

Urinary leukotriene E4 is a biomarker for chronic rhinosinusitis associated with leukotriene dysregulation irrespective of aspirin sensitivity status

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The association between elevated urinary leukotriene E4 (uLTE4) and aspirin-exacerbated respiratory disease (AERD) has been well established, and recent work has described elevated uLTE4 in association with asthma, chronic rhinosinusitis (CRS), eosinophilic CRS (eCRS), nasal polyposis, and allergy.¹⁻³ The utility of uLTE4 as a noninvasive biomarker for AERD and eCRS has been examined previously. For AERD, sensitivity and specificity are 76% and 89%, respectively, at a cutoff value of 166 pg/mg creatinine (Cr).¹ The optimal cutoff point for diagnosis of eCRS (defined here as > 10 eosinophils per high-power field) was found to be 106 pg/mg Cr with sensitivity of 57% and specificity of 86%.³ Heretofore, biomarkers in diagnosis of allergic fungal rhinosinusitis (AFRS) have seen limited exploration, with diagnosis remaining largely clinical and definitive diagnosis dependent on surgery.⁴ Given the common presentation of AFRS patients with a phenotype of nasal polyps, analysis of uLTE4 in this population may provide useful information. In this retrospective review of patients who underwent measurement of random uLTE4, we sought to assess whether uLTE4 carried value in predicting comorbidities and CRS subtypes using a threshold lower than the criterion value for the diagnosis of AERD.

Patients were grouped into three cohorts based on prior work: high (> 166 pg/mg Cr), moderately elevated (106–165 pg/mg Cr), and normal (< 106 pg/mg Cr) uLTE4 levels. Clinical aspirin intolerance, asthma, allergy, AFRS, and nasal polyp status were recorded. Exclusion criteria were age < 18 years, contaminated or diluted uLTE4, and diagnosis of granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis. Using these criteria, 175 patients were included in the study population. Recorded diagnoses were made by the treating otolaryngologist in consultation with allergy physicians. uLTE4 values were obtained using the liquid chromatography–mass spectrometry (LC-MS) method developed at Mayo Medical Laboratories.

Of the 158 CRS subjects, there was no difference in revision surgery rates between the normal-, moderately elevated-, and high-uLTE4 cohorts ($p = 0.59$). Patients in the “high” and “moderately elevated” groups were significantly more likely to have asthma and nasal polyps than those in the normal-uLTE4 group (Table 1). There was no significant difference in allergy or AFRS prevalence between these groups (Table 1). However, when comparing uLTE4 values in AFRS versus non-AFRS patients, uLTE4 was significantly lower in AFRS ($p = 0.049$) (Figure 1A). As expected, patients in the highest group were significantly more likely to have clinical diagnosis of AERD (Table 1). Patients in the moderately elevated- and high-uLTE4 group were significantly more likely to fall into the category of eCRS (Figure 1B).

TABLE 1. Patients’ demographic and clinical characteristics

Characteristic	Total cohort	uLTE4 group (pg/mg creatinine)			<i>p</i>
		<106	106 ≤ x < 166	≥166	
Number within group, n	175	118	23	34	
Age (years), mean ± SD	49.5 ± 15.8	49.3 ± 15.0	48.6 ± 17.6	50.8 ± 17.2	0.85
Male, n (%)	81 (46%)	58 (49%)	8 (35%)	15 (44%)	0.43
Female, n (%)	94 (54%)	60 (51%)	15 (65%)	19 (56%)	
Asthma, n (%)	120 (69%)	71 (60%)	16 (70%)	33 (97%)	<0.01
Allergy, n (%)	141 (81%)	91 (77%)	22 (96%)	28 (82%)	0.11
Chronic rhinosinusitis, n (%)	158 (90%)	101 (86%)	23 (100%)	34 (100%)	0.01
Nasal polyps, n (%)	120 (69%)	69 (58%)	18 (78%)	33 (97%)	<0.01
Aspirin-exacerbated respiratory disease, n (%)	36 (21%)	7 (6%)	4 (17%)	25 (73%)	<0.01
Allergic fungal rhinosinusitis, n (%)	20 (11%)	17 (14%)	2 (9%)	1 (3%)	0.16
Revision surgery, n (%)	142 (81%)	89 (75%)	21 (91%)	32 (94%)	0.02
uLTE4 level (pg/mg creatinine), mean ± SD	124.2 ± 132.3	58.9 ± 23.8	132.4 ± 18.4	345 ± 155.9	<0.01

Abbreviations: HPF, high-power field; SD, standard deviation; uLTE4, urinary leukotriene E4.
p values determined using ANOVA for continuous variables or chi-square test for categorical variables.

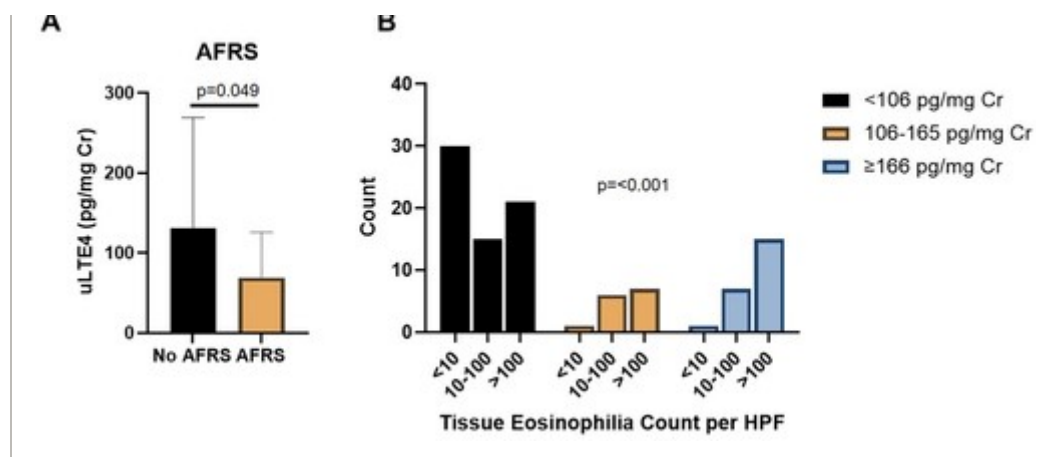


FIGURE 1

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(A) Comparison of urinary leukotriene E4 (uLTE4) values among patients with and without allergic fungal rhinosinusitis (AFRS). Central tendencies are displayed as means with standard deviations. (B) Bar graph displaying frequency of patients within each urinary leukotriene group by tissue eosinophil count per high-power field (HPF)

Increased prevalence of eCRS within the moderately elevated-uLTE4 group provides further support for the prior reported cutoff of 106 pg/mg Cr uLTE4³ as predictive for eCRS, reinforcing that eCRS may have a leukotriene-associated component in some patients.⁵ Patients in the moderately elevated-uLTE4 group were more likely to have asthma, which may guide suspicion for this comorbidity. In contrast to Santarelli et al.,² significance of allergy with elevated uLTE4 was not found. This could be related to our analysis of allergy as a subgroup in itself, whereas Santarelli et al. performed analyses on patients with CRS and comorbid allergy.

Unique to this study and previously unreported is the role of uLTE4 in AFRS patients. Significantly lower average uLTE4 in AFRS patients suggests that leukotriene metabolism is not a substantial inflammatory mechanism in AFRS. Alternative mechanisms in AFRS may involve IgE mediation of disease.⁶ uLTE4 may have some utility in differentiating AFRS from other patients with CRS with nasal polyposis (CRSwNP) phenotype. The current study was limited to 20 AFRS patients, and a larger analysis would be helpful in clarifying the clinical significance of uLTE4 in this patient population.

This study was limited by the nature of the patient population examined. Patients were selected retrospectively based on receiving an uLTE4 test, potentially selecting for patients more likely to present with AERD-like conditions.

In summary, while patients with uLTE4 levels ≥166 pg/mg Cr demonstrate phenotypic features classic of AERD, even those with moderately elevated uLTE4 (106–165 pg/mg Cr) were more likely to have CRS, polyps, asthma, and tissue eosinophilia. Patients with moderately elevated uLTE4 may not demonstrate aspirin intolerance clinically but share similarities to AERD in leukotriene pathway dysregulation. Therefore, cutoff of ≥106 pg/mg

Cr for uLTE4 may reflect an endotype of leukotriene dysregulation, with this subtype of CRS patients potentially benefitting from treatment classically tailored to AERD patients. In contrast, uLTE4 levels are significantly lower in AFRS patients, possibly relating to fundamental differences in pathogenesis. Further studies involving prospective populations will be essential for validating the role of uLTE4 in clinical diagnosis of CRS subtypes.

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None.

CONFLICTS OF INTEREST

None.

FINANCIAL DISCLOSURES

None.

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