

Correspondence

Life-threatening anaphylaxis to peanut — impossible to predict?

To the Editor:

Anxiety over the potential for severe reactions is one of the main drivers of impaired quality of life in patients with food allergies and in their families. The factors and mechanisms responsible for clinical reactivity may differ from those that affect disease severity, and it is likely that the potential biomarkers of each will also differ. The former are best addressed in population-based studies, preferably among peanut-sensitized individuals, to allow clear differentiation between those who are sensitized but tolerant from those who have a true allergy. For peanut allergy, quantification of allergen-specific IgE (by both measurement of serum level and skin prick testing) and the basophil activation test (BAT) can help identify those with true clinical reactivity.¹ However, the question of severity and prediction of future risk is best addressed among those with *confirmed* clinical peanut allergy.

Santos et al¹ recently reported that in children aged 5 to 6 years who were participating in the Learning Early about Peanut Allergy (LEAP) and Peanut Allergy Sensitization studies, the BAT was able to identify individuals with severe life-threatening anaphylaxis reactions at peanut challenge with high

specificity and high sensitivity. In contrast to the majority of other studies,² the study by Santos et al¹ found that skin prick test result and level of specific IgE to peanut were also predictive of severity with high specificity and sensitivity.

During subsequent review of the data, it became apparent that the severity analyses included patients without peanut allergy in the “nonsevere” group. In fact, the nonsevere group of 532 children included 457 patients (86%) who did not react at challenge, including 368 (81%) who showed no evidence of IgE sensitization to peanut. This could result in a significant overestimation of the specificity of predictive biomarkers. We therefore undertook a reanalysis of the study data, which are freely available at the web address www.itntrialshare.org (something we commend the authors for). When we included only those patients who reacted at challenge (ie, those with confirmed clinical allergy), we found the value obtained for the area under the receiver operator characteristic curve diagnostic characteristic to be significantly lower than those reported in the original analysis (Fig 1). Using the same cutoffs as those identified by Santos et al,¹ the inclusion of nonreactors in the original analysis significantly overestimates the specificity of the biomarkers to predict life-threatening reactions (Table 1). For example, although the BAT continued to outperform the other biomarkers, excluding nonreactive patients

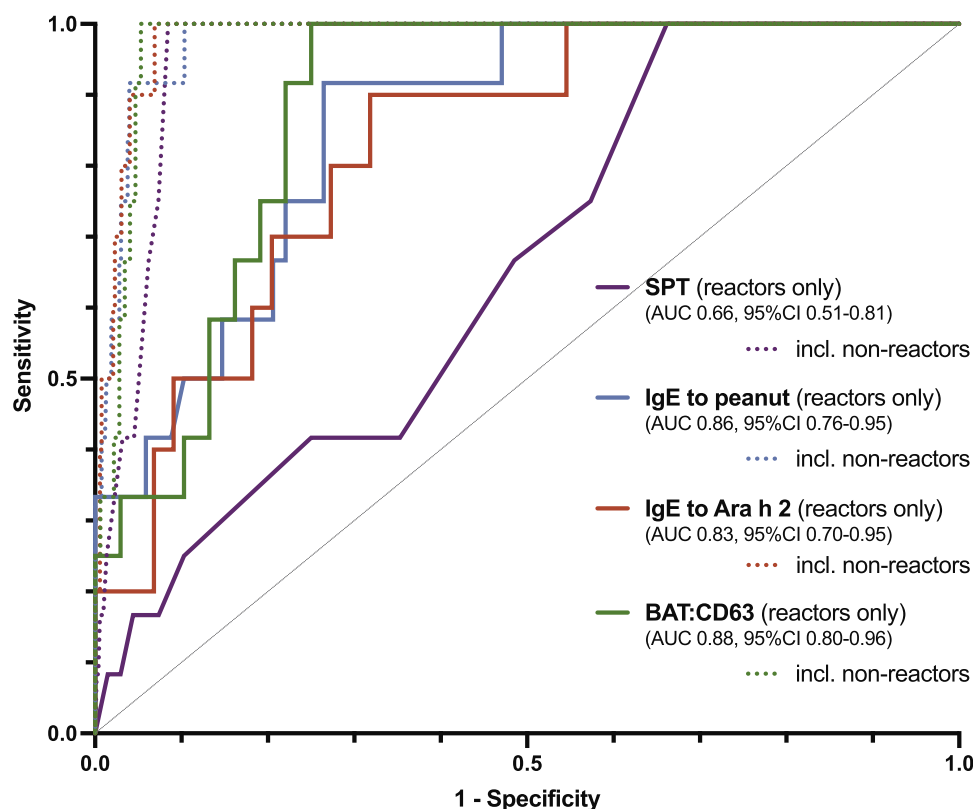


FIG 1. Receiver operating characteristic curve for the BAT and other biomarkers to identify those subjects in the LEAP and Peanut Allergy Sensitization cohorts who were at high-risk of developing severe life-threatening reactions during food challenge (according to the Common Terminology Criteria for Adverse Events score). Bold lines represent reanalysis of reactors only; dashed lines represent the original analysis, which included children who were not allergic to peanut at food challenge. *AUC*, Area under the receiver operating curve with 95% CIs; *SPT*, skin prick test.

TABLE I. Impact of including nonreactor patients when evaluating the diagnostic utility of different biomarkers to predicting the occurrence of life-threatening reactions to peanut in the LEAP and Peanut Allergy Sensitization studies

Parameter	Diagnostic cutoff		AUC	Sensitivity (%)	Specificity (%)	LR
BAT (% CD63 basophils)	48	Incl nonreactors	0.98	100 (100-100)	97 (95-98)	33.3
		Reactors only	0.88	100 (76-100)	75 (64 to 0.84)	4
IgE to Ara h 2	1.4 kU/L	Incl nonreactors	0.98	100 (100-100)	93 (91-98)	14.3
		Reactors only	0.83	100 (73-100)	46 (32-60)	1.8
IgE to peanut	5 kU/L	Incl nonreactors	0.98	100 (100-100)	90 (87-98)	10
		Reactors only	0.86	100 (76-100)	53 (41-64)	2.1
Peanut SPT	8mm	Incl nonreactors	0.96	100 (100-100)	92 (89-94)	12.5
		Reactors only	0.66	100 (76 to 100)	34 (24-46)	1.5

AUC, Area under the receiver operating characteristic curve; Incl, including; LR, likelihood ratio; SPT, skin prick test.

Diagnostic cutoffs as reported by Santos et al.¹

lowered the likelihood ratio from 33 to 4 (a “good” likelihood ratio is typically quoted as ≥ 10).

In summary, the model used by Santos et al.¹ may be predictive of life-threatening reactions in children aged 5 to 6 years whose peanut allergy status is *unknown* - and in whom the vast majority - 86% in the combined cohort of Santos et al - are *not* allergic to peanut. However, the more common clinical scenario is one in which clinicians wish to predict the risk of reaction in patients with *known* allergy or at least with IgE-sensitization to peanut. For this analysis, one must exclude nonreactors, as the research question is whether these tests predict severity rather than clinical reactivity. Unfortunately, others have also undertaken similar misleading analyses (including nonreactors as “nonsevere” reactors), resulting in a similar overestimation of predictive utility.³ Notably, although IgE to Ara h 2 had better diagnostic utility in differentiating individuals with true peanut allergy from those with asymptomatic sensitization,¹ among patients with true peanut allergy it was not significantly better than specific IgE to (whole) peanut at predicting severity, which is consistent with other reports.^{2,4}

We therefore urge caution when extrapolating the data presented in this and other reports^{1,3} to clinical practice. Individuals with peanut allergy and a history of anaphylaxis do tend to have higher levels of IgE sensitization than those without² peanut allergy; however, the overlap is so extensive that in practice, these biomarkers are not helpful in predicting life-threatening allergic reactions. The risk is that patients with low levels of specific IgE might be falsely reassured that

they cannot have anaphylaxis, whereas those with high levels are wrongly counseled that they are at high risk of severe reactions. More work is needed to address this very significant knowledge gap, as was recently acknowledged in an expert consensus report.⁵

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