International Variation in Severe Exacerbation Rates in Patients With Severe Asthma

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BACKGROUND: Exacerbation frequency strongly influences treatment choices in patients with severe asthma.

RESEARCH QUESTION: What is the extent of the variability of exacerbation rate across countries and its implications in disease management?

STUDY DESIGN AND METHODS: We retrieved data from the International Severe Asthma Registry, an international observational cohort of patients with a clinical diagnosis of severe asthma. We identified patients aged ≥ 18 years who did not initiate any biologics prior to baseline visit. A severe exacerbation was defined as the use of oral corticosteroids for ≥ 3 days or asthma-related hospitalization/ED visit. A series of negative binomial models were applied to estimate country-specific severe exacerbation rates during 365 days of follow-up, starting from a naive model with country as the only variable to an adjusted model with country as a random-effect term and patient and disease characteristics as independent variables.

RESULTS: The final sample included 7,510 patients from 17 countries (56% from the United States), contributing to 1,939 severe exacerbations (0.27/person-year). There was large between-country variation in observed severe exacerbation rate (minimum, 0.04 [Argentina]; maximum, 0.88 [Saudi Arabia]; interquartile range, 0.13-0.54), which remained substantial after adjusting for patient characteristics and sampling variability (interquartile range, 0.16-0.39).

INTERPRETATION: Individuals with similar patient characteristics but coming from different jurisdictions have varied severe exacerbation risks, even after controlling for patient and disease characteristics. This suggests unknown patient factors or system-level variations at play. Disease management guidelines should recognize such between-country variability. Risk prediction models that are calibrated for each jurisdiction will be needed to optimize treatment strategies.

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KEY WORDS: asthma; country; heterogeneity; prediction; severe exacerbation

Sudden worsening of symptoms referred to as exacerbations or flare-ups is a hallmark of the natural course of asthma.[1] Because exacerbations are a major cause of morbidity and economic burden,[2] reducing their risk is key to contemporary disease management.[1] In particular, exacerbation frequency is considered a major determinant in treatment decision-making for patients with severe asthma.[1] However, frequency of exacerbations and their severity can vary across settings. Such variation can lead to inconsistent treatment escalation or de-escalation strategies.[3] As such, setting-specific influences on exacerbation risk should be taken into consideration in designing disease management strategies. Although variations can be defined at different levels (eg, regions, countries, local health systems), because the locus of decision-making (eg, guideline development, health policymaking) is often at the country level, we focus on between-country variability in this work.

Part of variability in exacerbation rates across countries can be attributable to differences in case mix (ie, salient patient and disease characteristics that are associated with exacerbations [eg, lung function, symptom burden]). Such differences can be potentially accounted for by including patient characteristics in treatment recommendations, typically via using multivariable risk scores. Observed differences in exacerbation rate can also be in part due to the finite sample sizes of the studies documenting exacerbation rates. This is an inevitable consequence of sampling because an observed exacerbation rate is a noisy estimate of the actual rate when the sample size is small, generating spurious variability. Without considering case

ABBREVIATIONS: GINA = Global Initiative for Asthma; IQR = interquartile range; ISAR = International Severe Asthma Registry; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; OCS = oral corticosteroid

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Take-home Points

Study Question: Exacerbation frequency strongly influences treatment choices in patients with severe asthma, but the rate of exacerbations is different across countries. Does such between-country variation in exacerbation rates remain substantial after controlling for patient characteristics and randomness due to finite samples?

Results: We found substantial between-country variation in severe exacerbation rate, even after adjusting for observed patient characteristics and finite sample sizes. As such, differences in observed patient characteristics, including exacerbation history, only partially account for observed heterogeneity.

Interpretation: Two similar patients with same characteristics (including exacerbation history) from two different countries might be at substantially different risk of future exacerbations. Asthma management guidelines should promote multivariable risk prediction, with country-level calibration, to optimize treatment strategies.

mix and sampling variability, a naive estimate of variation can be exaggerated. This has been shown, for example, in the context of short-term mortality after myocardial infarction, where the observed variability across countries was reduced by 87% after controlling for patient characteristics and finite sample sizes.[4]

Understanding the extent of true heterogeneity, after attempting to control for patient characteristics and finite samples, is of paramount importance for formulating generalizable clinical management algorithms. This is also critical for designing efficient randomized trials. Using a standardized international registry of severe asthma, this study aims to assess the magnitude of explained and unexplained variation in severe asthma exacerbation rates across countries. Our particular focus is on biologic-naive patients with severe asthma because the assessment of exacerbation risk in such patients is a major factor in the decision to initiate biologics.

Study Design and Methods

This study has obtained ethics approval from the institutional review board of National University of Singapore (NUS-IRB-2021-877) and the Anonymized Data Ethics & Protocol Transparency Committee (ADEPT1924).

Data Source

The International Severe Asthma Registry (ISAR) (2015-2021) (https://isaregistries.org/) is a prospective international observational cohort of patients with a clinical diagnosis of severe, uncontrolled asthma across 19 countries (list provided in Table 1).[5] Details of the design and data collection strategy of ISAR is explained elsewhere.[6] In brief, there is a leading center in each country that oversees the data collection and quality assurance. The centers, ranging from one to 55 per country, are secondary or tertiary clinics for asthma.[7] Data are collected using medical charts and electronic report forms. Severe asthma is defined as asthma that requires treatment at inclusion according to the 2018 definitions of the Global Initiative for Asthma (GINA): GINA step 5 or uncontrolled asthma status at GINA step 4 (details in e-Appendix 1).[8,9] The registry contains a rich set of demographic and clinical characteristics including asthma symptoms and treatment, lung function, type 2 inflammation biomarkers, comorbidities, and health services use.[5]

Study Cohort

The study sample included patients with severe asthma who were aged $\geq$ 18 years and had not initiated any therapeutic antibodies (biologics) at baseline visit. We had access to the cohort recruited between 2015 and 2021. The index date was defined as the date of the baseline visit. Patients were followed-up to 365 days. We excluded patients with a follow-up period of $<$ 30 days or with missing visit dates. We also excluded countries with sample sizes less than five to prevent small-cell effects.

We used an intention-to-treat approach and did not adjust for changes in status of use of asthma medications or biologics during follow-up.[10] Only a small percentage of the included patients (8.2%) received treatment with biologics during follow-up. We carried out a sensitivity analysis with exclusion of those patients. All the ISAR patients were on medium or high doses of inhaled corticosteroids and long-acting beta-agonists (LABAs) at baseline.

Outcomes

The primary outcome was the rate of severe exacerbations in the next 365 days. Severe exacerbation was defined according to the American Thoracic Society/European Respiratory Society task force: use of oral corticosteroids (OCSs) for at least 3 days, or an occurrence of asthma-related hospitalization or ED visit.[11] In two participating countries that recorded OCS-requiring exacerbations without the start and end dates of OCS use, we assumed $\geq$ 3 days of OCS use for each recorded OCS-requiring exacerbation. Due to the study inclusion/exclusion criteria, there were no missing values in the outcome variable.

Covariates

In addition to country, we extracted 17 core prognostic patient characteristics for severe exacerbations from a larger set of potential candidates. This selection was conducted based on a survey of 70 leading experts in severe asthma care and management (e-Appendix 2).[12] We included three additional covariates for long-term use of asthma medications at baseline visit. The covariates were age; smoking status; BMI; asthma control; prebronchodilator measurement of FEV_1; fractional exhaled nitric oxide, blood eosinophil count; total severe exacerbations in the past year (calculated in the same way as follow-up severe exacerbations); total hospital visits in the past year; total ED visits in the past year; total use of invasive ventilations in the past year; long-term OCS use; use of steroid-sparing drugs; long-term use of long-acting muscarinic antagonists (LAMAs); use of a combination therapy of LABAs and LAMAs; long-term use of macrolides; and presence of allergic rhinitis, chronic rhinosinusitis, nasal polyps, and obesity. System-level covariates (eg, access to biologics,[13] quality of care,

TABLE 1] Heterogeneity in Patient Characteristics (Average Values) and Severe Exacerbation Rates Between Countries

Country	Sample Size	Severe Exacerbations During Follow-Up	Average Follow-Up, y	Severe Exacerbation Rate (Per y)	Baseline Severe Exacerbation Rate (Per y)	Use of Biologics During Follow-Up, %
Argentina	26	1	0.98	0.04	0.81	0
Australia	394	191	0.94	0.52	0.46	0
Bulgaria	180	74	0.76	0.54	1.08	1
Canada	149	25	1.00	0.17	0.81	7
Colombia	204	17	0.99	0.08	0.82	7
Denmark	229	25	0.99	0.11	0.03	9
Greece	94	18	0.92	0.21	0.67	9
Italy	800	186	0.95	0.25	0.29	13
Japan	107	14	1.00	0.13	0.89	14
South Korea	38	11	0.99	0.29	0.11	32
Kuwait	163	41	1.00	0.25	2.33	25
Saudi Arabia	45	33	0.80	0.92	4.60	11
Spain	209	108	0.94	0.55	1.00	14
Taiwan	141	48	0.93	0.37	0.99	29
United Arab Emirates	117	13	0.88	0.13	0.79	4
United Kingdom	434	328	1.00	0.76	4.86	22
United States	4,180	806	0.98	0.20	0.19	5
Total	7,510	1,939	0.97	0.27	0.67	8

indices related to the development or wealth of a country) were not included. This is because such factors are currently not considered in guideline development and health policymaking. Correspondingly, we excluded them to describe the components of heterogeneity that are not considered in contemporary asthma management strategies.

Statistical Analyses

Extreme values of covariates were examined case by case, with outliers flagged if deemed implausible and recoded as missing values.[14] A robust, random forest-based nonparametric algorithm (MissForest) was performed to impute missing predictor values.[15]

To test for differences in individual covariates across countries, we used one-way analysis of variance for univariate associations and Pearson χ^2 test for categorical covariates (asthma control and smoking status) with Bonferroni correction to take multiple hypothesis testing into consideration.[16]

We used negative binomial regression modeling for evaluating the effect of case mix and sampling on between-country variability. Based on diagnostic tests, we found that the negative binomial models without the zero-inflation component sufficiently captured the severe exacerbation pattern in the data (e-Appendix 3). To sequentially disentangle the effect of case mix and sampling variability, we used a series of negative binomial models. First, we fitted a naive fixed-effect model, with severe exacerbation count during the first 365 days of follow-up as the dependent variable and 17 dummy-coded indicators of countries as the fixed-effect terms. In case significant heterogeneity in severe exacerbation rates across countries was detected (based on the Wald χ^2 test[17]), the second step involved the addition of baseline patient characteristics as independent variables to test whether the between-country variation remained significant. To capture potential nonlinear relationships with the response variable, continuous covariates were modeled using thin-plate splines.[18] If the between-country effect was removed by the covariate adjustment, the conclusion would be that all variability across countries could be explained by case mix. Otherwise, a third step involved fitting an adjusted random-effects model to control for case mix and variability in the country effects due to the sample size within each country.[4] We would extract the empirical Bayes estimates of the random-effects term (country) along with 95% CIs.[4] In this context, the empirical Bayes estimate represents the shrinkage of a country effect toward the population mean depending on the relative magnitude of variance of the country effect and variance of between-country effects. We reported on country-specific severe exacerbation rates using the average marginal effect (details are provided in e-Appendix 4).[19,20] We plotted the estimated country effect for each of the following: naive model, adjusted fixed-effect model, and adjusted random-effects model. In a sensitivity analysis, we carried out a nested random-effects analysis to investigate the effect of regions (details are provided in e-Appendix 5).

All analyses were performed using R version 4.3.1 (R Core Team).

Results

Study Cohort

The final cohort included 7,510 individuals from 17 countries, followed for an average of 353 days (Fig 1). The total number of severe exacerbations was 1,939, corresponding to an annual rate of 0.27 per person-year (Table 1) (information on other covariates is provided in e-Appendix 6). The crude annual severe exacerbation rates varied considerably across countries, with an average value ± SD of 0.32 ± 0.25. Saudi Arabia and the United Kingdom had the highest values of 0.92 and 0.76, respectively, and Argentina and Colombia had the lowest values of, respectively, 0.04 and 0.08. We found significant between-country differences in all the covariates ($P < .001$) except for long-term use of LABAs and LAMAs ($P > .50$).

Between-Country Variability

In the naive fixed-effect model, the between-country effect was statistically significant (Wald χ^2 test $P < .001$). The country-specific model-based severe exacerbation rates varied with an interquartile range (IQR) of 0.13 to 0.54 events per year (Fig 2).

After including covariates, between-country effect only reduced slightly overall and remained significant ($P < .001$), implying the differences in the case mix only partially explained the variation in severe exacerbation rates across countries. This was reflected by the modest changes in the IQR to 0.15 to 0.43 events per year. However, estimates from individual countries changed differently with the inclusion of covariates. For instance, Greece had a small change of < 2% between the naive and adjusted models. This implies the case mix of patients with severe asthma in Greece was close to the international average. On the other hand, controlling for case mix changed the estimates substantially for Saudi Arabia (−49%) and the United Kingdom (−43%).

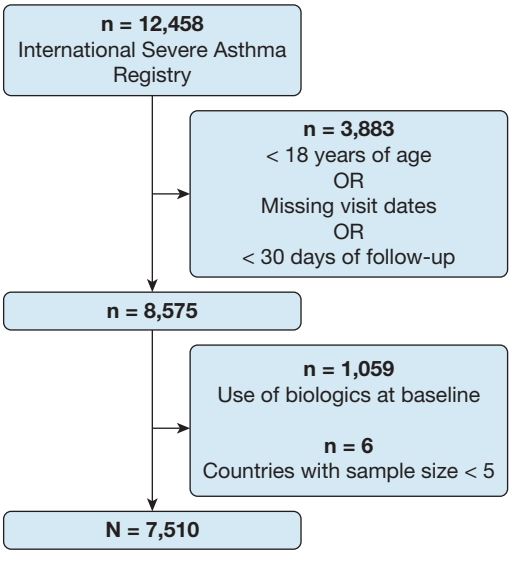


Figure 1 – *Flow diagram of the International Severe Asthma Registry cohort.*

Subsequently, we fitted an adjusted random-effects model to estimate country-specific effects. The estimates of country-specific severe exacerbation rates shrunk toward the overall mean at a modest level for most countries (e-Appendix 7, Fig 2). Consequently, it again led to small changes in the IQR to 0.16 to 0.39 events per year, indicating that sampling variability could only partially explain between-country heterogeneity.

Sensitivity analysis indicated that our overall results were largely insensitive to inclusion/exclusion of patients who received biologics during follow-up (e-Appendix 8) and that there was no substantial regional effect over and beyond country-level effects ($P = .56$) (e-Appendix 5).

Discussion

In an international observational cohort of patients with severe asthma, we discovered substantial between-country differences in severe exacerbation rates. The inclusion of core prognostic covariates at the patient level could only modestly explain the between-country variation, as supported by small changes in the estimates of country-specific severe exacerbation rates when covariates were added. Using a random-effects model to account for sampling could modestly reduce the estimated variation. Considerable variation remained unexplained, with the average of country-specific rates of severe exacerbation among the top 50% countries being 2.8 times that of the bottom 50%.

There are several potential reasons for unexplained differences in the severe exacerbation rates across countries. The natural course of severe asthma might indeed be truly different across countries. However, the inclusion of several clinically relevant variables did not explain away between-country differences. As such, system-level factors are also likely to contribute to the observed variability. Differences in health care systems (eg, access to biologics, biologic eligibility criteria, medication costs) can generate heterogeneity. Universal public coverage of essential medicines for asthma, particularly the combination therapy of inhaled corticosteroids and LABAs, can be another factor responsible for the unexplained heterogeneity.

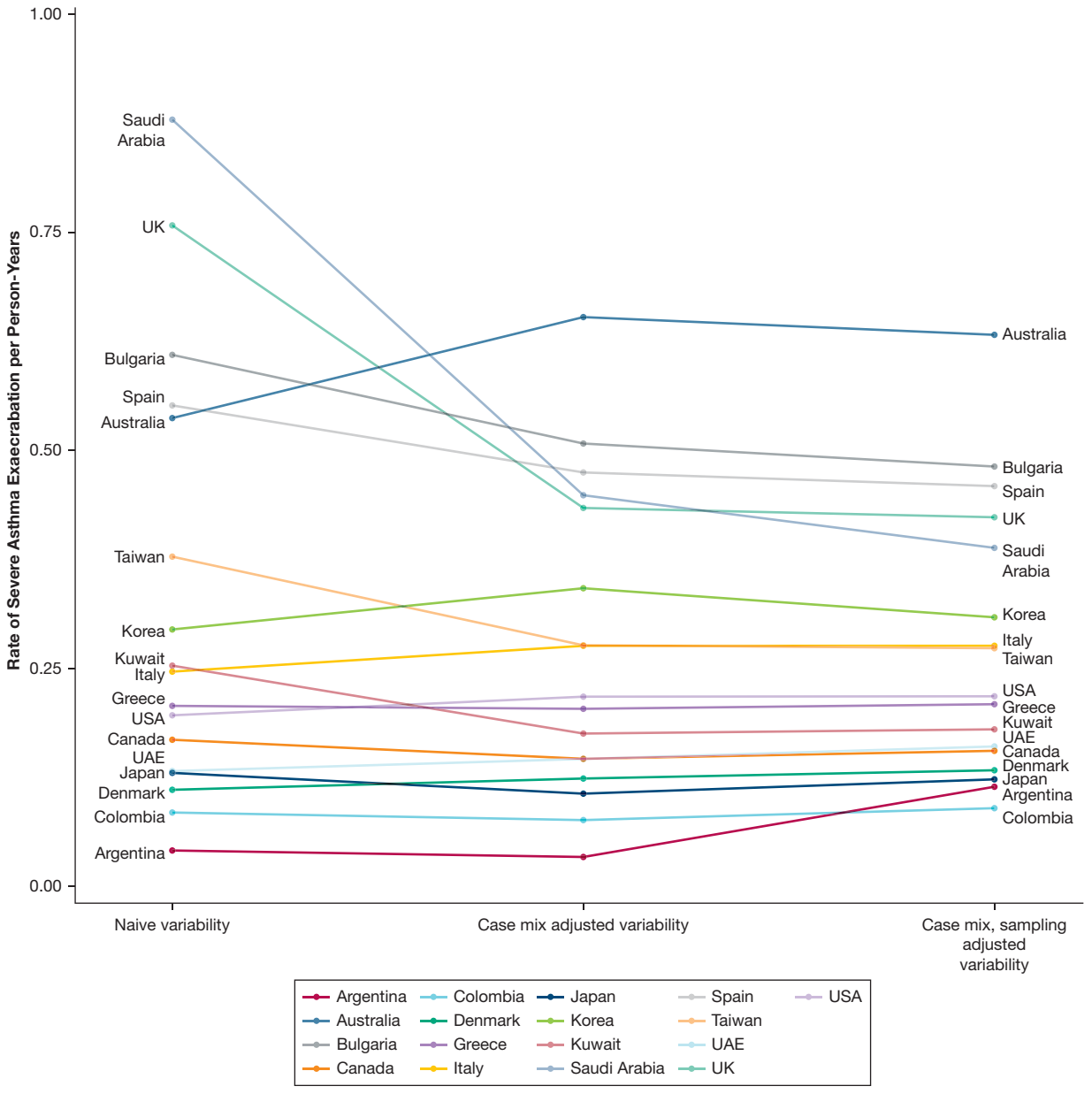


Figure 2 – *Estimates of country-specific severe asthma exacerbation rates (per person-years) using the average marginal effect framework for naive, case mix adjusted (fixed-effect), and case mix and sampling adjusted (random-effects) models. UAE = United Arab Emirates; UK = United Kingdom; USA = United States.*

Affordability of these medicines remains a major barrier to asthma management (including severe exacerbations) for low- and medium-income countries (eg, Mexico).[21] Furthermore, asthma management decisions in participating centers after recruitment of patients might be different, contributing to the variability in event rates. Examples include asthma education and training programs for inhaler use, treatment of comorbidity, and environmental control. Likely due to such interventions, the annual severe exacerbation rate generally decreased after enrollment in the study, albeit with varying degrees (eg, from 0.79 to 0.13 in the United Arab Emirates, from 0.29 to 0.25 in Italy). Moreover, environmental factors can play a role. For example, Saudi Arabia has a varied climate, and a large part of the country is often affected by regular sandstorms, which might explain part of the large differences in event rates compared with its neighboring coastal countries (eg, Kuwait, United Arab Emirates).

The literature is sparse on the extent of between-country variability. Wang et al[22] provided descriptive statistics of

clinical characteristics of severe asthma using an earlier version of the ISAR database. They noted substantial differences across five groups of countries in asthma outcomes, including exacerbation rates, but could not make a definitive statement on the between-group heterogeneity, given that they did not adjust for case mix and sampling variability. Using naive estimates may exaggerate the between-country variability. For instance, Calverley et al[23] found substantial international differences in exacerbation rates of COPD across 41 countries. However, such findings and interpretations on between-country variability, although relevant for depicting an overall picture of heterogeneity, may change once they adjust for the uncertainty due to finite sample sizes. Similarly, findings by Vermeire et al,[24] who used unadjusted estimates of between-country variability in asthma control and medication use among seven European countries, although varied, should be interpreted as not controlling for case mix and finite sampling.

Our study has important implications for practice and research. Our results question the merit of imposing unified treatment strategies for patients with severe asthma, without considering case mix and country-specific effects. According to our findings, patients with similar characteristics and asthma histories but from different countries might be at different risk of future exacerbations. Thus, the benefit of treatments in terms of reduction in exacerbation rate (eg, the number of treatments needed to prevent one exacerbation) may differ for otherwise similar patients across countries. We think international initiatives (eg, GINA) should emphasize multivariable risk calculations, which are further adapted to each setting (eg, via country-specific risk correction).[25]

Another important implication is for the design of future severe asthma trials, in which severe asthma exacerbation rate is often a key inclusion criterion (eg, more than one exacerbation in the last 12 months[26]). To achieve desired sample sizes, international coordinated efforts are required in such trials.[27] Ignoring between-country variability can lead to inefficient clinical trial designs. As an illustration, we took three participating countries with the lowest, middle (median), and highest values of observed severe exacerbation rate and explored statistical power calculations (Fig 3) (details of the methodology are provided in e-Appendix 9). To detect a 20% reduction in the severe exacerbation rate with 90% power, 12,699 patients per arm would be required in Argentina, whereas 2,503 patients would be needed in South Korea and only 1,432 patients per arm would be needed in Saudi Arabia. International clinical studies that recruit patients from specialty care should therefore balance the efficiency of their trial design and the representativeness of countries and regions.

The strengths of this study include access to a multinational prospective severe asthma registry that provided large sample sizes and consistent inclusion criteria. Sequential modeling of severe exacerbations enabled us to examine, in a stepwise fashion, unexplained variability in severe exacerbation rates. Our sampling adjusted exacerbation rates from the random-effects model provide objective baseline values for sample size calculations in future trials in severe asthma. However, limitations of our study should also be considered. Despite its wide acceptability, the American Thoracic Society/European Respiratory Society definition of exacerbation may underestimate the rate of true exacerbations among resource-constrained countries where patients have limited access to health care. We also cannot rule out that some of the observed variation can be due to the study protocol. Despite the ISAR's continuous efforts to unify the definition of severe asthma, the criteria still varied slightly across countries.[12] Standardization of definitions (eg, training data providers to carefully distinguish exacerbation from loss of asthma control) can mitigate such induced variability. Another limitation is that the ISAR is not a population-based registry. Most ISAR participants were recruited from specialty clinics and local registries in their respective participating countries, which are not necessarily representative of their respective severe asthma population. We note that the observed severe exacerbation rate in the ISAR is notably low (0.27/y) in comparison with existing severe asthma trials (eg, 1.84/y in the placebo arm of two multinational phase 3 trials of mepolizumab in severe eosinophilic asthma combined[28]). However, this is because trial samples are often highly enriched for patients at high risk of severe exacerbations (eg, requiring a higher number of exacerbations and eosinophil count at baseline).[28] We did not have access to several potentially important patient-level variables, including health literacy and adherence.[29] Finally, COVID-19, which occurred during the recruitment period of the ISAR, could have contributed to the unexplained variability because countries experienced COVID-19 waves at different time points.

Our study was aimed at documenting the extent of country-level heterogeneity in observed severe

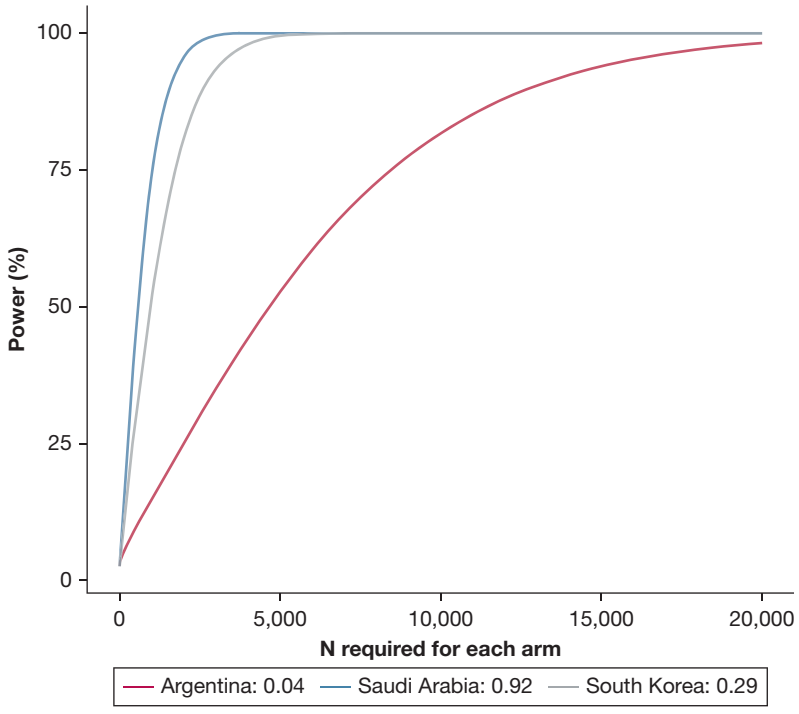


Figure 3 – *Power analysis for the lowest, median, and highest severe exacerbation rates (per person-y) observed in the International Severe Asthma Registry to detect a reduction of 20% in severe exacerbation rates from the comparator.*

exacerbation rates beyond case mix differences; to that end, we intentionally did not include such country-level factors in the analysis. The inclusion of such factors would make our study less informative in demonstrating the extent of variability that is likely being missed by guidelines. Investigating the causes of such between-country heterogeneity is indeed a very relevant topic for future research. Such a study should consider multiple factors, such as quality of care (eg, continuity of care, communications between general physicians and specialists, use of asthma action plans) and patients' experience of care and outcomes (using patient-reported outcomes measures). To improve representativity and hence generalizability, future studies should expand the network of registries and consider collaboration with continental registries (eg, Pan-European Severe Heterogeneous Asthma Research Collaboration, Patient-Centred).[30]

How can the field move forward? The considerable variability in exacerbation rates indicates the need for multivariable risk prediction. This research was indeed conducted as part of a larger study in developing and validating risk prediction models for severe asthma.[12] However, recent results show that no size fits all if trying to apply a single risk scoring tool to different settings.[25,31] Instead, multivariable prediction models will likely need to incorporate a country effect. Using a global multivariable model that is adapted to each country/setting is much preferred over country-specific models because individual countries are unlikely to have sufficient sample sizes, and research has shown that the resulting risk calculator will have suboptimal performance.[32] The ability to locally adapt a risk scoring algorithm is a key advantage of a regression-based risk modeling as opposed to simplistic tools (eg, management based on asthma control and exacerbation history alone).[25]

Interpretation

There is considerable heterogeneity in severe exacerbation rates in patients with severe asthma across countries. Differences in observed patient characteristics, including exacerbation history, only partially account for such heterogeneity. This indicates unknown or unmeasured patient factors or system-level variation at play, requiring further investigation. Our findings suggest that each country or jurisdiction adapt clinical recommendations for severe asthma to their setting for optimal treatment escalation strategies. Moreover, multivariable risk prediction models with setting-specific effects that are properly calibrated to their local settings should be promoted as part of our quest in improving the management of asthma and increasing the efficiency of severe asthma trials.

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