	75	51	1,534	68	
≥1	72	49	724	32	

CCI = Charlson Comorbidity Index.

Predictive Accuracy, Validation, and Risk Score Development. The variables from the final model developed on the derivation sample were included as independent variables, and a Cox PH regression was estimated using the validation sample. Model discrimination was assessed using the C-index. Hazard ratios (HRs) corresponding to the risk factor coefficients from the derivation sample final model were converted to scores by rounding to the nearest integer. The risk score was collapsed into "low," "medium," and "high" risk of developing uncontrolled severe asthma.

To assess model discrimination, the Cox PH model was also estimated on the overall (derivation + validation) cohort and the C-index was calculated. The risk score was then assigned to each patient in the cohort, based on the presence/absence of variables included in the final risk-scoring tool. Frequency distribution of patients classified according to the new risk scoring was calculated, as well as the proportion of patients who developed uncontrolled severe asthma within each score segment. A final Cox PH model was developed on the entire starting sample using risk score as the independent variable, and the corresponding C-index was calculated.

Results

A total of 2,405 patients were included in our study (Figure 1), of which 147 (6.1%) developed uncontrolled severe asthma. The mean (standard deviation) follow-up time was 352 (59) days with a median of 365 days and a minimum and maximum of 6 and 365 days, respectively. Table 1 compares the demographic characteristics of patients who developed uncontrolled severe asthma versus those who did not.

Model Development

Initial Screening. Factors excluded in this step due to insufficient observations (n < 30) included exhaled nitric oxide, urinary leukotriene levels, exhaled breath, sputum eosinophils, sputum neutrophils, and blood IgE results. These exclusions left the following development stage covariates: eosinophil level, age, race, sex, and CCI for the model development stage.

Model Development. The initial cohort of 2,405 was randomly divided to create a derivation cohort of 1,203 patients and a validation cohort of 1,202 patients. The Cox PH model results from the derivation sample revealed that only 2 variables—elevated eosinophil level and CCI score—were significant independent predictors of uncontrolled severe asthma ($P < 0.05$). Bootstrapping results showed that only elevated eosinophil level and CCI were significant in 500 or more samples. All other variables (age, race, sex) were removed from further modeling. A final model including only elevated eosinophil level and CCI score was run on the derivation sample to obtain the HRs for risk score development. The HRs obtained were rounded to the nearest integer to obtain risk scores for each variable as shown in Table 2. The C-index for this model with the final 2 independent variables was 0.79.

Validation and Risk Score Groups. The model reestimated in the validation cohort showed that regression coefficients from the validation sample were consistent with those from the derivation sample (Table 2). The C-index for model discrimination using the validation sample was 0.80.

The Cox PH model for the entire sample also resulted in coefficients consistent with the derivation and validation models and a C-index of 0.79 (Table 2).

Elevated eosinophils and CCI score were each assigned a risk score of 2. Thus the risk-scoring tool developed was as follows: A score of 0 indicated "low" risk of developing uncontrolled severe asthma; a score of 2 (presence of either elevated eosinophils ≥ 400 cells/μL or CCI score > 0) indicated "moderate" risk of uncontrolled severe asthma; a score of 4 (presence of elevated eosinophils ≥ 400 cells/μL and CCI score > 0) indicated "high" risk of uncontrolled severe asthma. Each patient was assigned a risk score accordingly, depending on the presence/absence of elevated eosinophils and CCI score.

Results of the Cox PH regression with risk score as the independent variable included (a) an HR for a risk score of 2 versus 0: 2.44 (1.71-3.50), and (b) an HR for a risk score of 4 versus 0: 3.13 (1.86-5.28). The C-index for this model was calculated to be 0.79.

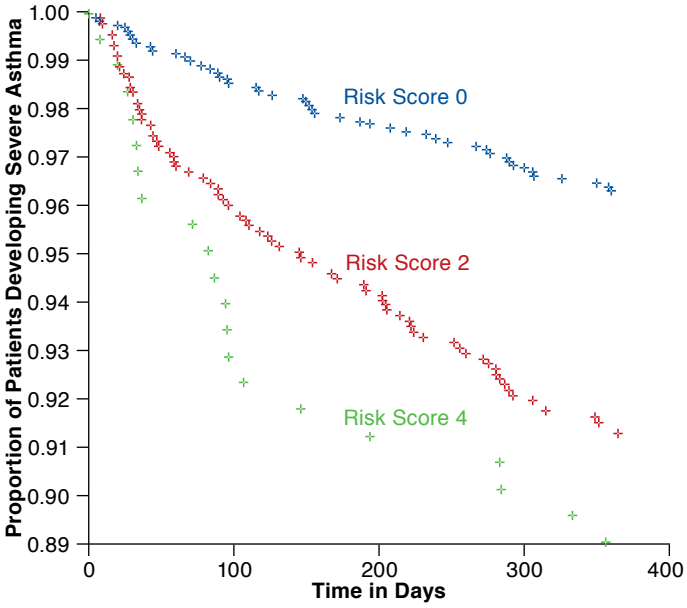
Figure 2 represents the Kaplan-Meier survival curves stratified by risk score. Patients with higher risk scores developed severe asthma at a faster rate.

TABLE 2 Hazard Ratios and Regression Coefficients

	Risk Score Points	Derivation Cohort			Validation Cohort			Entire Data		
		Regression Coefficients	Hazard Ratio (95% CI)	C-Index	Regression Coefficients	Hazard Ratio (95% CI)	C-Index	Regression Coefficients	Hazard Ratio (95% CI)	C-Index (Elevated Eosinophils and CCI Score)
Elevated eosinophils	2	0.64	1.90 (1.17-3.08)	0.79	0.59	1.79 (1.09-2.97)	0.80	0.61	1.84 (1.30-2.61)	0.79
CCI score greater than 0	2	0.69	2.00 (1.28-3.13)		0.62	1.86 (1.16-2.98)		0.66	1.94 (1.40-2.68)	

CCI = Charlson Comorbidity Index; CI = confidence interval.

FIGURE 2 Likelihood of Developing Severe Asthma by Risk Score



Patient classification analysis by risk score showed that 7.6% of patients (n = 183) were at high risk of developing uncontrolled severe asthma. Table 3 shows the cross-tabulation of patients by risk score and those who actually developed uncontrolled severe asthma eventually. There was a significantly greater proportion of patients in the risk score segment for 2 or 4 compared with 0 who developed uncontrolled severe asthma ($P < 0.001$). There was no significant difference between the number of uncontrolled severe asthma patients between risk score 2 and 4 ($P = 0.330$).

Discussion

Results of this study indicate that elevated peripheral eosinophil count and the presence of a general medical comorbidity as measured by the CCI are significantly and independently associated with the risk of uncontrolled severe asthma. Patients with uncontrolled severe asthma are responsible for a large proportion of asthma-related claim dollars,[1-5,24] highlighting the value in developing an easy-to-use prognostic tool to predict these events. A reliable scheme to predict which patients will likely go on to develop uncontrolled severe asthma is warranted, as more aggressive intervention may lead to lower cost and improved health outcomes for this group.

In an effort to quantify the risk of developing uncontrolled severe asthma in the presence of certain readily available measures, we attempted to develop a risk-predicting tool. To our knowledge, this is the first study to develop a risk-factor scoring mechanism for uncontrolled severe asthma that relies on the new ERS/ATS definitions and recommendations. In previous studies, we observed an inverse relationship between medication adherence and CCI score,[25] where persons with higher comorbidity burden have lower levels of adherence. Perhaps the CCI is partially capturing low adherence among sicker asthma patients, and that is why we find that persons with a CCI > 0 are associated with severity and control levels. Our models show consistent and high C-indices, indicating good model discrimination, which means that the model is able to accurately predict/differentiate, to a high degree, those who develop uncontrolled severe asthma versus those who do not.

Dichotomizing the risk score as > 0 and = 0, we found the sensitivity and specificity of our risk equation were 67% and 56%, respectively. The positive predictive value was 9% and the negative predictive value was 96%. Our risk model is applicable in clinical practice to identify patients who are more likely to incur greater resources and require diligent clinical management. As health care providers are increasingly consolidating into accountable care organizations, with lab tests becoming more used, our scoring tool allows payers and providers to evaluate risk based on routinely collected data. Eosinophil count is widely available as part of the complete blood count, a routine and inexpensive test, and CCI score can be calculated using existing patient records or past medical claims.

TABLE 3 Classification of Patients by Risk Score

Risk Score	Asthma Severity		Total
	Uncontrolled Severe	Nonsevere	
0	48 (4%)	1,264 (96%)	1,312
2	79 (9%)	831 (91%)	910
4	20 (11%)	163 (89%)	183

Limitations

This study should be viewed in light of several limitations. Data on certain other phenotypic factors such as IgE, neutrophils, and sputum eosinophils were scarce; therefore, our data cannot offer insights on the relative prognostic value of these potential measures. Regardless, including infrequently used laboratory factors in a risk equation would limit widespread adoption of the tool. Pre-index comorbidities were identified based on ICD-9-CM codes present on medical claims. Disease code-based case finding methods, while not ideal, are widely cited in the literature.

We only studied persons who had an eosinophil test before developing severe asthma. This restriction excluded 42% of potential subjects, and it is possible that those who were retained in our sample might be more likely to have uncontrolled severe asthma, and the relationships we report can only be applied to similar asthma patients. With a larger sample of data, other variables may have been found to be significantly associated with the risk of developing severe asthma. Future research using a larger external validation sample is warranted.

We used retrospective data available in electronic health records, claims data, and laboratory data but did not have access to patient-reported measures of asthma control (e.g., Asthma Control Questionnaire), so we could not examine risk factors for patients with uncontrolled severe asthma that were not also accompanied by use of systemic corticosteroids, hospitalization, or diminished lung function. This limitation could have underestimated the total population of uncontrolled severe asthma. Additionally, this study included comorbidities listed in the CCI only. Other comorbidities, such as allergy, that could affect eosinophil elevation or disease progression were not included.

Conclusions

We have developed and tested a novel risk scale to help identify patients likely to progress to uncontrolled severe asthma using readily available information that may also be evaluated retrospectively using medical claims and standard lab data. Elevated blood eosinophil level at ≥400 cells/μL and CCI score >0 were associated with an increased risk of developing severe disease. Use of this equation should be considered as a guide for therapy management.

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DISCLOSURES

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Study concept and design were contributed primarily by Casciano, Krishnan, Small, and Martin, along with Li and Dotiwala. Dotiwala, Casciano, Small, and Li collected the data, along with Martin and Li and Krishnan. Data interpretation was provided by Martin, Casciano, and Li, with assistance from the other authors. The manuscript was written by Li, Casciano, Dotiwala, and Small, with assistance from the other authors, and revised by Dotiwala, Small, Li, and Martin, with assistance from Krishnan and Casciano.

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