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The burden of severe asthma in sub-Saharan Africa: Findings from the African Severe Asthma Project

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Background: Severe asthma is associated with high morbidity, mortality, and health care utilization, but its burden in Africa is unknown.
Objective: We sought to determine the burden (prevalence, mortality, and activity and work impairment) of severe asthma in 3 countries in East Africa: Uganda, Kenya, and Ethiopia.
Methods: Using the American Thoracic Society/European Respiratory Society case definition of severe asthma, we analyzed for the prevalence of severe asthma (requiring Global Initiative for Asthma [GINA] steps 4-5 asthma medications for the previous year to achieve control) and severe refractory asthma (remains uncontrolled despite treatment with GINA steps 4-5 asthma medications) in a cohort of 1086 asthma patients who had been in care for 12 months and had received all GINA-recommended medications. Asthma control was assessed by the asthma control questionnaire (ACQ).
Results: Overall, the prevalence of severe asthma and severe refractory asthma was 25.6% (95% confidence interval [CI], 23.1-28.3) and 4.6% (95% CI, 3.5-6.0), respectively. Patients with severe asthma were (nonsevere vs severe vs severe refractory) older (39, 42, 45 years, $P = .011$), had high skin prick test reactivity (67.1%, 76.0%, 76.0%, $P = .004$), had lower forced expiratory volume in 1 second percentage (81%, 61%, 55.5%, $P < .001$), had lower quality of life score (129, 127 vs 121, $P < .001$), and had higher activity impairment (10%, 30%, 50%, $P < .001$). Factors independently associated with severe asthma were hypertension comorbidity; adjusted odds ratio 2.21 (1.10-4.47), $P = .027$, high bronchial hyperresponsiveness questionnaire score; adjusted odds ratio 2.16 (1.01-4.61), $P = .047$ and higher ACQ score at baseline 2.80 (1.55-5.08), $P = .001$.
Conclusion: The prevalence of severe asthma in Africa is high and is associated with high morbidity and poor quality of life. (J Allergy Clin Immunol Global 2024;3:100209.)

Key words: *Severe asthma, burden of severe asthma, severe asthma determinants, sub-Saharan Africa*

Asthma is a heterogeneous disease usually characterized by chronic airway inflammation and accompanied by a history of recurrent or persistent respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that varies over time and intensity, along with variable airflow obstruction.[1] Globally, asthma affects 334 million people, and in Africa, the prevalence of asthma is estimated at 7.0% and 9.6% in rural and urban areas, respectively.[2-5]

A subgroup of patients with asthma continues to experience persistent respiratory symptoms with a high need for medications. These patients are considered to have severe asthma. Case definitions for severe asthma have been proposed by different organizations including the World Health Organization (WHO), the Global Initiative for Asthma (GINA), the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the Innovative Medicine Initiative.[6-9] WHO defines severe asthma as asthma that is uncontrolled that can result in risk of frequent severe exacerbations (or death); adverse reactions to medications; and/or chronic morbidity (including impaired lung function or reduced lung growth in children).[7] WHO recognizes 3 groups of severe asthma: untreated severe asthma, difficult-to-treat

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Abbreviations used
ACQ: Asthma control questionnaire
ASAP: African Severe Asthma Project
ATS: American Thoracic Society
BHQ: Bronchial hyperresponsiveness questionnaire
CI: Confidence interval
ERS: European Respiratory Society
FENO: Fraction of exhaled nitric oxide
FEV: Forced expiratory volume
FEV_1: Forced expiratory volume in 1 second
GINA: Global Initiative for Asthma
ICS: Inhaled corticosteroid
WHO: World Health Organization

severe asthma, and treatment-resistant severe asthma. Treatment-resistant or refractory severe asthma includes asthma for which control is not achieved despite the highest level of recommended treatment or is lost when treatment is tapered.[7] ATS/ERS defines severe asthma as asthma that requires high-dose inhaled corticosteroid (ICS) therapy plus a second controller (and/or systemic corticosteroids) to prevent asthma from becoming uncontrolled or asthma that remains uncontrolled despite this therapy.[6] GINA defines severe asthma as asthma that requires GINA step 4 or 5 with high-dose ICS therapy and regular oral corticosteroid therapy.

The prevalence of severe asthma among those with diagnosed asthma ranges from 3% to 10% in different studies.[10-12] A study from Sweden estimated prevalence of severe asthma at population level to be 4.8% when the ATS/ERS definition was used and 6.1% when the GINA definition was applied among patients identified with asthma in the community.[13] Although the prevalence of severe asthma is low, severe asthma patients experience the highest asthma burden including mortality and health care utilization. Available evidence shows that severe asthma can be responsible for up to 50% of the total asthma-related health care costs through hospital admissions, use of emergency services, and unscheduled physician visits.[14,15] In addition, severe asthma is associated with much lower quality of life.[16]

Severe asthma constitutes a distinct phenotype with unique characteristics ranging from demographic (late onset) to immunologic (high IgE), and from genetic (*ADAM33* gene) to microbiotic.[17-24] These findings have guided and continue to guide development of novel therapies.[24] The National Heart, Lung, and Blood Institute severe asthma research program found severe asthma to be associated with late onset, less atopy (lower blood eosinophil levels, fewer positive skin tests), history of sinopulmonary infections, and asthma symptoms during routine activity.[23]

Other factors reported to be associated with asthma severity include female sex (possibly due to endocrine differences),[11] tobacco smoking,[25,26] air pollution,[27] increased airway inflammation as measured by fraction of exhaled nitric oxide (FENO),[28] use of drugs such as β-blockers, angiotensin-converting enzyme inhibitors, and aspirin,[27] psychologic and psychiatric disorders such as depression and anxiety,[29] and comorbid conditions such as allergic rhinitis and gastroesophageal reflux disease.[30-32] Genetic variations have also been described in severe asthma, with the following genes the most frequently implicated: *ADAM33, TGF-β1,* genes encoding IL-4 receptor (IL-4Rα), TNF, cortactin *(CTTN),* and PHD finger protein 11 *(PHF11).*[33-40]

Achieving adequate asthma control in low-resource settings is challenging, and identifying the prevalence of and determinants of severe asthma is one way to identify the best treatment modalities and hence improve asthma care in these settings. In Africa, the prevalence, burden (health care utilization, disease exacerbation, and mortality rates), and characteristics of severe asthma are not known; however, data from elsewhere on severe asthma points to differences across countries, with some of these attributed to asthma management systems and access to treatment.[41] We conducted this analysis on patients enrolled into the African Severe Asthma Project (ASAP) to determine the burden (prevalence, mortality, quality of life, exacerbation, and work and activity impairment) of severe asthma in the 3 East African countries of Uganda, Ethiopia, and Kenya.

METHODS

Study design, setting, and participants

ASAP was a multicenter prospective cohort study across 3 East African countries (Uganda, Kenya, and Ethiopia) and has previously been described.[42] Using the ATS/ERS case definition of severe asthma, we looked for the prevalence of severe asthma and severe refractory asthma among patients who completed 12 months follow-up and had received all GINA-recommended asthma medications. Asthma control was assessed using the asthma control questionnaire (ACQ).[43] The design and implementation of ASAP has been previously published.[42] Briefly, patients enrolled into ASAP underwent spirometry according to the ATS/ERS guidelines[44] using a Pneumotrac spirometer with Spirotrac V software (Vitalograph, Maids Moreton, Buckingham, United Kingdom). The National Health and Nutrition Examination Survey references values were used.[45,46] Skin prick testing was performed and interpreted according to published international guidelines.[47] Briefly, after obtaining consent from the participant, the skin was cleaned with 70% alcohol and sites of allergen application marked with a pen at 2 cm intervals. One drop of each allergen was put beside the mark starting from the palm side toward the elbow, and starting with normal saline and ending with histamine. A sterile lancet was used to pierce the skin through the drop, with a new one used for each drop. Readings were taken after 15 minutes, with the size of the wheal measured at its widest diameter and the diameter perpendicular to the widest diameter. An average wheal diameter of ≥3 mm indicated a positive reaction. Allergens were determined via an Immunospec SkinPrickTest (Immunotek, Madrid, Spain). FENO testing was performed with the NObreath FENO monitor according to the manufacturer's instructions (Bedfont Scientific, Maidstone, Kent, United Kingdom). Complete blood count and stool-concentrated microscopy were performed.

Patient follow-up

Enrolled asthma patients were provided with all indicated asthma medications according to the GINA guidelines[48] and assessed for asthma control, medication adherence, and outcomes (exacerbations, quality of life, work productivity and activity impairment, hospitalizations, and mortality) at baseline, monthly until month 6, and then at months 9 and 12. Quality of life was assessed by the asthma quality of life questionnaire developed by Juniper et al.[49] Depression was assessed with the Patient

Health Questionnaire 9 (PHQ-9)[50] and work productivity and impairment by Work Productivity and Activity Impairment (WPAI).[51] We used the bronchial hyperresponsiveness questionnaire (BHQ) developed by Riemersma et al[52] to look for bronchial hyperresponsiveness.

Definitions

Severe asthma was defined according to the ATS/ERS definition of severe asthma. A team of pulmonologists adjudicated each case at the end of follow-up of all patients to determine which patients fulfilled the case definition. The adjudication created 3 groups of patients, as follows: not severe asthma, severe asthma, and severe refractory asthma/treatment-resistant asthma.

Severe asthma. Severe asthma was defined as asthma that required treatment with guideline-suggested medications for GINA step 4-5 asthma (high-dose ICS and long-acting β-agonist or leukotriene modifier/theophylline) for the previous year or systemic corticosteroid therapy for ≥50% of the previous year to prevent it from becoming uncontrolled, or disease that remained uncontrolled despite this therapy. Uncontrolled asthma was defined as consistently having an ACQ score of ≥1.5.

Severe refractory asthma. Severe refractory asthma was defined as disease requiring medication levels that fulfilled the ATS/ERS criteria and remained uncontrolled (ie, patient had an ACQ of ≥1.5 at the end of 12 months in the study).

Asthma exacerbations. Asthma exacerbations were defined using the ATS/ERS definition of asthma exacerbations[53] and those by Fuhlbrigge et al.[54]

Statistical analysis

Descriptive statistics were used to summarize enrolled patient characteristics. Categorical variables are presented as frequencies and percentages for nonmissing data. Continuous variables are reported as medians with 25th and 75th percentiles (Q1, Q3). Baseline characteristics are presented overall and by patient groups (not severe asthma, severe asthma, and severe refractory asthma). The percentages in each group were compared by the chi-square test for trend, and medians were compared by the Kruskal-Wallis test. The impact of severe asthma on patients' lives (asthma control, exacerbations, quality of life, work productivity, and activity impairment) was calculated by patient groups. The median values of these measures (of patients' lives) were calculated for each group and compared by the Kruskal-Wallis test. A multivariable logistic model was fitted to determine the independent association of the variables of interest with severe refractory asthma. The STATA command 'mi test' was used to test for model coefficients. Variables whose coefficients were not significant ($P > .05$) were dropped from the model until a final fit was obtained. Results from the final fit are presented as adjusted estimates. Variables of scientific importance were retained in the final model even if these were not significant. All analyses were performed by STATA v15 software (StataCorp, College Station, Tex). $P < .05$ was considered statistically significant unless otherwise specified.

Ethical considerations

Ethical approval was obtained from the Mulago Hospital research and ethics committee (MHREC 875), the Uganda National Council for Science and Technology, and from local ethics committees in each country: the Kenyatta National Hospital–University of Nairobi ethics review committee (327/04/2016) and the Ethiopia–Addis Ababa University College of Health Sciences institutional review board (AAUMF-01-008). All patients provided written informed consent. All patients aged ≥18 years provided informed consent, while assent was obtained for participants aged <18 years.

Patient and public involvement

Patients and the public were not involved in any way in the design and conduct of the study.

RESULTS

Patient characteristics

A total of 1086 participants fulfilled the analytic criteria of having completed 12 months follow-up and having received GINA-recommended medications. Up to 28.6% (n = 310) of these patients were male, with a median age of 40 years. The details of the demographic and clinical characteristics of these patients are shown in Table I. At baseline, up to 21.9% of the patients had uncontrolled asthma (ACQ ≥ 1.5). The proportion of patients with uncontrolled asthma (ACQ ≥ 1.5) at each follow-up visit is shown in Fig E1 in this article's Online Repository at www.jaci-global.org.

Prevalence of severe asthma and severe refractory asthma

The prevalence of severe asthma and severe refractory asthma was 25.6% (95% confidence interval [CI], 23.1-28.3) and 4.6% (95% CI, 3.5-6.0), respectively (Table II).

The prevalence of severe asthma was 27% in Kenya, 27.1% in Uganda, and 19.9% in Ethiopia; and the prevalence of severe refractory asthma was 7.7% in Kenya, 3.9% in Uganda, and 3.2% in Ethiopia.

At baseline, patients with severe asthma were (nonsevere, severe, severe refractory) older (39, 42, 45 years, $P = .011$), had high skin prick test reactivity (67.1%, 76.0%, 76.0%, $P = .004$), had lower forced expiratory volume in 1 second (FEV_1) values (81%, 61%, 55.5%, $P < .001$), and were prescribed more courses of oral steroids (0, 2, 2, $P < .001$), as shown in Table I.

Impact of severe asthma

The impact of asthma by severity status is represented in Table III and Fig 1. The median (Q1, Q3) number of exacerbations experienced during the 12 months follow-up was 0 (0, 1) overall but rose to 2 (0, 4) among those with severe refractory asthma. The median (Q1, Q3) total quality of life score was 135 (111.5, 162), and was lower among those with severe asthma at 127 (101, 154.5), and severe refractory asthma at 121 (98, 144) ($P < .001$). Patients with severe refractory asthma and severe asthma had a higher percentage of activity impairment than those without severe asthma: severe refractory asthma, 50% (20%, 70%); severe asthma, 30% (0, 60%); and not severe asthma 10% (0, 40%) ($P < .001$).

TABLE I. Study participants' baseline characteristics by severe asthma status

Characteristic	All (N = 1086)	Severe asthma status			*P* value
		Not severe (n = 808)	Severe (n = 278)	Severe refractory (n = 50)	
Male sex	310 (28.6)	232 (28.8)	78 (28.2)	12 (24.5)	.587
Age (years), median (Q1, Q3)	40 (25, 53)	39 (24, 52)	42 (28, 54)	45 (34, 57)	.011
Age (years) at asthma diagnosis, median (Q1, Q3)	25 (13, 36)	25 (14, 37)	24 (12, 33)	30 (16, 40)	.101
Adult-onset asthma (≥19 years)	680 (64.7)	516 (65.6)	164 (62.1)	32 (69.6)	.725
Family history of asthma	584 (54.2)	421 (52.5)	163 (59.3)	29 (60.4)	.042
Smoking (current/former)	59 (5.4)	43 (5.3)	16 (5.8)	2 (4.0)	.947
Secondhand smoke exposure	78 (7.2)	56 (6.9)	22 (7.9)	4 (8.0)	.580
Biomass exposure	792 (73.2)	610 (75.8)	182 (65.7)	38 (76.0)	.026
Cough	479 (44.2)	326 (40.5)	153 (55.0)	32 (64.0)	<.001
Wheeze	433 (39.9)	282 (35.0)	151 (54.3)	29 (58.0)	<.001
BMI (kg/m^2), median (Q1, Q3)	24.3 (20.8, 28.8)	24.5 (20.9, 29.0)	24.0 (2.4, 27.9)	24.9 (21.0, 30.1)	.360
Pre-BD FVC% predicted, median (Q1, Q3)	94 (77, 109)	97 (80, 111)	86 (68, 101)	80 (67, 95)	<.001
Pre-BD FEV_1% predicted, median (Q1, Q3)	76 (54, 95)	81 (61, 98)	61 (46, 85)	55.5 (45, 75)	<.001
Pre-BD FEV_1/FVC ratio, median (Q1, Q3)	0.71 (0.56, 0.81)	0.72 (0.59, 0.82)	.62 (.50, .75)	0.63 (0.50, 0.78)	<.001
BD reversibility	19.5 (12.3, 31)	18.0 (10.0, 29.1)	21.9 (14.1, 35.6)	14.5 (10, 42.1)	.001
Ova/cysts	1 (0.2)	1 (0.3)	0 (.0)	0 (0.0)	.520
Uncontrolled asthma (ACQ > 1.5)	643 (60.7)	437 (55.4)	206 (76.0)	42 (85.7)	<.001
BHQ, median (Q1, Q3)	70 (48, 96)	66 (44, 92)	80 (57, 110)	100 (63, 125)	<.001
No. of exacerbations in past year, median (Q1, Q3)	3 (1, 10)	3 (1, 10)	6 (2, 15)	5 (2, 10)	<.001
No. of courses of oral steroids prescribed, median (Q1, Q3)	1 (0, 4)	0 (0, 3)	2 (0, 7)	2 (0, 5)	<.001
3 or more exacerbations in past year	652 (60.3)	452 (56.3)	200 (71.9)	34 (68.0)	<.001
Any hospitalization in past year	234 (21.7)	148 (18.4)	86 (31.1)	15 (30.0)	<.001
Any ICS therapy	145 (13.9)	107 (14.0)	38 (13.7)	15 (30.0)	.051
Not receiving any asthma medication	116 (10.7)	116 (14.4)	0 (.0)	0 (0.0)	<.001
HIV	55 (6.1)	45 (6.8)	10 (4.3)	2 (4.7)	.186
Hypertension	130 (12.0)	99 (12.3)	31 (11.2)	12 (24.0)	.212
Obesity	215 (20.0)	164 (20.6)	51 (18.5)	14 (28.0)	.758
Tuberculosis	7 (0.6)	6 (0.7)	1 (.4)	1 (2.0)	.830
GERD	199 (18.3)	140 (17.3)	59 (21.2)	11 (22.0)	.127
Rhinosinusitis	228 (21.0)	160 (19.8)	68 (24.5)	12 (24.0)	.113
Skin prick test					
At least 1 positive result	755 (69.5)	542 (67.1)	213 (76.6)	38 (76.0)	.004
2-3 positive results	204 (18.8)	150 (18.6)	54 (19.4)	11 (22.0)	.544
FENO (ppb)					
Median (Q1, Q3)	23 (11, 45)	23 (10, 45)	22 (12, 46)	18 (12, 56)	.910
FENO ≥35 ppb	301 (34.0)	227 (35.1)	74 (31.0)	16 (35.6)	.456
Absolute eosinophil count					
Median (Q1, Q3)	230 (120, 430)	240 (120, 430)	230 (120, 440)	210 (125, 405)	.802
>300 cells/μL	310 (37.0)	229 (37.4)	81 (35.8)	12 (30.0)	.378

Data are presented as medians (Q1, Q3) or counts (percentages).

BD, Bronchodilator; *BMI,* body mass index; *FVC,* forced vital capacity; *GERD,* gastroesophageal reflux disease; *HIV,* human immunodeficiency virus.

Incidence of mortality

The number of patients who died during the 12 months follow-up is provided in Table IV. Overall, 5 patients (0.35%) died during the follow-up period, and the incident ratio of death was higher among participants with uncontrolled asthma (7.9), although this was not statistically significant ($P = .197$).

Factors associated with severe refractory asthma

Factors associated with failure of disease to be controlled by month 12 despite GINA step 4 therapy are presented in Table E1 in the Online Repository at www.jaci-global.org. The significantly associated factors were hypertension comorbidity (adjusted odds ratio 2.21, 95% CI [1.10-4.47], $P = .027$), high BHQ score (adjusted odds ratio 2.16, 95% CI [1.01-4.61], $P = .047$), and higher ACQ score at baseline (adjusted odds ratio 2.80, 95% CI [1.55-5.08], $P = .001$). All other factors we examined did not reach a statistically significant association.

DISCUSSION

In this study, we found that 25.6% of patients required high-intensity treatment, so their asthma was categorized as severe. We also found that 4.6% of the cases remained uncontrolled despite high-intensity treatment, so these patients' asthma was categorized as severe refractory.

The rates of severe asthma (25.6%) and severe refractory asthma (4.6%) found in this cohort of patients are much higher than reported elsewhere.[11-13] In Denmark, von Bülow et al[11] reported a prevalence of severe asthma of 8.1% among 61,583

TABLE II. Prevalence of severe asthma and refractory severe asthma at month 12 by country, sex, and age groups

Characteristic	No.	Severe asthma status					
		Not severe, no. (%)	Severe asthma		Severe refractory asthma		*P* value*
			No. (%)	95% CI	No. (%)	95% CI	
Overall	1086	808 (74.4)	278 (25.6)	23.1-28.3	50 (4.6)	3.5-6.0	
Country							
Kenya	248	181 (73.0)	67 (27.0)	21.8-32.9	19 (7.7)	4.9-11.7	.026
Uganda	617	450 (72.9)	167 (27.1)	23.7-30.7	24 (3.9)	2.6-5.7	
Ethiopia	221	177 (80.1)	44 (19.9)	15.1-25.7	7 (3.2)	1.5-6.5	
Sex							
Male	310	232 (74.8)	78 (25.2)	20.6-30.3	12 (3.9)	2.2-6.7	.809
Female	774	575 (74.3)	199 (25.7)	22.7-28.9	37 (4.8)	3.5-6.5	
Age							
<25 years	269	210 (78.1)	59 (21.9)	17.4-27.3	9 (3.4)	1.7-6.3	.027
25-39 years	262	198 (75.6)	64 (24.4)	19.6-30.0	9 (3.4)	1.8-6.5	
40-54 years	319	227 (71.2)	92 (28.8)	24.1-34.2	12 (3.8)	2.1-6.5	
55+ years	227	165 (72.7)	62 (27.3)	21.9-33.5	20 (8.8)	5.7-13.3	

*Chi-square test.

TABLE III. Impact of asthma by severity status during 12 months follow-up

Characteristic	Overall (N = 1086)	Not severe (n = 808)	Severe (n = 278)	Severe refractory (n = 50)	*P* value
No. of asthma exacerbations by 12 months	(n = 1082) 0 (0, 1)	(n = 804) 0 (0, 1)	(n = 278) 0 (0, 1)	(n = 50) 2 (0, 4)	<.001
Had at least 1 exacerbation in 12 months follow-up	363 (33.6)	265 (33.0)	98 (35.3)	31 (62.0)	.002
No. of hospitalizations by 12 months	(n = 1081) 0	(n = 804) 0	(n = 277) 0 (0, 1)	(n = 50) 0 (0, 1)	.004
Any hospitalization in 12 months follow-up	237 (21.9)	151 (18.8)	86 (31.1)	15 (30.0)	<.001
Received at least 1 course of oral/systemic steroid prescription in 12 months follow-up	734 (68.0)	485 (60.4)	249 (89.9)	44 (89.8)	<.001
Quality of life score	(n = 924) 135 (112, 162)	(n = 684) 139 (117, 165)	(n = 240) 127 (101, 155)	(n = 45) 121 (98, 144)	<.001
Work productivity and activity impairment					
Percentage overall work impairment	(n = 916) 0	(n = 673) 0	(n = 243) 0	(n = 45) 0	.812
Percentage work time missed	(n = 916) 0	(n = 673) 0	(n = 243) 0	(n = 45) 0	.073
Percentage impairment while working	(n = 916) 0	(n = 673) 0	(n = 243) 0	(n = 45) 0	.992
Percentage activity impairment	(n = 923) 20 (0, 50)	(n = 679) 10 (0, 40)	(n = 244) 30 (0, 60)	(n = 45) 50 (20, 70)	<.001
No. of school days missed because of asthma in the last year	(n = 212) 1 (0, 7)	(n = 168) 1 (0, 5)	(n = 44) 3 (0, 12.5)	(n = 8) 1 (0, 7)	.148

Data are presented as nos. (%) or median (Q1, Q3).

patients with asthma, while Hekking et al[12] found a prevalence of severe refractory asthma of 3.6% among 2,312 Dutch asthma patients. Generally, the prevalence of severe asthma is estimated to be between 5% and 10%.[11-13,55] There are several reasons why we found higher rates of severe asthma in this population. First, it has been previously reported that asthma severity tends to be higher among persons of African descent.[56-59] Higher severe asthma rates and poor treatment outcomes among Africans have been attributed to socioeconomic factors that affect access to medication as well as exposure to environmental factors such as air pollution, genetics, and differences in airway inflammation levels.[59-62]

Another possible explanation for the higher rates could be lack of access to effective medications for asthma by patients in our settings. In studies performed elsewhere on severe asthma, country-level differences were noted, with asthma management systems and access to treatment postulated to contribute to these differences.[48] At enrollment, only 13.9% of the patients were receiving ICS treatment, and 60.7% had uncontrolled asthma. In a national prevalence survey of asthma in Uganda, over 90% of persons with symptoms of asthma had never been diagnosed.[63] We, however, prescribed to all patients recruited onto the study guideline-recommended treatment and ensured that these patients received this treatment throughout the study's duration. Therefore, we corrected for the lack of access to effective medications for asthma in our cohort of asthma patients. Even then, it may be that lack of controller treatment for a long time could have influenced the proportion of our patients with severe asthma as a result of airway remodeling. A selection bias is also possible because this study was conducted at tertiary-care hospitals in capital cities of the participating countries. This might mean that patients with

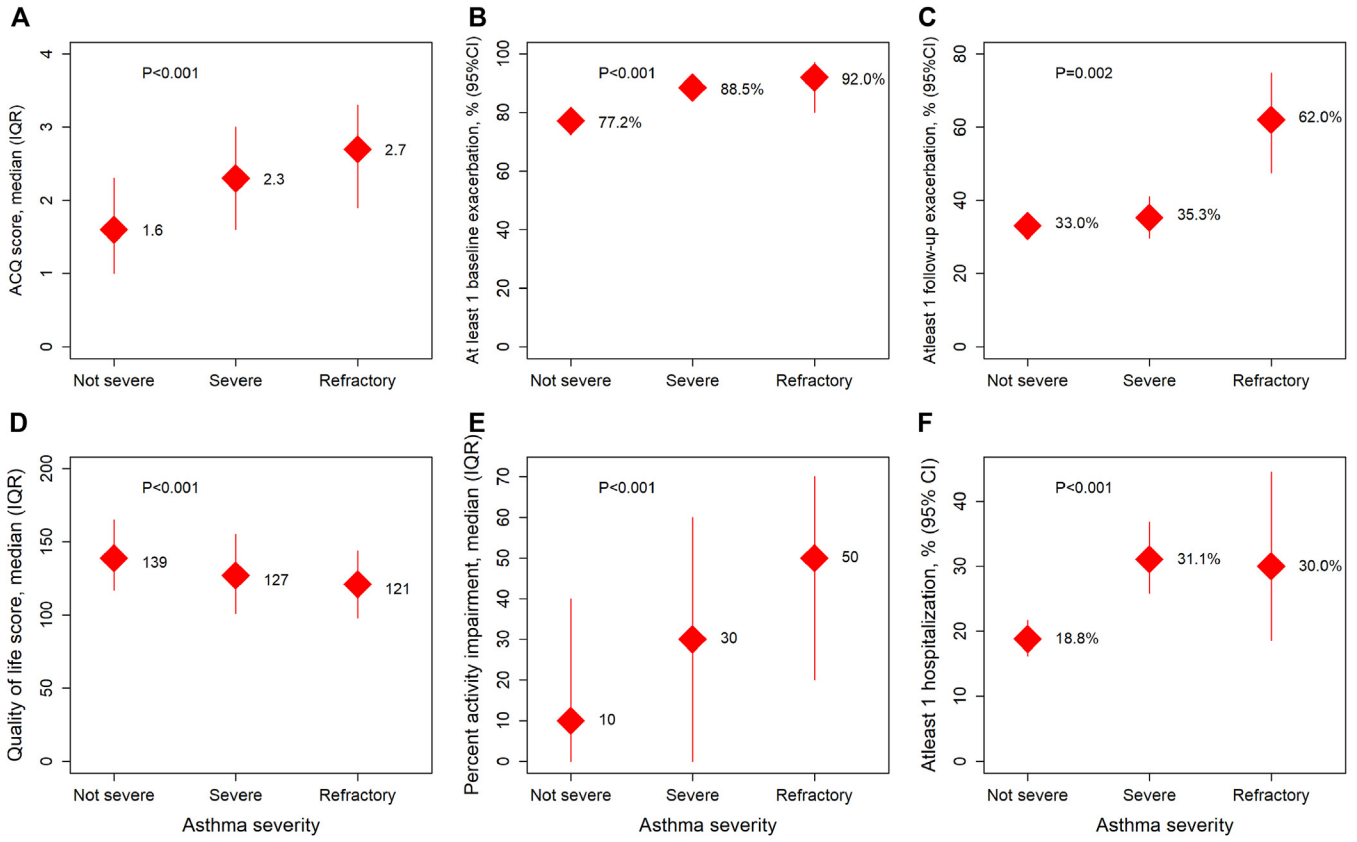

FIG 1. Impact of severe asthma. Asthma severity by ACQ score **(A)**, exacerbations in the past year **(B)**, exacerbations by month 12 **(C)**, quality of life **(D)**, activity impairment **(E)**, and number of hospitalizations **(F)**.

TABLE IV. Incidence of mortality by asthma control at last visit

Asthma control	No. of patients*	Died, no. (%)	Person months	IR (95% CI) per 10,000 months	IRR (95% CI)	*P* value
Overall	1,435	5 (0.35)	14,837	3.2 (1.3, 7.7)		
Controlled (ACQ ≤ 1.5)	1,184	3 (0.25)	12,315	2.4 (0.8, 7.6)	1.00	
Uncontrolled (ACQ > 1.5)	251	2 (0.80)	2,522	7.9 (2.0, 31.9)	3.25 (0.54, 19.53)	.197

IR, Incidence rate; *IRR,* incidence rate ratio.
*Includes only those with ACQ data at last visit.

more severe symptoms were enrolled. Another bias could have been introduced as a result of loss to follow-up. Many patients did not adhere to the follow-up schedule and were therefore not included in the severity analysis. It is possible that patients with severe disease were the most likely to adhere to the follow-up schedule, whereas those with mild disease were more likely to drop out of follow-up.

This study revealed that the asthma of a substantial number of asthmatic patients (4.6%) remained uncontrolled despite high-intensity treatment. Such patients normally have poor health outcomes, and it is important to consider tailored treatment modalities for this patient group. Targeted therapies like biologics have emerged, but their use in low-resource settings is limited.[64] Given the magnitude of severe asthma, investments for improving access to these therapies in low-resource settings should be prioritized.

We explored the impact of asthma on patients in this study. We found higher asthma mortality among male subjects and people older than 55 years. Older age has previously been reported as a risk factor for asthma death.[65] The higher death rate among male patients in this study is contradictory to what most studies have found, with most studies reporting higher death rates among women. Watson et al[65] in a large database analysis in the United Kingdom found that death was highest among women aged 45 years and above. According to Asthma+Lung UK,[66] there were 5100 asthma deaths among women compared to 2300 deaths among men in the past 5 years. Higher mortality among male subjects was also observed in our previous study, in which mortality incidence rates were higher among male compared to female patients, at 34.2% versus 24.6%.[67] This reverse of association of sex and death in asthma in our studies may be associated with poor health-seeking behavior among men, but this result needs further

study. As found in other studies, patients with severe asthma had lower quality of life, higher activity impairment, and more exacerbations.[68]

Our study's main strength is in being the first study in sub-Saharan Africa that has enrolled a large number of patients across 3 countries. We were able to provide patients with all the medications they needed in order to assess the intensity of treatment they needed to achieve disease control. The main limitation of our study is loss to follow-up, with many patients not having complete data to analyze for severe asthma. We were also not able to conduct genetic analysis at this time, although genetic material was collected. Assessments of other biomarkers of asthma severity, such as sputum cell counts, specific IgE to determine allergic sensitization, and total IgE measurements, were also not conducted.

In conclusion, the prevalence of severe asthma in sub-Saharan Africa is high and is associated with high morbidity and mortality, and poor quality of life. Further studies are needed to determine drivers of the observed high prevalence of severe asthma.

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REFERENCES

1. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. Lancet 2006;368(9537):733-43.
2. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 2012;12:204.
3. Adeloye D, Chan KY, Rudan I, Campbell H. An estimate of asthma prevalence in Africa: a systematic analysis. Croatian Med J 2013;54:519-31.
4. Weinberg EG. Urbanization and childhood asthma: an African perspective. J Allergy Clin Immunol 2000;105:224-31.
5. Enilari O, Sinha S. The global impact of asthma in adult populations. Ann Glob Health 2019;85:2.
6. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
7. Bousquet J, Mantzouranis E, Cruz AA, Aït-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol 2010;126:926-38.
8. Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax 2011;66:910-7.
9. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med 2000;162:2341-51.
10. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. Eur Respir J 2003;22:470-7.
11. von Bülow A, Kriegbaum M, Backer V, Porsbjerg C. The prevalence of severe asthma and low asthma control among Danish adults. J Allergy Clin Immunol Pract 2014;2:759-67.
12. Hekking PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. J Allergy Clin Immunol 2015;135:896-902.
13. Backman H, Jansson SA, Stridsman C, Eriksson B, Hedman L, Eklund BM, et al. Severe asthma—a population study perspective. Clin Exp Allergy 2019;49:819-28.
14. Godard P, Chanez P, Siraudin L, Nicoloyannis N, Duru G. Costs of asthma are correlated with severity: a 1-yr prospective study. Eur Respir J 2001;19:61-7.
15. Serra-Batlles J, Plaza V, Morejon E, Comella A, Brugues J. Costs of asthma according to the degree of severity. Eur Respir J 1998;12:1322-6.
16. Guilbert TW, Garris C, Jhingran P, Bonafede M, Tomaszewski KJ, Bonus T, et al. Asthma that is not well-controlled is associated with increased healthcare utilization and decreased quality of life. J Asthma 2011;48:126-32.
17. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med 2010;181:315-23.
18. Melén E, Pershagen G. Pathophysiology of asthma: lessons from genetic research with particular focus on severe asthma. J Intern Med 2012;272:108-20.
19. Nariya S, Lynch S, Harris J, Choy D, Arron J, Boushey H, et al. The airway microbiome in severe asthma. Am J Respir Crit Care Med 2014;189:A2423.
20. Cox M, Liang Z, Brinkmann F, Duff R, Gibeon D, Alshafi K, et al. Altered airway microbiome in severe asthma. Am J Respir Crit Care Med 2012;185:A6717.
21. Chanez P, Wenzel SE, Anderson GP, Anto JM, Bel EH, Boulet LP, et al. Severe asthma in adults: what are the important questions? J Allergy Clin Immunol 2007;119:1337-48.
22. Mathias RA, Grant AV, Rafaels N, Hand T, Gao L, Vergara C, et al. A genome-wide association study on African-ancestry populations for asthma. J Allergy Clin Immunol 2010;125:336-46.e4.
23. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's severe asthma research program. J Allergy Clin Immunol 2007;119:405-13.
24. Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. J Allergy Clin Immunol 2005;115:459-65.
25. Althuis MD, Sexton M, Prybylski D. Cigarette smoking and asthma symptom severity among adult asthmatics. J Asthma 1999;36:257-64.
26. Siroux V, Pin I, Oryszczyn M, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the genetics and environment of asthma. Eur Respir J 2000;15:470-7.
27. Slaughter JC, Lumley T, Sheppard L, Koenig JQ, Shapiro GG. Effects of ambient air pollution on symptom severity and medication use in children with asthma. Ann Allergy Asthma Immunol 2003;91:346-53.
28. Dweik RA, Sorkness RL, Wenzel S, Hammel J, Curran-Everett D, Comhair SA, et al. Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma. Am J Respir Crit Care Med 2010;181:1033-41.
29. Lehrer P, Feldman J, Giardino N, Song HS, Schmaling K. Psychological aspects of asthma. J Consult Clin Psychol 2002;70:691.
30. Bresciani M, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P, et al. Rhinosinusitis in severe asthma. J Allergy Clin Immunol 2001;107:73-80.
31. Pearlman AN, Chandra RK, Chang D, Conley DB, Peters AT, Grammer LC, et al. Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. Am J Rhinol Allergy 2009;23:145.
32. Ten Brinke A, Sterk P, Masclee A, Spinhoven P, Schmidt J, Zwinderman A, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2005;26:812-8.
33. Wenzel SE, Balzar S, Ampleford E, Hawkins GA, Busse WW, Calhoun WJ, et al. IL4Rα mutations are associated with asthma exacerbations and mast cell/IgE expression. Am J Respir Crit Care Med 2007;175:570-6.
34. Sandford AJ, Chagani T, Zhu S, Weir TD, Bai TR, Spinelli JJ, et al. Polymorphisms in the *IL4, IL4RA,* and *FCERIB* genes and asthma severity. J Allergy Clin Immunol 2000;106:135-40.
35. de Faria IC, Faria EJd, Toro AA, Ribeiro JD, Bertuzzo CS. Association of TGF-beta1, CD14, IL-4, IL-4R and *ADAM33* gene polymorphisms with asthma severity in children and adolescents. J Pediatr (Rio J) 2008;84:203-10.
36. Hedlin G, Bush A, Carlsen KL, Wennergren G, De Benedictis F, Melen E, et al. Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. Eur Respir J 2010;36:196-201.
37. Chagani T, Pare PD, Zhu S, Weir TD, Bai TR, Behbehani NA, et al. Prevalence of tumor necrosis factor-α and angiotensin converting enzyme polymorphisms in

mild/moderate and fatal/near-fatal asthma. Am J Respir Crit Care Med 1999;160: 278-82.
38. Ma SF, Flores C, Wade MS, Dudek SM, Nicolae DL, Ober C, et al. A common cortactin gene variation confers differential susceptibility to severe asthma. Genet Epidemiol 2008;32:757-66.
39. Zhang Y, Leaves NI, Anderson GG, Ponting CP, Broxholme J, Holt R, et al. Positional cloning of a quantitative trait locus on chromosome 13q14 that influences immunoglobulin E levels and asthma. Nat Genet 2003;34:181-6.
40. Foley SC, Mogas AK, Olivenstein R, Fiset PO, Chakir J, Bourbeau J, et al. Increased expression of *ADAM33* and *ADAM8* with disease progression in asthma. J Allergy Clin Immunol 2007;119:863-71.
41. Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of severe asthma worldwide: data from the international severe asthma registry. Chest 2020;157:790-804.
42. Kirenga B, Chakaya J, Yimer G, Nyale G, Haile T, Muttamba W, et al. Phenotypic characteristics and asthma severity in an East African cohort of adults and adolescents with asthma: findings from the African severe asthma project. BMJ Open Respir Res 2020;7:e000484.
43. Juniper E, O'Byrne P, Guyatt G, Ferrie P, King D. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.
44. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
45. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. Am J Respir Crit Care Med 1999;159:179-87.
46. Ford ES. The epidemiology of obesity and asthma. J Allergy Clin Immunol 2005; 115:897-909.
47. Dreborg S. The skin prick test in the diagnosis of atopic allergy. J Am Acad Dermatol 1989;21:820-1.
48. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2017. Available at: https://ginasthma.org/archived-reports/.
49. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992;47:76-83.
50. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606-13.
51. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4: 353-65.
52. Riemersma R, Postma D, Kerstjens H, Buijssen K, Boezen M, Aalbers R, et al. Development of a questionnaire for the assessment of bronchial hyperresponsiveness. Prim Care Respir J 2009;18:287-93.
53. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
54. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA Jr, Gern J, et al. Asthma outcomes: exacerbations. J Allergy Clin Immunol 2012;129(3 suppl): S34-48.
55. Rönnebjerg L, Axelsson M, Kankaanranta H, Backman H, Rådinger M, Lundbäck B, et al. Severe asthma in a general population study: prevalence and clinical characteristics. J Asthma Allergy 2021;14:1105-15.
56. Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, et al. National surveillance for asthma—United States, 1980-2004. MMWR Surveill Summ 2007; 56:1-54.
57. Stewart KA, Higgins PC, McLaughlin CG, Williams TV, Granger E, Croghan TW. Differences in prevalence, treatment, and outcomes of asthma among a diverse population of children with equal access to care: findings from a study in the military health system. Arch Pediatr Adolesc Med 2010;164:720-6.
58. Akinbami LJ, Moorman JE, Simon AE, Schoendorf KC. Trends in racial disparities for asthma outcomes among children 0 to 17 years, 2001-2010. J Allergy Clin Immunol 2014;134:547-53.e5.
59. Haselkorn T, Lee JH, Mink DR, Weiss ST;TENOR Study Group. Racial disparities in asthma-related health outcomes in severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2008;101:256-63.
60. Thakur N, Oh SS, Nguyen EA, Martin M, Roth LA, Galanter J, et al. Socioeconomic status and childhood asthma in urban minority youths. The GALA II and SAGE II studies. Am J Respir Crit Care Med 2013;188:1202-9.
61. Ortega VE, Meyers DA. Pharmacogenetics: implications of race and ethnicity on defining genetic profiles for personalized medicine. J Allergy Clin Immunol 2014;133:16-26.
62. Nyenhuis SM, Krishnan JA, Berry A, Calhoun WJ, Chinchilli VM, Engle L, et al. Race is associated with differences in airway inflammation in patients with asthma. J Allergy Clin Immunol 2017;140:257-65.e11.
63. Kirenga BJ, de Jong C, Katagira W, Kasozi S, Mugenyi L, Boezen M, et al. Prevalence and factors associated with asthma among adolescents and adults in Uganda: a general population based survey. BMC Public Health 2019;19:1-9.
64. Krings JG, McGregor MC, Bacharier LB, Castro M. Biologics for severe asthma: treatment-specific effects are important in choosing a specific agent. J Allergy Clin Immunol Pract 2019;7:1379-92.
65. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. Respir Med 2007;101:1659-64.
66. Asthma+Lung UK. Women almost twice as likely to die from asthma than men. Press release, April 27, 2022. Available at: https://www.asthmaandlung.org.uk/media/press-releases/women-almost-twice-likely-die-asthma-men.
67. Kirenga BJ, de Jong C, Mugenyi L, Katagira W, Muhofa A, Kamya MR, et al. Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study. Thorax 2018;73:983-5.
68. Hossny E, Caraballo L, Casale T, El-Gamal Y, Rosenwasser L. Severe asthma and quality of life. World Allergy Organ J 2017;10:28.