

Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study

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ABSTRACT

Data on asthma treatment outcomes in Africa are limited. 449 patients with asthma (age 5–93 years) in Uganda were followed up for 2 years to determine rates of exacerbations and mortality and associated factors. During follow-up the median number of exacerbations per patient was 1 (IQR 0–5) and 17 patients died (3.7%, 27.3 deaths per 1000 person years). Considering only the first year of follow-up, 59.6% of the patients experienced at least one exacerbation, 32.4% experienced three or more exacerbations. A multivariable model showed that the likelihood of experiencing at least one exacerbation in the first year of follow-up was lower with better baseline asthma control (higher asthma control test (ACT) score), with OR 0.87 (95% CI: 0.82 to 0.93, $P=0.000$), and was higher with more exacerbations in the year prior to enrolment (OR for log number of exacerbations 1.28, 95% CI: 1.04 to 1.57, $P=0.018$). Better asthma control (OR 0.93, 95% CI: 0.88 to 0.99, $P=0.021$) and number of baseline exacerbations (OR 1.35, 95% CI: 1.11 to 1.66, $P=0.005$) were also the only factors that were independently associated with experiencing three or more exacerbations during the first year of follow-up. The only factor found to be associated with all-cause mortality was FEV₁, with higher recent FEV₁ associated with lower all-cause mortality (OR 0.30, 95% CI: 0.14 to 0.65; $P=0.002$). Rates of asthma exacerbations and mortality are high in Uganda and are associated with poor asthma control. Health systems should be strengthened to care for asthma patients.

BACKGROUND

Asthma exacerbations and mortality are the worst asthma treatment outcomes.¹ Asthma exacerbations are responsible for most asthma morbidity, healthcare utilisation, poor quality of life and precede most asthma deaths.² Some patients experience frequent asthma exacerbations (defined usually as experiencing at least three exacerbations in a year). These patients have been described as having an exacerbation-prone asthma phenotype in some literature³ and are at the greatest risk of adverse asthma outcomes, including death. The risk factors for exacerbations include low use of inhaled corticosteroids, allergic rhinitis, seasonal changes, gastro-oesophageal disease, psychosocial factors, recurrent chest infections, aspirin intolerance, cigarette smoking, non-adherence to medications, obesity and higher number of exacerbations in the past year.³

Globally, asthma mortality is estimated at 0.19/100 000 population.⁴ According to a recent analysis of asthma mortality in 46 countries, asthma mortality rates were observed to be decreasing in the 1990s through the 2000s but have recently stagnated.⁴ Asthma mortality rate was 0.44 deaths per 100 000 people in 1993 and reduced to 0.19 deaths per 100 000 people in 2006 but no significant change was observed between 2006 and 2012.⁴ There are significant disparities in asthma mortality between countries, with low and middle income countries having the highest number of asthma deaths. Risk factors for asthma mortality include older age, gender, African race, low use of inhaled corticosteroids (ICS), inappropriate use of long-acting β agonists (LABAs), fixed airway obstruction (lack of reversibility), previous exacerbation, low FEV₁ and psychological and psychosocial factors.⁵

Data on asthma exacerbations and mortality and their predictors in Africa are severely limited. We therefore set up this prospective cohort study called the Uganda Registry for Asthma and Chronic Obstructive Pulmonary Disease (URAC) to document the rates of asthma exacerbations and mortality, and their predictors in Uganda.

METHODS

URAC is conducted in the chest clinics of six tertiary hospitals in Uganda, namely Mulago Hospital, Mbarara Hospital, Mbale Hospital, Hoima Hospital, Arua Hospital and Gulu Hospital. For the current analysis, only patients enrolled at Mulago Hospital are included. The Mulago Hospital Research and Ethics Committee and the Uganda National Council for Science and Technology approved this study. All patients with asthma who were 5 years and older for whom consent was provided were enrolled and followed up every 6 months for 2 years. Using a standardised clinical record form (CRF), data on patients' socio-demographics, clinical and lung function were collected. Asthma control was measured at each visit using the Asthma Control Test (ACT). All patients underwent spirometry according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using a Pneumotrac spirometer with Spirotrac V software (Vitalograph Ltd, Buckingham, UK). Predicted parameters were based on NHANES III models for African Americans. Asthma medication prescriptions were based on GINA guidelines.

Median number of exacerbations per patient over the entire 2-year follow-up period was

calculated. The proportions of patients experiencing at least one exacerbation and at least three exacerbations during the first year of follow-up were calculated. First data on exacerbations were considered to avoid recall bias and because of the high attrition rate (32.5%) and the fact that less than 50% of the cohort could be followed up by this time. Exacerbations were defined according to the ATS/ERS definitions. Death was by postmortem reports and verbal autopsy, and all-cause mortality was considered. Incidence of death was calculated as the number of deaths during the total follow-up period divided by the total follow-up time in years. Factors associated with all-cause mortality were analysed using the Cox proportional hazards model with age at death used as the survival time variable while factors associated with exacerbations (at least one and at least three exacerbations per year were determined using logistic regression.

RESULTS

From 13 August 2013 to 24 April 2016, 449 patients with asthma (28.3% male, median age 33 years (IQR 20–48)) were enrolled into the URAC Registry at Mulago Hospital. Patients' socio-demographic characteristics are presented in table 1. At baseline, 32.2% of the patients had controlled asthma and 33.0% had evidence of airflow obstruction on spirometry (ie, had FEV₁/FVC ratio <0.70). Smoking was reported by 12% of the patients, HIV by 6%, history of tuberculosis treatment by 6.2%, nasal congestion by 88.2% and heartburn by 60.6%. A total of 147 (32.7%) patients were on either ICS alone or ICS/LABA at baseline.

Exacerbations

The proportion of patients who experienced at least one exacerbation during the first year was 59.6% (268) while 32.4% (133) experienced at least three exacerbations in the first year. At the bivariate level, experiencing at least one exacerbation in the first year was associated with respiratory rate (OR 2.58, 95% CI: 1.01 to 6.57, P=0.047), having used ICS prior to the clinic visit (OR 2.93, 95% CI: 1.56 to 5.48, P=0.001), number of baseline exacerbations (OR 1.47, 95% CI: 1.21 to 1.79, P≤0.001), asthma control test (ACT) scores (OR 0.89, 95% CI: 0.85 to 0.94, P≤0.001) and FEV₁ (OR 0.56, 95% CI: 0.35 to 0.89, P=0.014); while experiencing three or more exacerbations was associated with age (OR 1.71, 95% CI: 1.17 to 2.50, P=0.006), number of baseline exacerbations (OR 1.48, 95% CI: 1.22 to 1.79, P<0.001), having used ICS prior to the clinic visit (OR 1.96, 95% CI: 1.14 to 3.35, P=0.014), respiratory rate (OR 2.14, 95% CI: 1.04 to 4.40, P=0.039), ACT scores (OR 0.84, 95% CI: 0.79–0.89, P<0.001), FEV₁ (OR 0.64, 95% CI: 0.41 to 0.99, P=0.044), FEV₁/FVC ratio (OR 0.11, 95% CI: 0.03 to 0.46, P=0.011) and exposure to biomass smoke exposure (OR 0.54, 95% CI: 0.30 to 0.99, P=0.048).

At multivariate analysis the only factors independently associated with experiencing at least one exacerbation in the first year of follow-up were ACT score (OR 0.87, 95% CI: 0.82 to 0.93, P=0.000) and number of baseline exacerbations (OR 1.28, 95% CI: 1.04 to 1.57, P=0.018). ACT score (OR 0.93, 95% CI: 0.88 to 0.99, P=0.021) and number of baseline exacerbations (OR 1.35, 95% CI: 1.11 to 1.66, P=0.005) were also the only factors independently associated with experiencing three or more exacerbations during the first year of follow-up.

Table 1 Baseline patients' characteristics

Characteristic	Number	Percentage
Male gender	127	28.3
Age groups		
<15	54	12.0
15–24	87	19.4
25–34	91	20.3
35–44	83	18.5
45–54	60	13.4
55–64	38	8.5
65+	36	8.0
Respiratory symptoms		
Cough	379	84.4
Sputum	214	47.7
Wheezing	434	96.7
Shortness of breath	436	97.0
Lung function abnormalities		
FEV ₁ /FVC ratio<0.70	148	33.0
FEV ₁ ≥80% predicted	211	47.0
FEV ₁ %, 50–79% predicted	163	36.3
FEV ₁ %, 30–49% predicted	58	12.9
FEV ₁ %, <30% predicted	17	3.8
Asthma control		
Uncontrolled, ACT<15	126	28.1
Partially controlled, 15≤ACT≤19	174	38.8
Controlled, ACT>19	149	33.2
Medications		
Salbutamol inhaler	318	70.8
Inhaled corticosteroids	83	18.5
Combination inhalers (steroid, LABA)	64	14.3
Leukotriene modifiers	66	14.7
Risk factors and comorbid conditions		
History of smoking	54	12.0
Exposure to bio-mass*	390	86.9
Ever been treated for TB	28	6.2
HIV positive	27	6.0
Nasal congestion or rhinorrhea	396	88.2
Heart burn/acid irritation	272	60.6

*Including use of wood, charcoal and kerosene for cooking or lighting.
ACT, Asthma Control Test; LABA, long-acting β agonist; TB, tuberculosis.

Mortality

Overall 17 patients died (3.7%), 11 (64.7%) from circumstances judged to be asthma related (online supplementary table 2). The incidence of all-cause mortality was 27.3 per 1000-person years, male vs female, 34.2 vs 24.6, incidence death rate ratio 1.39 (0.42–4.09) and increased with age (online supplementary table 1). At bivariate analysis, all-cause mortality was associated with FEV₁ and FVC (adjusted hazard ratio 0.30, 0.14–0.65, P=0.002; and 0.28, 0.12–0.68, P=0.005) respectively while history of tuberculosis treatment (adjusted HR 3.10, 1.00–9.65, P=0.051) and use of herbs (adjusted HR 3.86, 0.99–15.04, P=0.052) were associated with higher mortality but only as a trend (table 2). At multivariate analysis only FEV₁ remained independently associated with

Table 2 Factors associated with exacerbations and all-cause mortality at multivariate analysis

Factor	OR (95% CI)	P values
At least one exacerbation/year		
ACT score	0.87 (0.82 to 0.93)	0.000
Number of baseline exacerbations*	1.28 (1.04 to 1.57)	0.018
At least three exacerbations/year		
ACT score	0.93 (0.88 to 0.99)	0.021
Number of baseline exacerbations*	1.35 (1.11 to 1.66)	0.005
All-cause mortality		
Recent FEV ₁ *	0.30 (0.14 to 0.65)	0.002

*Log transformed because of skewness, interpretation should be done at the log scale. Note: analysis considers only the first year of follow-up.

ACT, Asthma Control Test.

all-cause mortality (HR 0.30, 95% CI: 0.14 to 0.65, P=0.002).

DISCUSSION

Our study has shown that 59.6% of patients with asthma experience at least one exacerbation in a year, 32.4% experience at least three exacerbations in a year, and the all-cause mortality rate is 3.7% (27.3 per 1000 person years). Exacerbations were less likely with better baseline asthma control and more likely with higher number of baseline exacerbations. Mortality was lower with higher recent FEV₁.

The rates of exacerbations and mortality observed in this study are much higher than the rates observed in developed settings and higher than the 1% asthma mortality rate for Uganda reported in the Global Burden of Disease report.^{4–8} For example, De Marco *et al* reported a mortality incidence rate of only 1.1/1000 person years in a cohort of Italian young adults (20–44 years) followed up for 7 years.⁷ Although the 27.3/1000 person years found in our cohort could be because we reported all-cause mortality while the De Marco study reported asthma-specific mortality, the 27-fold higher mortality rate we observed in this study indicates that asthma mortality rates in Uganda are very high. The associations between exacerbations and mortality with asthma control, number of baseline exacerbations and FEV₁ have been previously reported.^{5,7} Both the ACT and FEV₁ are measures of asthma control; ACT uses symptoms, medication use and work impairment to assess asthma control, while FEV₁ is an objective measure of the severity of airflow obstruction, a component of asthma control. Therefore, the grim asthma treatment outcomes in this study are most likely a reflection of uncontrolled asthma due to limited access to asthma treatment in our setting. The higher rates may also be race related, since the African race has been found to be associated with more severe asthma.⁹ The lack of use of recommended asthma medications, particularly ICS in

this cohort, calls for efforts to increase availability and affordability of asthma medication. Increased access to medicines has been reported to result in better asthma treatment outcomes in some settings, such as the case of Brazil where hospitalisations were significantly reduced with increased access to medications.¹⁰ In conclusion, the rates of asthma exacerbations and mortality observed in this study are very high and require strengthening of the health systems to improve asthma care in Uganda.

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Contributors BJK conceived the idea of the project and wrote the initial proposal. TvdM, MRK and HMB critically advised the writing of the proposal. CdJ and LM supported data analysis. WK and AM performed patients' clinical reviews. All authors critically reviewed and contributed to manuscript writing.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Mulago Hospital Research and Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Online supplemental material for the manuscript “Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study.”

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METHODS

Design and setting

URAC is a prospective cohort study of asthma and chronic obstructive pulmonary disease (COPD) patients in Uganda. Enrollment into this registry started in August 2013 and continues. Asthma and COPD patients diagnosed in the chest clinics of 6 tertiary hospitals in Uganda namely Mulago hospital, Mbarara hospital, Mbale hospital, Hoima hospital, Arua hospital and Gulu hospital are enrolled into this registry. For the current analysis only, patients enrolled at Mulago hospital are included. Mulago hospital is the national referral hospital of Uganda, situated in the heart of Kampala, the capital city of Uganda. The hospital has a bed capacity of 1500 beds.

Study procedures

Asthma diagnosis: Diagnosis of asthma is made by attending physicians in the respective chest clinics. Once a diagnosis of asthma is made, patients undergo spirometry at the registry clinic. Asthma patients who have fixed airflow obstruction (i.e. their FEV₁ does not increase by $\geq 12\%$ (and $\geq 200\text{ml}$) after administration of 400 μg of salbutamol) are excluded and registered as having COPD.

Patients who are referred for registration as having COPD but show reversible airflow obstruction are registered as asthma patients. Spirometry is conducted and interpreted according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using a Pneumotrac[®] spirometer with Spirotrac[®] V software (Vitalograph Ltd., Buckingham, United Kingdom).³ Predicted parameters are based on NHANES III models for African Americans.⁴

Registration into the registry and follow up: All asthma patients diagnosed in the chest clinics are reviewed by a dedicated registry medical officer for enrollment into the registry. A clinical record form (CRF) is used to collect the following baseline data: socio-demographics, asthma risk factors, respiratory symptoms and signs, vital signs, anthropometry, spirometry, number of exacerbations, visits to health facilities and hospitalization due to respiratory symptoms in years preceding the registration, asthma medications use and asthma control assessed with the asthma control test (ACT¹). Patients are followed up every six months, at each visit the following data is collected: respiratory symptoms and signs, vital signs, anthropometry, spirometry, number of exacerbations, visits to health facilities and hospitalization due to respiratory symptoms since the last visit, asthma medications use and asthma control assessed by ACT¹

Patient management: Dedicated registry clinicians and nurses review all enrolled patients. The registry clinicians have received asthma management training by the investigators according to GINA guidelines and prescriptions are made according to GINA guidelines.⁵ During registry visits the medical officer can prescribe and advise treatment according to his discretion. The registry does not provide medication to patients or any incentives such as transport refund. Patients continue to obtain their asthma medications from the hospital pharmacy or other sources such as private pharmacies. The registry nurse reminds patients of their next follow up visits and patients who miss visits are contacted by telephone to encourage them to attend the clinic. Patients also continue to attend their regular chest clinic visits as required by their attending physicians

Asthma exacerbations: In this study, an exacerbation was defined according to the ATS/ERS definition as “events characterized by a change from the patient’s previous status”.⁶ We considered only exacerbations that required a patient to either visit a health facility or to be

hospitalized (i.e. moderate to severe exacerbations) as recommended by the ATS/ERS guidelines.⁶

Mortality data collection: All-cause mortality data is collected, attempts are made to establish cause of death. For patients who die in hospital we obtain data on the cause of death from hospital charts or postmortem reports if available. If a patient dies outside the hospital the registry team uses a verbal autopsy form (developed according World Health Organization (WHO) guidelines⁷) to collect circumstances surrounding death and the possible cause of death from relatives or care takers. A period of two weeks is allowed after death for the verbal autopsy interview.

Statistical analysis

Patients baseline socio-demographic, clinical and lung function characteristics were summarized as proportions. For continuous variables, mean or median plus standard deviation and interquartile range are presented, depending on data normality.

The proportion of patients experiencing at least one exacerbation was calculated as well as the proportion of patients with ≥ 3 exacerbations in a year and stratified by gender and age group. Incidence of death was calculated as number of deaths during the total follow up period divided by total follow up time in years. Incidence rates were also stratified by gender and age group.

To determine factors associated with all-cause mortality, survival analysis using Cox Proportional Hazards model was used with age at death considered the survival time. Hazard Ratios (HR) for death are presented along with their 95% confidence intervals (95% CI). Factors associated with experiencing at least 1 or ≥ 3 exacerbations per year were determined using logistic regression, by defining a binary outcome as 1 if one had ≥ 3 exacerbations per year at least once during the first year of follow-up and zero if otherwise. Firstly, each factor was regressed separately and then factors with P values less than or equal to 0.20 were subjected to multiple logistic regression. For the Cox regression, no adjusted estimates were produced since only one factor (recent FEV₁) was independently associated with death. To arrive at a better fit for the logistic regression, backward model building was conducted using the likelihood ratio test (LRT). In addition, a better fit was checked for multicollinearity problems using the variance inflation factor (VIF). In case multicollinearity existed (VIF>10), centering of continuous variables was considered, else variables with less significance or scientific meaning were dropped.

Ethics

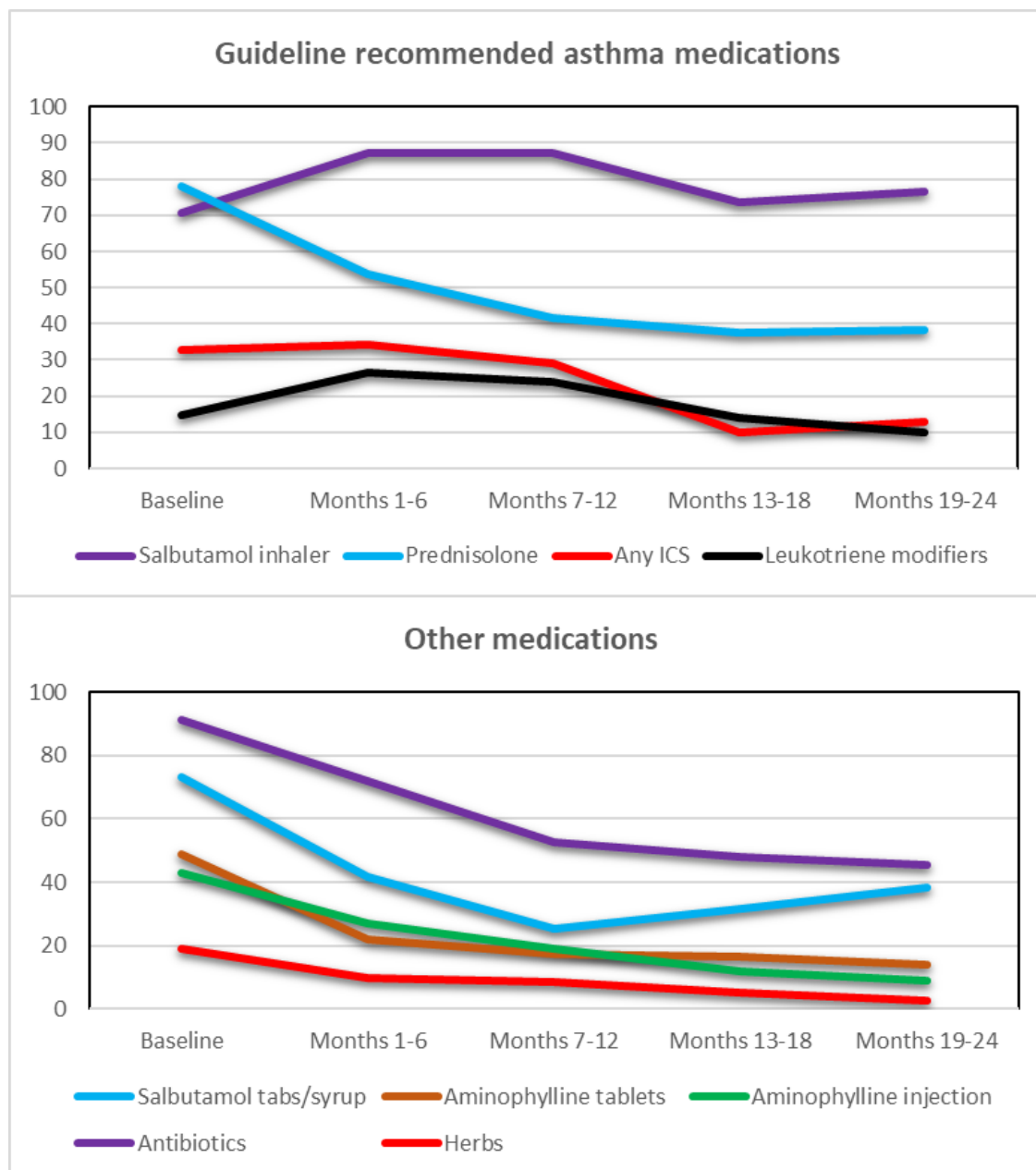
Ethics approval was obtained from the Mulago Hospital Research and Ethics committee and the Uganda National Council for Science and Technology. Participants provided written informed consent and were free to terminate study participation at any time during the study. For children aged 5-7 years parental/guardian consent was obtained while for children between the ages of 8-18 years we obtained their assent and parental/legal guardian consent.

RESULTS

Asthma medication use

We recorded medications patients were taking for the treatment of asthma at baseline and at each follow up visit. The trajectories of the different medications use at baseline and during follow up are shown in supplementary figure 1. At baseline use of any inhaled corticosteroid (ICS) either as standalone ICS or in combination with a long acting beta agonist (ICS/LABA) inhalers, salbutamol inhaler, oral prednisolone, leukotriene modifiers tablets, salbutamol tablets/salbutamol syrups, aminophylline tablets, antibiotics and herbs were 32.7%, 70.8%, 78.2%, 14.7%, 73.1%, 48.8%, 91.3% and 18.9% respectively. The proportion of patients on

any ICS increased to 34.3% by month six of follow up and dropped to 12.9% by month 24 of follow up.

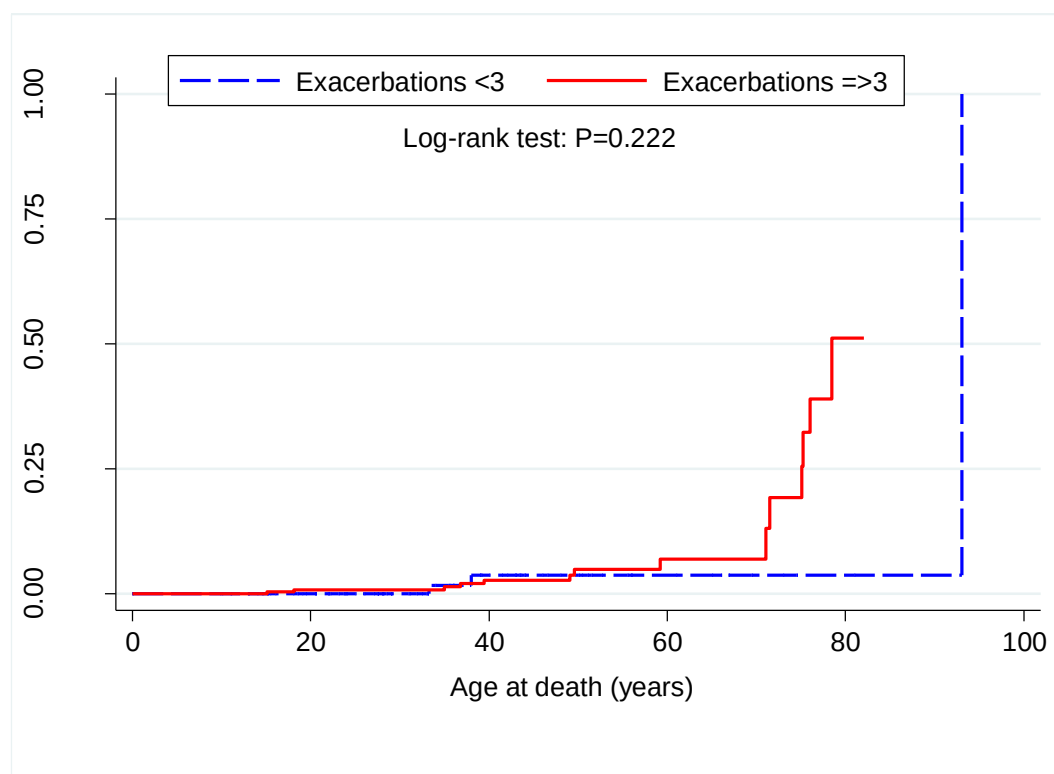


ICS=inhaled corticosteroids

Supplementary Figure 1. Trajectory of asthma medications use in the study among study patients

Relationship between all-cause mortality and frequent exacerbations (≥ 3 /year)

A total of 17 patients died overall and 133 (32.4%) patients experienced 3 or more exacerbations in a year. Twelve of the 17 patients who died (70.6%) were in the group who experienced 3 or more exacerbations; 4 of these deaths were judged to be due to other causes other than asthma (one was due to stroke, one due to heart failure, one due to intestinal obstruction and one due to anaemia). Figure 2 below



Supplementary Figure 2. Kaplan Meier plot of all-cause mortality rates by frequent exacerbation category

Supplementary tables

Supplementary Table 1 Rates of experiencing ≥ 3 exacerbations per year and mortality among study participants stratified by gender and age group

Group	Experienced ≥ 3 exacerbations per year		all-cause Mortality			
	Number of asthmatics N (%)	Rate ratio 95% CI	Number of deaths N (%)	Person years	Incidence rate [†] (deaths per 1000 years) 95% CI	Incidence rate ratio 95% CI
Overall	133 (32.4)		17 (100)	622.0	27.3 (17.0-44.0)	
Gender						
Male	32 (27.6)	0.8 (0.6 – 1.1)	6 (35.3)	175.6	34.2 (15.3-76.0)	1.39 (0.42-4.09)
Female	101 (34.2)	1	11 (64.7)	446.4	24.6 (13.6-44.5)	1
Age group						
<15	11 (21.2)	0.6 (0.3 – 1.3)	0 (0.0)	74.0	0.0 (---)	0.0 (---)
15-24	26 (32.9)	0.9 (0.5 – 1.8)	2 (11.8)	115.9	17.3 (4.3-69.0)	0.09 (0.01-0.49)
25-34	18 (21.4)	0.6 (0.3 – 1.2)	1 (5.9)	122.3	8.2 (1.2-58.0)	0.04 (0.00 – 0.34)
35-44	27 (34.2)	1.0 (0.5 – 1.9)	4 (23.5)	126.3	31.7 (11.9-84.4)	0.17 (0.04-0.67)
45-54	26 (44.8)	1.3 (0.7 – 2.4)	2 (11.8)	93.3	21.4 (5.3-85.7)	0.11 (0.01-0.60)
55-64	17 (47.2)	1.4 (0.7 – 2.6)	1 (5.9)	52.7	19.0 (2.7-134.6)	0.10 (0.00-0.79)
65+	8 (34.8)	1	7 (41.2)	37.5	186.7 (88.9-391.2)	1

[†] Number of deaths divided by person years [†]Year 1 and 2

Supplementary Table 2. Results of bivariate analysis of factors associated with exacerbations and all-cause mortality

Factor	≥1 exacerbation/year		≥3 exacerbation/year		All-cause mortality	
	OR (95% CI)	p-value	OR (95% CI)	p-value	HR (95% CI)	p-value
Age (years) [‡]	1.08 (0.77 – 1.51)	0.665	1.71 (1.17 – 2.50)	0.006		
Gender: male	0.74 (0.48 – 1.14)	0.170	0.73 (0.46 – 1.17)	0.195	0.65 (0.22 – 1.98)	0.452
ACT score	0.89 (0.85 – 0.94)	<0.001	0.84 (0.79 – 0.89)	<0.001	1.36 (0.50 – 3.66)	0.544
Ever been treated for TB	1.30 (0.57 – 2.99)	0.536	0.76 (0.31 – 1.85)	0.541	3.10 (1.00 – 9.65)	0.051
HIV status						
Positive	Reference		Reference		Reference	
Negative	0.79 (0.34 – 1.83)	0.585	0.89 (0.38 – 2.06)	0.786	0.88 (0.11 – 6.91)	0.902
Unknown	0.49 (0.15 – 1.53)	0.218	1.01 (0.31 – 3.27)	0.990	2.26 (0.23 – 22.17)	0.484
Nasal congestion or rhinorrhea	0.94 (0.50 – 1.77)	0.854	0.79 (0.42 – 1.50)	0.480	1.91 (0.25 – 14.55)	0.531
Heart burn/acid irritation	1.28 (0.85 – 1.91)	0.233	1.23 (0.80 – 1.90)	0.335	0.94 (0.34 – 2.59)	0.907
Recent use of ICS	2.93 (1.56 – 5.48)	0.001	1.96 (1.14 – 3.35)	0.014	0.58 (0.20 – 1.68)	0.314
Recent BMI [‡]	1.10 (0.50 – 2.42)	0.808	1.74 (0.76 – 3.97)	0.189	0.49 (0.05 – 4.62)	0.534
Recent respiratory rate [‡]	2.58 (1.01 – 6.57)	0.047	2.14 (1.04 – 4.40)	0.039	0.84 (0.09 – 7.56)	0.873
Recent SPO2	0.95 (0.89 – 1.02)	0.167	0.98 (0.93 – 1.03)	0.432	0.96 (0.87 – 1.05)	0.369
Number of baseline exacerbations [‡]	1.47 (1.21 – 1.79)	<0.001	1.48 (1.22 – 1.79)	<0.001	1.10 (0.72 – 1.67)	0.668
Recent FEV1 [‡]	0.56 (0.35 – 0.89)	0.014	0.64 (0.41 – 0.99)	0.044	0.30 (0.14 – 0.65)	0.002
Recent FEV ₁ /FVC ratio	0.52 (0.17 – 1.62)	0.259	0.11 (0.03 – 0.46)	0.011	0.53 (0.02 – 16.32)	0.718
Recent FVC [‡]	0.58 (0.33 – 1.03)	0.064	0.79 (0.45 – 1.40)	0.424	0.28 (0.12 – 0.68)	0.005
History of smoking	0.86 (0.47 – 1.57)	0.614	1.58 (0.85 – 2.92)	0.145	0.50 (0.11 – 2.23)	0.363
Exposure to bio-mass	0.69 (0.36 – 1.29)	0.242	0.54 (0.30 – 0.99)	0.048	0.73 (0.20 – 2.61)	0.626
Recent use of herbs	2.09 (0.66 – 6.58)	0.210	2.16 (0.79 – 5.89)	0.132	3.86 (0.99 – 5.04)	0.052
Reversibility [‡]	1.19 (0.93 – 1.52)	0.158	1.04 (0.81 – 1.34)	0.735	0.87 (0.50 – 1.51)	0.612

[‡] log transformed because of skewness, interpretation should be done at the log scale, note: analysis considers only the first year of follow up

Supplementary Table 3. Circumstances surrounding death for each individual patient who died and probable causes of death

Serial No.	Circumstances surrounding death	Probable cause of death	Exacerbation group (≥ 3 , <3)
1.	Admitted with cough, wheezing and failure to breath for 2 days.	Asthma	≥ 3
2.	Got an attack, failed to breath and died on administration of oxygen in hospital.	Asthma	≥ 3
3.	Admitted to heart institute with body swelling, developed headache, and later died.	Kidney failure/or heart failure	<3
4.	Developed an attack and passed on at home	Asthma	≥ 3
5.	She developed an attack and passed on at home.	Asthma	<3
6.	Developed respiratory problems and died	Asthma	<3
7.	Developed cough and fast breathing, had a high blood pressure, got a stroke, then passed on	stroke	≥ 3
8.	Suddenly developed an attack & died shortly afterwards.	Asthma	≥ 3
9.	Developed an attack and died shortly afterwards	Asthma	≥ 3
10.	Developed an asthmatic attack after 3weeks of discharge and passed away.	Asthma	≥ 3
11.	Developed a severe asthma attack at home and shortly passed away	Asthma	≥ 3
12.	Had body swelling and died	Heart failure.	<3
13.	Had progressively worsening of chest pain and difficulty in breathing and suddenly stopped breathing	Heart failure or cardiac cause	≥ 3
14.	Had no respiratory symptoms but developed abdominal distension and died on arrival in the hospital	Intestinal obstruction	≥ 3
15.	Suddenly got an attack and died afterwards	Asthma	<3
16.	Developed cough & fast breathing was rushed to a clinic where death occurred	Asthma	≥ 3
17.	Had recurrent anemia	Anemia	≥ 3

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