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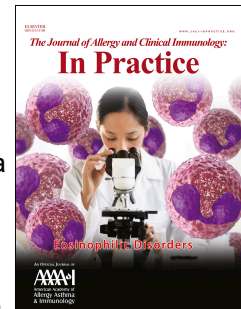
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**Predicting Outcomes of Baked Egg and Baked Milk Oral Food Challenges by
Using a Ratio of Food-Specific IgE to Total IgE**

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24 **Clinical Implications (35/40):** The Ratio of specific IgE to total IgE for egg white and milk
25 were predictive of outcomes of baked egg and baked milk challenges, respectively; however, the
26 Ratio was not more predictive than sIgE alone.

27

The prevalence of food allergy (FA) is increasing, with hen's egg and cow's milk allergies the most common in the pediatric population.(1) However, the majority of egg- and milk-allergic individuals tolerate baked goods containing egg and milk, respectively.(2) Consumption of baked forms of these foods improves nutrition, social inclusion, quality of life, and may accelerate resolution of egg and milk allergy.(2)

Oral food challenges (OFCs) are time consuming, resource intensive, and involve risk of severe reaction.(3, 4) Along with clinical history, specific IgE (sIgE) levels and skin prick testing (SPT) guide clinicians in diagnosing IgE-mediated FA, and are used when considering an OFC. Total IgE (tIgE) is often obtained with sIgE. Prior studies have evaluated the ratio of sIgE to tIgE ("the Ratio") in predicting OFC outcomes, with varied results.(5, 6) The value of the Ratio in evaluating baked egg and baked milk OFCs has not been previously been assessed. The objectives of this study were to 1) compare pre-challenge Ratio values to post-challenge outcomes for baked egg and baked milk and 2) determine if the Ratio better predicts the outcome of OFCs compared to sIgE alone.

With the approval of the Boston Children's Hospital's IRB, we retrospectively reviewed medical records of all OFCs to baked egg and baked milk at our institution from 2010-2016. Patients, aged 1-18 years, were included if they had a clinical history (eg. hives, wheezing, vomiting, hypotension within 2 hours of ingestion) and/or testing consistent with IgE-mediated FA (sIgE ≥ 0.35 kU/L) and underwent supervised baked egg and/or baked milk OFC. sIgE and tIgE levels were obtained within 12 months prior to OFC. The Ratio, (sIgE/tIgE)x100, was calculated for all patients. Due to inability to calculate a ratio without a detectable sIgE level, patients with undetectable sIgE were excluded. Open OFCs were performed with parental consent and/or patient assent as appropriate. A negative OFC was defined as consumption of the

entire prescribed amount of food protein without reaction. For positive OFCs, the reaction severity was defined based on the World Allergy Organization definition.⁽⁷⁾ A total of 253 open, physician-supervised baked egg and baked milk OFCs were analyzed.

Demographic characteristics are presented in Table 1 and highlighted by a median age of 8 years and 70% male. Of the OFCs, 77.5% were negative, (71.7% for baked egg, 88.5% for baked milk). Comparisons of sIgE and Ratio values in negative and positive challenges are presented in Figure 1A. For baked egg OFCs, median Ratio for egg white was 1.19% (IQR 0.48-2.42) in positive challenges versus 0.71% (IQR 0.24-1.79) in negative challenges ($p=0.02$). In baked egg OFCs, median Ratio for ovomucoid was 0.50% (IQR 0.24-1.41) in positive challenges versus 0.44% (IQR 0.16-1.10) in negative challenges ($p=0.47$). For baked milk OFCs, median Ratio for milk was 3.68% (IQR 1.09-9.73) in positive challenges versus 0.75% (IQR 0.32-2.64) in negative challenges ($p=0.02$). Predictive performance of the Ratio was calculated at multiple decision points for egg white, ovomucoid, and milk as presented in Table E1.

Positive OFC reactions were primarily Grade 1 or Grade 2 (98%) in severity, with only one Grade 3 reaction. Only 4 challenges to baked egg and 4 challenges to baked milk required treatment with epinephrine. The Ratio was not a significant predictor of severity of reaction ($p=0.20$ for egg white, $p=0.36$ for ovomucoid, $p=0.33$ for milk).

To compare the predictive value of the Ratio to sIgE alone, receiver operator characteristic (ROC) curves were generated (Figure 1B). The Ratio did not perform better than sIgE alone in predicting OFC outcome for egg white (0.62 versus 0.68, $p=0.24$), ovomucoid (0.54 versus 0.58, $p=0.55$), or milk (0.73 versus 0.69, $p=0.70$).

This is the first assessment of the Ratio as a predictor of the outcome of baked egg and baked milk OFCs. Although the Ratio for positive OFCs was significantly higher than for

negative OFCs, analysis of ROC curves did not show the Ratio was a superior predictor of OFC outcome compared with sIgE alone.

The Ratio has been studied as a predictor of outcomes for OFCs to other foods including unbaked egg and milk. Gupta et al. evaluated OFCs and divided foods into persistent food allergens (tree nut, peanut, shellfish, and seeds) and less persistent food allergens (milk, soy, wheat, and egg).(5) In that study, the Ratio was a better predictor of OFC outcome than sIgE, but the trend was driven by persistent food allergens.(5) The Ratio for less persistent food allergens (including milk and egg) was not superior to sIgE alone in predicting OFC outcome.(5) Similarly, Mehl et al. reported significant correlation with the Ratio and OFC outcome for unbaked milk and egg; however, the Ratio was not more accurate than sIgE alone.(6)

In the current food allergy practice parameter, measuring tIgE is not recommended.(8) Although tIgE is increased in many patients with food allergy, there is insufficient evidence to support the use of tIgE in diagnosing food allergy.(8) tIgE costs \$54 at our institution, and around \$100 at commercial labs. Avoiding sending potentially unnecessary tIgE tests could be a cost-effective measure.

Our study was performed at a single pediatric academic institution, which may restrict generalizability. Furthermore, only patients with an obtained and detectable sIgE and tIgE were included, thus excluding some challenges with incomplete data. While we evaluated a relatively large number of OFCs; our lack of significant difference between ROC curves may have been related to sample size. Although IgE testing was obtained within one year prior to challenge, these values may change over that period biasing our findings. We did not assess if the patients subsequently underwent OFC to unbaked milk or egg, as that was beyond the scope of the study.

In summary, the Ratio was not a better predictor than sIgE alone. Although there were significant differences among the Ratio values for positive and negative OFCs, ROC curves demonstrated that the Ratio was not superior to sIgE alone. Based on our findings, we do not recommend using the Ratio or obtaining a tIgE level when considering OFCs to baked egg or baked milk.

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Figure Legend**Figure 1:**

A. Differences between median specific IgE (sIgE) and median Ratio (sIgE / Total IgE x 100) for different tests prior to baked egg and baked milk challenges. Challenges resulting in a negative, no reaction, outcome (diagonal fill) are compared to those with a positive, yes reaction, outcome (solid fill). Differences in the distribution of the sIgEs and Ratios between the negative and positive outcomes were assessed with the Wilcoxon rank-sum test.

B. Receiver operator characteristic (ROC) curves for the sIgE test compared with the Ratio test. There was no statistical difference between areas under the curves (AUCs) of these two tests for any of the challenges.

Table 1: Demographics of children undergoing challenge to baked egg or baked milk

Characteristic	Baked Egg (n=166)	Baked Milk (n=87)
Age (years), Mean $\pm$ SD	8.0 $\pm$ 3.9	8.8 $\pm$ 3.9
Male Sex, n (%)	118 (71.1%)	60 (69.0%)
History of Asthma, n (%)	82 (49.4%)	46 (54.1%)
OFC Outcome		
Passed	119 (71.7%)	77 (88.5%)
Failed	47 (28.3%)	10 (11.5%)
Total IgE (unit/mL), Median [IQR]	407 [189-1023]	256 [120-739]
Specific IgE (kU/L), Median [IQR]		
Egg white (n=166)	3.1 [1.5-7.2]	---
Ovomucoid (n=115)	1.4 [0.9-3.7]	---
Milk (n=87)	---	2.6 [1.2-7.9]

SD: standard deviation, OFC: oral food challenge, IQR: interquartile range

Table E1: Sensitivity and Specificity of various potential decision points for the ratio

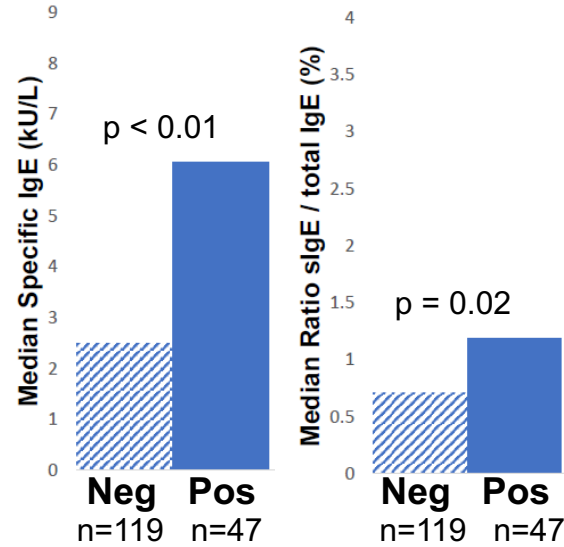
	Potential decision points for the ratio				
	0.5%	1.0%	1.5%	2.0%	2.5%
Egg White					
Sensitivity (%)	74	55	43	36	23
Specificity (%)	40	60	70	78	83
PPV (%)	33	35	36	40	35
NPV (%)	80	77	75	76	73
Ovomucoid					
Sensitivity (%)	50	36	22	11	8
Specificity (%)	51	75	78	86	91
PPV (%)	32	39	32	27	30
NPV (%)	69	72	69	68	69
Milk					
Sensitivity (%)	90	80	70	60	50
Specificity (%)	36	58	65	69	74
PPV (%)	16	20	21	20	20
NPV (%)	97	96	94	93	92

PPV: Positive Predictive Value, NPV: Negative Predictive Value

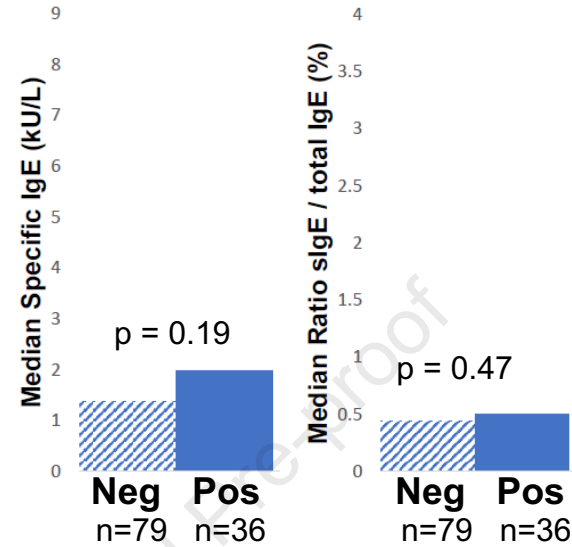
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Baked Egg Challenges

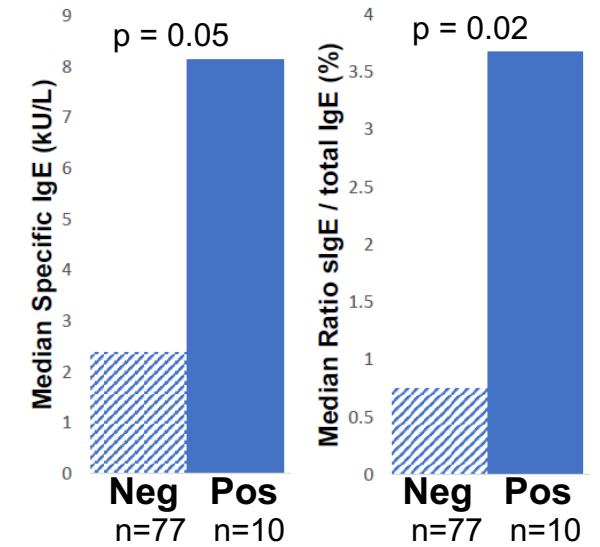
(egg white IgE)

**Baked Egg Challenges**

(ovomucoid IgE)

**Baked Milk Challenges**

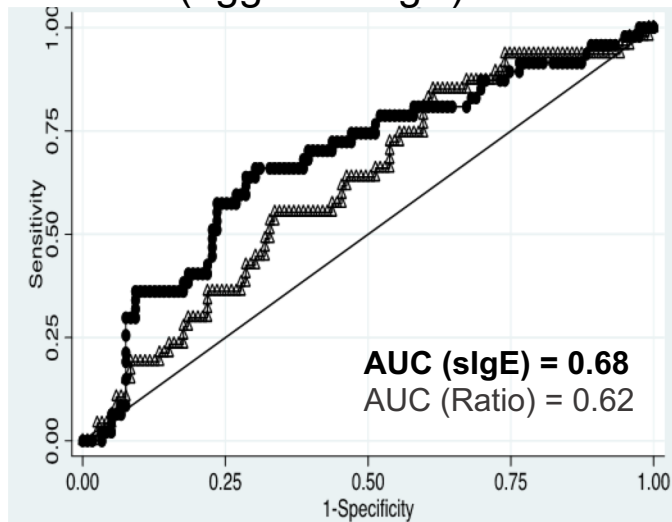
(milk IgE)



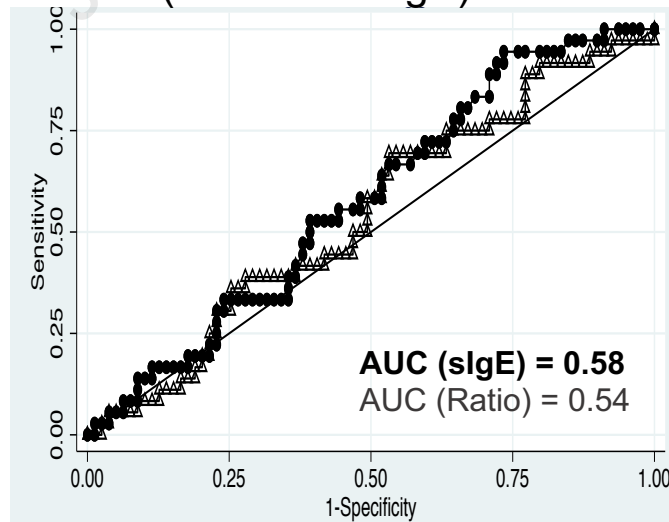
B

Baked Egg Challenges

(egg white IgE)

**Baked Egg Challenges**

(ovomucoid IgE)

**Baked Milk Challenges**

(milk IgE)

