

Letter to the Editor

Validation of the Cork-Southampton Food Challenge Outcome Calculator in a Canadian sample

To the Editor:

We have previously demonstrated the clinical usefulness and diagnostic value of a calculator (the Cork-Southampton calculator) using routinely collected data in predicting oral food challenge (OFC) outcomes in a diverse sample of children in an Irish pediatric allergy clinic.¹ The calculator consists of 6 clinical factors: skin prick test responses, serum specific IgE levels, total IgE levels minus serum-specific IgE levels, symptoms, sex, and age. The probability scores generated by the calculator range from 0 (no allergy) to 1.0 (allergy), corresponding to a 0% to 100% chance of a positive or negative outcome. Our model showed an advantage in clinical prediction compared with serum specific IgE levels only, skin prick test responses only, and serum specific IgE levels plus skin prick test responses (92% accuracy vs 57% to 81%, respectively).¹

We have examined the wider utility of the calculator in a different clinical setting, with different criteria for selection of children for challenge, different challenge protocols, and different food preparations. In addition, we now report likelihood ratios (LRs), and in response to correspondence on our previous article, we have developed a prechallenge probability level at, above, or below which a clinician can manage a patient's ongoing food allergy care without recourse to OFCs.

The retrospectively collected dataset consisted of children in Montreal, Quebec, Canada, who had undergone food challenges for peanut, milk, or egg in a tertiary pediatric allergy clinic (Table I). The mean age of the sample ($n = 46$) was 7.4 years (Table I). The cases were chosen consecutively from existing clinic datasets. Analyses were carried out for all 6 clinical factors and for skin prick test responses and serum specific IgE measurements only (separately and together). Analysis was performed (by A.D.) blind to OFC outcomes.

Seventeen patients underwent food challenge for peanut, 9 for egg, and 20 for milk. There were 8 positive and 9 negative results for peanut, 1 positive and 8 negative results for egg, and 6 positive and 14 negative results for milk. Egg OFCs included raw, baked, and meringue egg.

In total, 42 (91%) of 46 OFC outcomes were correctly predicted based on prechallenge data. In the case of peanut OFCs, the calculator correctly predicted 15 of 17 outcomes, with all 8 positive and 7 of 9 negative results correctly predicted. The single positive OFC result for egg was correctly predicted, as were 7 (88%) of 8 negative outcomes. Milk OFC outcomes were predicted correctly in 19 (95%) of 20 cases (all 6 positive and 13 of 14 negative milk OFC results). The only incorrect prediction for milk OFC outcomes had an intermediate probability of 0.6 (and the result was negative).

The LRs, probabilities, and CIs for the full dataset and for SPT responses and specific IgE levels only are reported in Table II. The LR is the likelihood of a given result in a clinically allergic child as a ratio of the likelihood of a similar result in a healthy child. LRs can range from 0 to infinity. Findings with LRs of greater than 1 argue for the diagnosis of interest; the bigger the number, the greater the likelihood of the disease. Findings with LRs that lie

TABLE I. Clinical characteristics of the sample ($n = 46$)

	No.	Percent
Male/female sex	34/12	74/26
Skin or oral or gastrointestinal or upper respiratory tract symptoms only*	24	52
Upper respiratory tract and gastrointestinal or 2 systems*	15	33
Lower respiratory tract or 3 systems*	6	13
Cardiovascular or 4 systems*	1	2

	Peanut ($n = 17$)	Milk ($n = 20$)	Egg ($n = 9$)
Age (y), mean (SD)	7.4 (4.4)	5.8 (3.9)	6.2 (4.1)
SPT wheal (mm), mean (SD)	4.2 (3.0)	5.5 (3.8)	4.8 (3.6)
Specific IgE (kU _A /L), mean (SD)	3.5 (2.0)	3.5 (1.8)	1.7 (1.1)
Total IgE (kU/L), mean (SD)	1609 (856)	1390 (655)	3000 (1876)

*There were no significant differences ($P > .05$) in the number and severity of symptoms experienced among the 3 foods.

between 0 and 1 argue against the diagnosis; the closer the LR is to 0, the less likely the disease.

There was very little percentage difference (0.3%) in the LRs for SPT responses or specific IgE levels separately, and therefore we have reported the combined accuracy of SPT responses and specific IgE levels.

The positive LR for the full model (skin prick test responses, serum specific IgE levels, total IgE levels, symptoms, sex, and age) was 99.0 (95% CI, 12.75-684), and the negative LR was 0.21 (95% CI, 0.1-0.52). This means that 10 in every 10 cases will receive a correct positive diagnosis and 8 in every 10 cases will receive a correct negative diagnosis using the full model. This can be compared with SPT responses and specific IgE levels only, which allow for correct diagnosis of 10 in every 14 positive cases and 10 in every 13 negative cases.

Using the output from our analyses, we constructed a nomogram (Fig 1), which displays the probability that a patient is allergic to the food being used for the OFC. From Fig 1, a patient with a pretest probability of 80.00% and an LR of 1 would have an 80.00% chance of a positive diagnosis, a patient with a pretest probability of 45% and an LR of 0.02 would have a 26% chance of a positive diagnosis, and a patient with a pretest probability of 5% and an LR of 0.2 would have a 98% chance of a negative diagnosis. Put simply, it is possible to use the pretest probability of an outcome based on clinical experience or accepted decision points (eg, 80% severe symptoms [ie, cardiovascular], together with SPTs of 8 and specific IgE levels of 12) and the LR. A line can be drawn from this pretest probability through the LR to identify the posttest probability. However, the calculator, which will be available online soon, can perform this and other tasks within seconds.

For the present dataset, our results show the level of prechallenge probability at which a clinician could proceed to food allergy management without OFCs as greater than 70% (thick green line) for likely positive OFC results and less than 40% for likely negative OFC results (thick red line). The yellow line represents the intermediate area around a probability of 50%, where false-positive and false-negative results are most likely to lie (40% to 69%). Only 17% of our cases fell within this middle third.

TABLE II. LR, probabilities, and 95% CIs for the overall sample

	Positive LR	Estimated 95% CI	Posterior probability (odds)	Estimated 95% CI
Positive test result: All model variables included	99.00 (∞)	2.75-684.00	100% (703701.60)	66% to 100%
Negative test result: All model variables included	0.21	0.10-0.52	13% (0.10)	7% to 27%
Positive test result: SPT response and specific IgE level only	3.91	1.46-10.00	73% (2.80)	51% to 88%
Negative test result: SPT response and specific IgE level only	0.49	0.29-0.86	26% (0.30)	17% to 38%

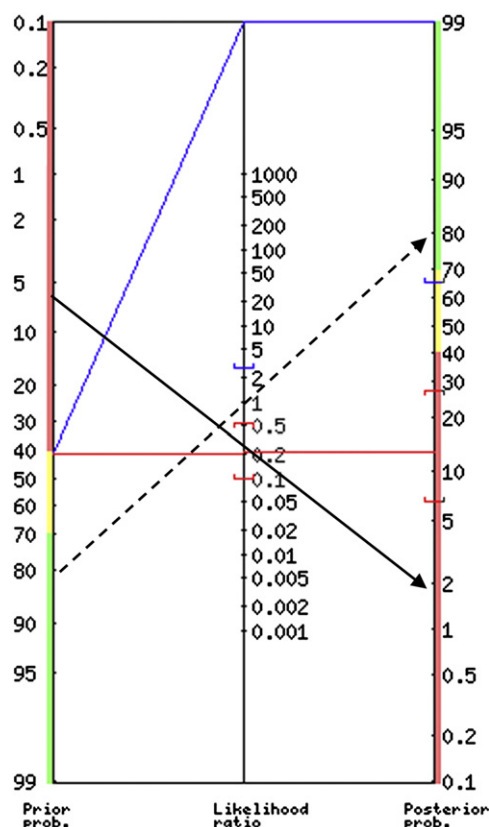


FIG 1. The nomogram displays the probability that a patient would have a positive OFC result with milk, egg, or peanut. *Green section*, OFC result likely positive (>70.00%); *red section*, OFC result likely negative (<40.00%); *yellow section*, intermediate probability (40.00% to 69.00%). This nomogram is dependent on the pretest probability shown by using the calculator and the LR. The red horizontal line crossing the center point delineates between possible positive and negative diagnosis based on numeric values used in the nomogram. The blue line represents the receiver operating characteristic curve. Therefore a patient with a pretest probability of 80.00% and an LR of 1 would have an 80.00% chance of a positive diagnosis (*broken arrow*), and a patient with a pretest probability of 5.00% and an LR of 0.2 would have only a 2.00% chance of a positive diagnosis (*unbroken arrow*).

We have demonstrated the international translatability of the Cork-Southampton calculator in assisting clinicians and researchers. We have added LRs for the calculator, and we also suggest OFC calculator-generated prechallenge probabilities of OFC outcomes that clinicians could use to defer OFCs (0.7 for positive and 0.4 for negative OFC results). Units could decide to use different levels according to their own criteria.

The issue of intermediate probabilities (Fig 1, yellow region) is important. The “incorrect” result for one of the cases studied had a probability of 50%, which is not strictly “incorrect” because the object of using probabilities is to provide a continuum along which the likelihood of a positive or negative result lies. It is notable also that the only incorrectly predicted cases (after challenge) were false-positive results. In all tests a small number of false-positive results will occur by chance alone. In terms of clinical risk management of food allergy, false-positive results are probably preferable to false-negative results.

We must note some limitations to the present study: the small sample size used for analysis and the infrequency ($n = 1$) of positive challenges with egg. Although it could be suggested that the tool might not be suitable for patients without prior reactions to the food (ie, high specific IgE levels/skin prick test responses and no known prior ingestion of the specific food), this sample type is currently under investigation in an ongoing study.

We have also shown its applicability with data generated *a priori* from a different clinic setting and patient groups and that it can accommodate different preparations of the index foods (raw or baked egg as with pasteurized egg).

We intend to further validate the calculator in real time in diverse partner clinics worldwide and to explore its applicability in secondary and possibly primary care settings. This calculator is intended as a further aide to clinical decision making. The aim of the model is to support decision making by clinicians and not to replace it.

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