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Blood eosinophil count correlates with severity of respiratory failure in life-threatening asthma and predicts risk of subsequent exacerbations

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ABSTRACT

Background: An elevated blood eosinophil count when asthma is stable predicts exacerbations and therapeutic response to corticosteroids or biologics targeting eosinophils. Few studies have examined the prognostic value of blood eosinophils measured at exacerbation.

Aim: To elucidate the relationship between a spot blood eosinophil count--measured at the onset of a life-threatening asthma exacerbation--with indices of exacerbation severity and risk of subsequent exacerbations.

Methods: Real-world, retrospective review of all life-threatening asthma cases admitted at 4 public hospitals in Singapore between 2011-2015. We assessed the trends and correlations between blood eosinophil count on admission with arterial blood gas values, duration of mechanical ventilation, and risk of death, hypoxic ischemic encephalopathy or respiratory arrest. Risk of future exacerbations among survivors was modelled using Cox regression and survival curves.

Results: There were 376 index life-threatening exacerbations with median blood eosinophil count (5-95th percentiles) of $0.270 \times 10^9/L$ ($0-1.410 \times 10^9/L$). Arterial pH decreased and PCO_2 increased with increasing eosinophil count. Duration of mechanical ventilation and risk of death, hypoxic ischaemic

encephalopathy or respiratory arrest did not vary with eosinophils. Among 329 survivors who were followed-up over a median of 52 months, blood eosinophils $\geq 1.200 \times 10^9/L$ was associated with an increased hazard of emergency visits and/or admissions for asthma (hazard ratio 1.8, 95% confidence interval 1.1-2.9, $p=0.02$).

Conclusion: In this study of life-threatening asthma, we found that a spot blood eosinophil count correlates with severity of respiratory failure and predicts risk of subsequent exacerbations.

INTRODUCTION

Eosinophils are key inflammatory cells of “T2 high” asthma.¹ A blood eosinophil count is an easily-acquired biomarker that correlates reasonably well with sputum eosinophilia,²⁻⁴ and elevated blood eosinophils have been shown to predict future exacerbation risk⁵⁻⁸ as well as treatment response to corticosteroids and anti-IL-5, anti-IL-5-receptor-alpha or anti-IL-4 receptor alpha antibodies.⁹⁻¹⁷ Most studies have investigated blood eosinophils when asthma is in stable state but not during an exacerbation of asthma.¹⁸ Blood eosinophil count varies between exacerbation and stable-state,¹⁹⁻²¹ and the usefulness of measuring a spot blood eosinophil count during an exacerbation in relation to short-term outcome of the exacerbation as well as the long-term outcome of asthma is not known.

Life-threatening asthma exacerbations are the most serious events which may result in death.²²⁻²⁴ There is still a significant number of asthma deaths recorded worldwide (0.19 deaths per 100,000 in 2012) and improvements in asthma deaths have stalled in the past decade,²⁵ emphasising the need to better understand factors that can predict the severity of an exacerbation, particularly those that could lead to fatal or near-fatal respiratory failure. Autopsy studies have shown the presence of intense eosinophil inflammation in the lungs of patients dying in status asthmaticus,^{26, 27}

indicating that eosinophils are important pathogenetic cells that contribute to severity of an exacerbation. Because it is usually difficult to obtain lung specimens to evaluate the presence of eosinophils, we have turned to using the blood eosinophil count as a surrogate to assess the presence of airway eosinophils during an exacerbation of asthma.

Here, we conducted a retrospective multicentre national study of life-threatening asthma exacerbations treated in Singapore hospitals. We assessed the relationship of a spot blood eosinophil count measured at life-threatening asthma presentation with various indices of exacerbation severity, including arterial blood gas values, duration of mechanical ventilation, and risk of death, hypoxic ischemic encephalopathy or respiratory arrest. In addition, we evaluated whether a spot blood eosinophil count measured at the onset of life-threatening asthma was associated with risk of future exacerbations leading to hospitalization/emergency department visit in those who survived the episode.

METHODS

Study design

This study was a retrospective medical records review of adult (≥ 18 years old) life-threatening asthma admissions between January 2011 to December 2015 in four participating public hospitals in Singapore (Changi General Hospital, National University Hospital, Singapore General Hospital and Tan Tock Seng Hospital). Life-threatening asthma cases were identified from intensive care unit/high-dependency unit censuses at participating hospitals and defined according to the British Thoracic Society/Scottish Intercollegiate Guidelines Network²⁸ criteria, as an acute exacerbation of asthma with features or signs of severe respiratory failure (any one of peak expiratory flow $< 33\%$ best of predicted, $SpO_2 < 92\%$, arterial $PO_2 < 8$ kPa, normal arterial partial pressure of carbon dioxide [PCO_2], silent chest, cyanosis, poor respiratory effort, arrhythmia,

exhaustion, altered conscious level, hypotension), or raised arterial PCO₂ and/or requiring mechanical ventilation. Only the first (index) life-threatening exacerbation within the study period was included if a patient had experienced multiple life-threatening asthma admissions.

Variables and measurements

We collected data on age, demographics, smoking status, previous follow-up history, exacerbation history in the previous year, history of life-threatening asthma, onset of symptoms and any identified triggers. The following comorbidities were extracted from medical records: sinonasal disease, obstructive sleep apnea, gastroesophageal reflux disease, depression, anxiety, aspirin exacerbated respiratory disease, cardiac disease (including ischemic heart disease, valvular heart disease and arrhythmias) and diabetes mellitus. Treatment regimen before index life-threatening asthma exacerbation was classified according to Global Initiative for Asthma (GINA) 2018 [Step 1: as-needed short-acting beta2-agonist (SABA), Step 2: low-dose inhaled corticosteroids (ICS), Step 3: low-dose ICS+LABA (combined inhaled corticosteroids and long-acting beta2-agonist), Step 4: medium/high-dose ICS+LABA, Step 5: tiotropium, oral corticosteroids and biologics). ICS doses were expressed as fluticasone propionate equivalents.

Absolute blood eosinophil count (expressed as $\times 10^9$ cells/L) was obtained from first full blood count taken on admission. All participating hospitals used routine automated flow-cytometry methods for complete blood count analysis according to established quality control protocols. To quantify the severity of respiratory failure, arterial pH, PCO₂, bicarbonate and PO₂:FiO₂ ratio (defined as the ratio of arterial oxygen partial pressure to fractional inspired oxygen) were extracted from first arterial blood gas drawn during the admission.

We tracked the occurrence of asthma exacerbation requiring admission/emergency visit in survivors of the index life-threatening asthma exacerbation by questioning patients and cross-checking with discharge summaries and emergency department records. Each subject was followed up for at least 1 year.

Statistics

Data were expressed as number (%) for categorical data or median (25th-75th percentile) for other nonparametric variables. Previous analyses on blood eosinophils in asthma were limited by selection of arbitrary cutpoints, hence we used two unbiased statistical approaches. The first approach was to analyse eosinophil counts as a continuous nonparametric variable. Arterial pH and arterial PCO₂ were graphed against continuous values of eosinophil count using locally weighted scatterplot smoothing (Lowess) with a 5-smoothing-point window, and correlations were assessed with Spearman's test. The second approach was to analyse eosinophil counts according to tertiles, a method used by previous studies on blood or sputum eosinophil counts.^{6, 29} This approach enabled us to analyse relationships between three different ranges of eosinophil counts: the lowest tertile containing zero or low counts, the second tertile containing a range of clinically-important eosinophil count thresholds identified from previous asthma studies, and the third tertile containing values far exceeding normal physiologic ranges. To test for monotonic trends from lowest to highest tertile, one-way analysis of variance (ANOVA) with linear contrast analysis, the Jonckheere-Terpstra trend test or Linear-by-linear Analysis were used for normally distributed continuous data, nonparametric ordinal data or categorical data respectively.

We analysed the occurrence of exacerbations after surviving index life-threatening asthma exacerbation using Cox time-to-event analyses, with adjustment for potential confounding covariates of ICS dose and smoking status. Hazard ratios for risk of exacerbation were calculated for different eosinophil thresholds at 0.1 x 10⁹ cells/L increments.

All statistical analyses were performed using SPSS version 20 and graphs were constructed using Graphpad Prism version 8. P value <0.05 was taken as statistically significant.

Ethics

The study was granted waiver of informed consent by institutional review board (Singhealth Centralized IRB: 2016/2154).

RESULTS

Life-threatening asthma exacerbations

We recorded 376 patients presenting with index life-threatening asthma exacerbations between 2011-2015 for analysis (Figure 1). One hundred and fifty-four patients (41.0%) were male with a mean age of 55 years, of whom 88 (23.4%) were current smokers.

47 (12.5%) died during the index life-threatening asthma admission and 10 (2.7%) experienced hypoxic ischemic encephalopathy or cardiorespiratory arrest but survived. Median duration of mechanical ventilation was 2 days and median length of stay in intensive care/high-dependency was 3 days.

Blood eosinophil counts

The distribution of blood eosinophil counts on index admission for life-threatening asthma is shown in Figure 2. Median eosinophil count was 0.270×10^9 cells/L and the ranges for first, second and third eosinophil tertiles were $0-0.1 \times 10^9$ /L (n=135), $0.11-0.50 \times 10^9$ /L (n=116) and ≥ 0.51 cells $\times 10^9$ /L (n=125), respectively. Those in the highest eosinophil tertiles were more likely to be male, younger, current smokers, have no prior regular follow-up and only on SABA as required (GINA Step 1) (Table 1). With increasing eosinophil tertile, respiratory tract infection was less likely to be a

precipitant, and there was also a lower prevalence of comorbidities such as cardiac disease and diabetes. No significant associations were found between eosinophil count and exacerbations requiring emergency department visit or admissions in the year prior to the index life-threatening asthma exacerbation, probability of death/hypoxic ischaemic encephalopathy/respiratory arrest or duration on mechanical ventilation.

Blood eosinophils and arterial blood gas indices

Figure 3A and 3B show the relationship between pH and PCO₂ with blood eosinophils. There was a significant negative correlation between pH and eosinophils (Spearman $\rho = -0.857$, $p < 0.001$), and a significant positive correlation between PCO₂ and eosinophils (Spearman $\rho = 0.189$, $p < 0.001$). pH and PCO₂ values according are shown in Figures 3C and 3D for each eosinophil tertile. There was a significant trend of decreasing pH with increasing eosinophil tertile (Jonckheere-Terpstra trend test, $p < 0.001$). Similarly, there was a significant increasing trend of arterial PCO₂ with increasing eosinophil tertile (Jonckheere-Terpstra trend test, $p < 0.001$).

Arterial HCO₃ and PO₂:FiO₂ data were available for 371 and 245 patients respectively. There was no significant correlation between eosinophils with arterial bicarbonate (Spearman's $\rho = -0.037$, $p = 0.48$) or with PO₂:FiO₂ ratio (Spearman's $\rho = 0.023$, $p = 0.72$). Similarly, no significant trend was detected for bicarbonate or PO₂:FiO₂ ratio with increasing eosinophil tertile (Jonckheere-Terpstra trend test, $p = 0.63$ and $p = 0.86$ respectively).

Blood eosinophils and future exacerbations requiring emergency department visit or hospitalization

Median follow-up after surviving index life-threatening asthma ($n = 329$) was 52 months (interquartile range 37-69 months, min-max 14.5-87 months). 166 (50.5%) experienced a recurrent exacerbation leading to hospitalization or emergency department visit in the follow-up period, and median time to next exacerbation was 8.25 months (interquartile range 3.2-20 months). A nonlinear

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increase in exacerbation risk was observed with increasing blood eosinophil count (Figure 4A). Eosinophil counts up to about $0.9 \times 10^9/\text{L}$ were associated with a nonsignificant decreased risk of exacerbation (hazard ratios < 1.0). Further increases of eosinophils between $>0.9 \times 10^9/\text{L}$ and $<1.2 \times 10^9/\text{L}$ were associated with nonsignificant trend of increased exacerbation risk. The first occurrence of a significant increased risk of exacerbation was at an eosinophil count of 1.200×10^9 cells/L (hazard ratio 1.8, 95% confidence interval 1.1-2.9, $p=0.02$). At this eosinophil count threshold, there was increased cumulative probability of recurrent exacerbation leading to hospitalization or emergency room visit by survival curve analysis (Log-Rank $p=0.018$), as shown in Figure 4B.

Other analyses

We repeated the analyses using blood eosinophil count expressed as percentage (%) of total leukocyte count. Absolute and percentage eosinophil counts were highly correlated (Spearman's $\rho=0.960$, $p<0.001$). Similar to the analysis with absolute eosinophil count, significant negative correlation between pH and percentage eosinophil count (Spearman's $\rho=-0.199$, $p<0.001$) and significant positive correlation between PCO₂ and percentage eosinophil count (Spearman's $\rho=0.178$, $p=0.001$) were found. An eosinophil count threshold of $\geq 13\%$ was associated with increased hazard of exacerbation (hazard ratio 2.3, 95% CI 1.1-4.8, $p=0.02$).

DISCUSSION

In this largest study of life-threatening asthma to date, we found that a spot blood eosinophil count, measured when a patient presents to hospital for life-threatening asthma, correlates with severity of respiratory failure and predicts risk of subsequent exacerbations. An increase in eosinophil count was significantly associated with both a decrease in arterial pH and an increase in arterial PCO₂. Over a median follow-up of over 4 years, blood eosinophils $\geq 1.2 \times 10^9$ cells/L at index life-threatening asthma exacerbation was associated with shorter time to next

emergency department visit or hospitalization for asthma. Our study provides proof-of-concept of the measuring a biomarker during an exacerbation can provide useful prognostic information. Our results strikingly underscore that acute asthma exacerbations represent an excellent opportunity to phenoendotypes patients or identify treatable traits which can be potentially targeted to alter severity of the exacerbation itself and modify long-term disease trajectory beyond the exacerbation.

Most studies on blood eosinophils in asthma have been performed in cohorts with stable asthma, while the few studies which evaluated the role of blood eosinophils during exacerbation focused on non-life threatening exacerbations. A small pilot study from Japan (n=47) did not find any differences among patients hospitalized for asthma exacerbation in initial vital signs, requirement for ventilatory support or disposition between those with eosinophils $\geq 0.3 \times 10^9/\text{L}$ compared with those with eosinophils $< 0.3 \times 10^9/\text{L}$, but the study was underpowered.³⁰ A study of 1316 patients admitted with non-life threatening exacerbations reported that an eosinophil count of $\geq 0.4 \times 10^9$ cells/L was associated with a reduction in late readmission risk of 41% and a decrease in frequent late readmission of 63%.³¹ An important limitation in many of these studies is the arbitrary selection of eosinophil count thresholds which were presumably extrapolated from studies evaluating blood eosinophil count as a pharmacodynamic biomarker of response to biologics, for example, ≥ 0.150 or $0.300 \times 10^9/\text{L}$ for mepolizumab, $\geq 0.300 \times 10^9/\text{L}$ for benralizumab and $\geq 0.400 \times 10^9/\text{L}$ for reslizumab.^{9, 10, 32} However, it cannot simply be assumed that thresholds for pharmacodynamic response are the same as for disease prognostication. In contrast, our study examined the effect of blood eosinophil count as a continuum over a broad range without predefined thresholds. The relationship between eosinophil count and blood gas indices of pH and PCO_2 was continuous without an obvious cut-point, whereas we identified a threshold eosinophil count which was associated with increased risk of subsequent exacerbation. There was no association between blood eosinophil count and duration of mechanical ventilation or length of stay in intensive care/high dependency unit. This may be because arterial blood gas is an intermediate

outcome measure, whereas duration of mechanical ventilation and length of stay in intensive care/high dependency unit are dependent on many other factors which may not be directly related to illness severity, such as institutional factors (e.g. bed occupancy, availability of general ward beds) and practice variation in ventilator weaning, extubation and discharge from intensive care.

A host of factors may contribute to variability of blood eosinophil count, including heterogeneity of inflammatory phenotype (i.e. eosinophilic and non-eosinophilic phenotypes), prior use of and adherence to systemic or inhaled corticosteroids, diurnal variation, meals, exercise and smoking.³³ Despite this, few studies have controlled for these sources of variability when examining blood eosinophils. We lacked data on systemic steroid use and adherence to inhaled corticosteroid prior to presentation with life-threatening asthma, which are expected to suppress peripheral eosinophils. Nevertheless, this does not negate our finding that low blood eosinophils, either occurring spontaneously or due to suppression by prior exposure to systemic or inhaled steroids, is associated with better outcomes, whereas high or non-suppressed blood eosinophils is associated with worse outcomes.

Blood eosinophil count is a reasonably good surrogate marker for airway eosinophilia, with the caveat that there are subgroups of patients who demonstrate either isolated blood eosinophilia without sputum eosinophilia, or isolated sputum eosinophilia without blood eosinophilia.³⁴ A single raised blood eosinophil measurement is associated with persistently elevated counts on repeated measures,^{35, 36} and eosinophilic respiratory exacerbations portend a higher likelihood of subsequent eosinophilic exacerbation.³⁷ Taken together, these data suggest that high blood eosinophils could be taken as a biomarker of eosinophilic asthma, and by corollary a biomarker of response to treatments targeted at eosinophilic asthma. Our data demonstrated an obvious divergence of long-term disease trajectory at the threshold BEC of 1.2×10^9 cells/L, suggesting that this group may exhibit the severe eosinophilic phenotype characterised by frequent exacerbations.³⁸ This high threshold of 1.2×10^9

cells/L may be a reflection of the increase in IL-5 in the bone marrow to increase the terminal maturation of eosinophils into the blood stream as may occur during exacerbations. On the other hand, the absence of increased hazard of exacerbations at lower eosinophil thresholds might have been due to the common practice of prescribing ICS-containing regimens to life-threatening asthma patients who survive to discharge, which might mitigate the risk of subsequent exacerbations amongst those with non-severe eosinophilic asthma.

We have shown many correlations that all support the potential relevance of eosinophil count in life-threatening asthma, but this should not be misconstrued as an endorsement to substitute blood eosinophil count in place of arterial blood gas or other existing clinical assessments in triaging and managing these patients. Instead, the implication is that acute exacerbation represents an opportunity to phenoendotype patients or identify treatable traits so as to potentially alter acute outcomes and for secondary prevention of future exacerbations. Treatment options for acute exacerbation are currently limited, and there is an unmet need for precision treatment of asthma exacerbations, which are in turn heterogeneous with myriad clinicopathobiologic subtypes. Current precision treatment of asthma is based on phenoendotyping patients when stable, yet phenoendotyping patients at acute exacerbation is an unproven but potentially feasible alternative paradigm for asthma management. Emerging data indicate that biologics may modulate and reduce the severity of acute exacerbations.^{39, 40} Furthermore, a small, preliminary study found that benralizumab administered as a single dose at acute exacerbation at the emergency department can reduce the severity and rate of subsequent exacerbation.⁴¹ Future studies should investigate whether administering anti-eosinophil treatments at the onset of an eosinophilic asthma exacerbation has efficacy in reducing acute severity and/or modifying the long-term clinical course of disease, and whether treatment responders can be identified from a spot blood eosinophil count measured at exacerbation.

Our study has several limitations. The results are based on retrospective analysis and should be interpreted with caution. Nevertheless, the main variables used in this study (blood eosinophil count, arterial blood gas indices, death, exacerbations leading to healthcare utilization) are objective and unbiased measures even though they were collected retrospectively. Life-threatening asthma is relatively uncommon and asthma deaths are even rarer, making it challenging to conduct a prospective study with adequate sample size and power within a practical timeframe. We were unable to track exacerbations that were treated at non-participating hospitals. We did not extract important variables such as adherence, mechanical ventilation parameters, repeated eosinophil counts over time, discharge medications, or asthma severity in the recovery phase. Other biomarkers such as serum IgE or exhaled nitric oxide were not measured because these are not indicated in the acute management of life-threatening exacerbations. We were also unable to exclude pulmonary eosinophilic syndromes in the current dataset.

To conclude, we found that a spot blood eosinophil count, measured when a patient presents to hospital for life-threatening asthma, correlates with severity of respiratory failure and predicts risk of subsequent exacerbations.

CONFLICTS-OF-INTEREST

KFC has received honoraria for participating in Advisory Board meetings of GlaxoSmithKline, Astrazeneca, Novartis, Merck, Boehringer Ingelheim and Teva regarding treatments for asthma and chronic obstructive pulmonary disease and has also been remunerated for speaking engagements. MK has received speaking fees and honoraria paid through her employer (Singapore General Hospital) from Astrazeneca, GlaxoSmithKline and Sanofi. The other authors have no conflicts-of-interest to declare.

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FIGURE LEGENDS

Figure 1. Flow diagram of patients

Figure 2. Histogram of absolute blood eosinophil counts. Each bar represents a range of 0.1×10^9 cells/L.

Figure 3. Relationship between blood eosinophil count with arterial pH and PCO₂. Scatterplot of pH and PCO₂ against continuous blood eosinophil values with fitted Lowess smoothing curve (**A, B**), and by blood eosinophil count tertiles with median and interquartile range (**C, D**). P-values are shown for Spearmann test (**A, B**; correlation coefficient, rho, also displayed) and the Jonckheere-Terpstra trend test (**C,D**).

Figure 4. **A.** Hazard ratios (black solid line) and 95% confidence intervals (gray bands) for recurrent exacerbation leading to emergency room visit/hospitalization after surviving life-threatening asthma, at different blood eosinophil thresholds. Blood eosinophil counts were obtained at life-threatening asthma exacerbation. Hazard ratio of 1 is denoted by dashed black line. **B.** Cumulative probability of an asthma exacerbation at blood eosinophil threshold of 1.200×10^9 cells/L

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TABLES

Table 1. Patient characteristics according to blood eosinophil count tertiles.

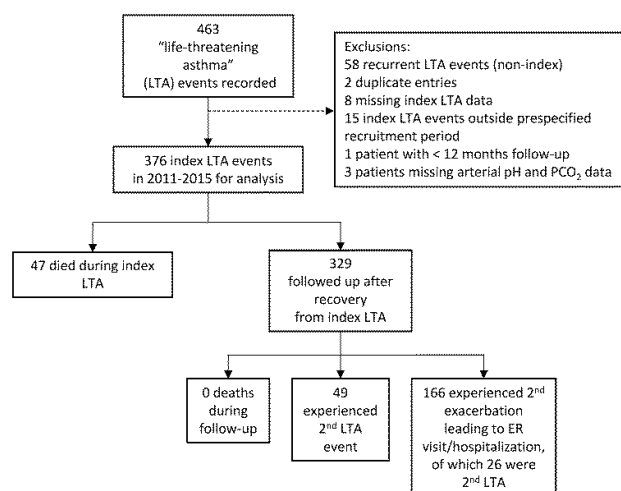
Variable	Entire cohort	Blood eosinophil count (x10 ⁹ cells/L)			p-value for linear trend
		Tertile 1	Tertile 2	Tertile 3	
		0-0.1	>0.1-0.5	>0.5	
n	376	135	116	125	
Sex					<0.001
Male	154 (41.0%)	39 (28.9%)	50 (43.1%)	65 (52.0%)	
Female	222 (59.0%)	96 (71.1%)	66 (56.9%)	60 (48.0%)	
Age (years)	55 ± 18	62 (45-72)	56 (40-68)	54 (38-64)	<0.001
Smoking status					0.005
Current smoker	88 (23.4%)	20 (14.8%)	29 (25.0%)	39 (31.2%)	
Former smoker	45 (12.0%)	18 (13.3%)	15 (12.9%)	12 (9.6%)	
Never smoker	243 (64.6%)	97 (71.9%)	72 (62.1%)	74 (59.2%)	
Regular follow-up prior to index					0.02
LTA					
Yes	318 (84.6%)	123 (91.1%)	94 (81.0%)	101 (80.8%)	
No	58 (15.4%)	12 (8.9%)	22 (19.0%)	24 (19.2%)	
Comorbidities					
Cardiac	56 (14.9%)	27 (20.0%)	17 (14.7%)	12 (9.6%)	0.02
Diabetes	59 (15.7%)	26 (19.3%)	21 (18.1%)	12 (9.6%)	0.03
Aspirin exacerbated respiratory disease	17 (4.5%)	8 (5.9%)	4 (3.4%)	5 (4.0%)	0.45
Anxiety	2 (0.5%)	0 (0.0%)	1 (0.9%)	1 (0.8%)	0.37
Sinonasal disease	46 (12.2%)	16 (11.9%)	11 (9.5%)	19 (15.2%)	0.42

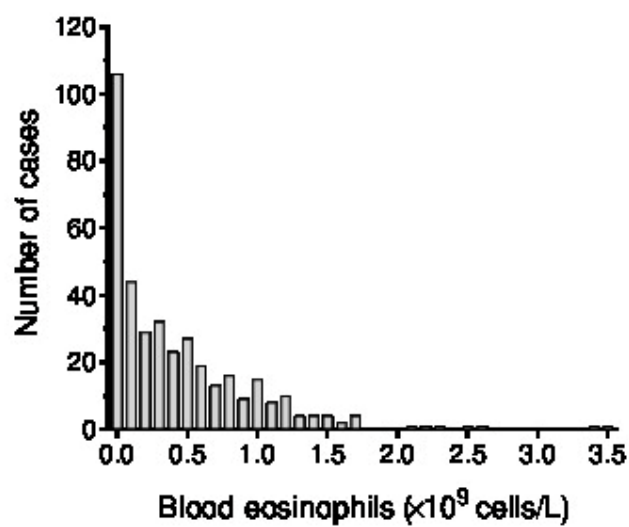
Obstructive sleep apnea	18 (4.8%)	7 (5.2%)	7 (6.0%)	4 (3.2%)	0.55
Gastroesophageal reflux disease	20 (5.3%)	11 (8.1%)	5 (4.3%)	4 (3.2%)	0.07
Depression	14 (3.7%)	6 (4.4%)	5 (4.3%)	3 (2.4%)	0.39
Number of LTA episodes in the past					0.20
0	312 (83.0%)	105 (77.8%)	103 (88.8%)	104 (83.0%)	
1	51 (13.6%)	22 (16.3%)	13 (11.2%)	16 (12.8%)	
≥2	13 (3.4%)	8 (5.9%)	0 (0.0%)	5 (4.2%)	
Number of ED visits and hospitalizations for asthma exacerbation in the past year					0.99
0	253 (67.3%)	89 (65.9%)	81 (69.8%)	83 (66.4%)	
1	64 (17.0%)	26 (19.3%)	15 (12.9%)	23 (18.4%)	
≥2	59 (15.7%)	29 (14.8%)	20 (17.3%)	19 (15.2%)	
GINA treatment step before index LTA					
Step 1	122 (32.4%)	32 (23.7%)	40 (34.5%)	50 (40.0%)	0.005
Step 2	53 (14.1%)	23 (17.0%)	18 (15.5%)	12 (9.6%)	0.09
Step 3	64 (17.0%)	26 (19.3%)	23 (19.8%)	15 (12.0%)	0.13
Step 4	111 (29.5%)	43 (31.9%)	26 (22.4%)	42 (33.6%)	0.79
Step 5	26 (6.9%)	11 (8.1%)	9 (7.8%)	6 (4.8%)	0.52
Onset					0.07
<6 hours	33 (8.8%)	6 (4.5%)	13 (11.2%)	14 (11.2%)	
6-24 hours	55 (14.7%)	19 (14.2%)	18 (15.5%)	18 (14.4%)	

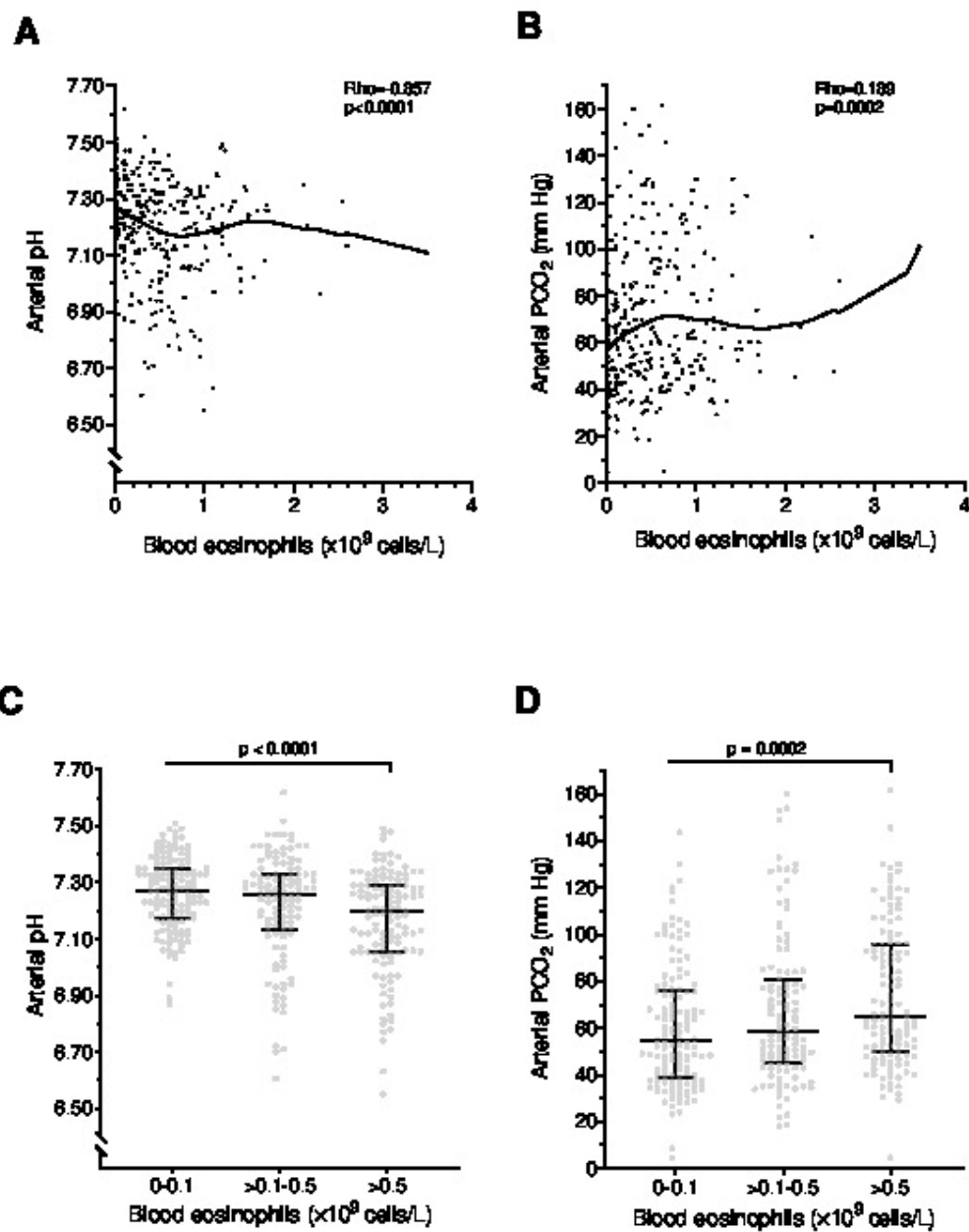
1-2 days	116 (30.9%)	38 (28.4%)	41 (35.3%)	37 (29.6%)	
>2 days	171 (45.6%)	71 (53.0%)	44 (37.9%)	56 (44.8%)	
Precipitant					
Allergen	7 (1.9%)	0 (0.0%)	4 (3.4%)	3 (2.4%)	0.14
Pneumonia	15 (4.0%)	8 (5.9%)	2 (1.7%)	5 (4.0%)	0.41
Irritants	14 (3.7%)	3 (2.2%)	5 (4.3%)	6 (4.8%)	0.27
Respiratory tract infection	220 (58.5%)	90 (66.7%)	69 (59.5%)	61 (48.8%)	0.004
Number of days on mechanical ventilation	2 (1-3)	2 (1-4)	2 (1-4)	2 (1-3)	0.10

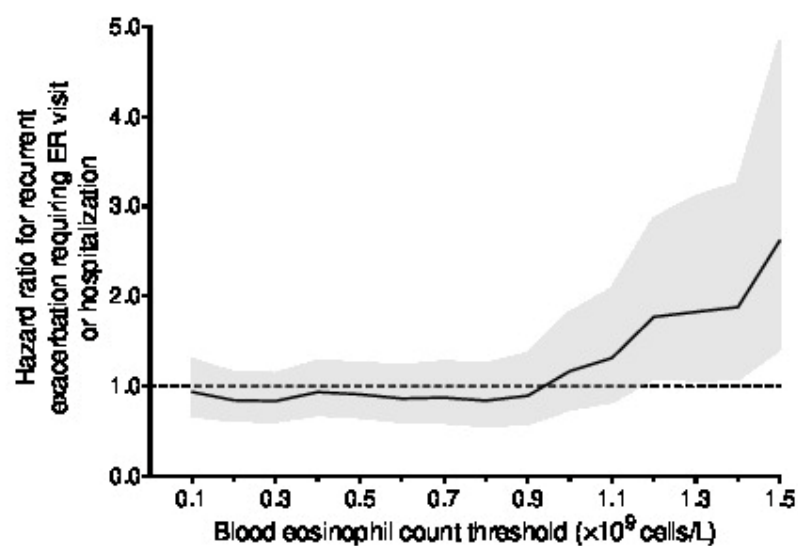
P-values are for test of monotonic trend with increasing blood eosinophil count tertile group.

LTA: Life-threatening asthma, GINA: Global Initiative for Asthma, ED emergency department.







A**B**