Critique of logistic regression in analysing treatment response in severe eosinophilic asthma

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To the Editor:

HAMADA *et al.* [1] investigated distinct treatment response trajectories to mepolizumab in patients with severe eosinophilic asthma. They evaluated clinical remission at 12 months, defined by three criteria: well-controlled symptoms, absence of exacerbations, and no requirement for oral corticosteroid maintenance. Using logistic regression analysis, they compared remission rates across different response trajectories and identified baseline characteristics that could predict these trajectories. This comprehensive approach provided valuable insights into the heterogeneity of treatment responses and potential predictive factors for optimal therapeutic outcomes.

The methodological approach taken by HAMADA *et al.* [1] warrants careful consideration. While they employed logistic regression, it is crucial to acknowledge its inherent assumptions and limitations. Logistic regression is a parametric model that assumes linearity in the log-odds scale (though nonlinear in probability space) and requires specific distributional assumptions. However, biological systems, particularly in severe eosinophilic asthma, often exhibit complex, nonlinear and nonparametric patterns. The application of logistic regression to such data might oversimplify these intricate relationships and potentially lead to biased conclusions [2–4].

The limitations of logistic regression when applied to nonlinear and nonparametric data stem from several fundamental constraints and assumptions. At its core, logistic regression fits data to a sigmoid function ($P(Y=1) = 1/(1 + e^{-(\beta_0 + \beta_1 X_1 + \ldots + \beta_n X_n)})$), which forces relationships into an S-shaped curve. However, complex biological relationships, such as those in severe eosinophilic asthma, often do not conform to this pattern. Treatment responses might exhibit multiple inflection points or threshold effects that a simple sigmoid function cannot capture.

The model's basic assumptions further compound these limitations. Logistic regression assumes linearity in log-odds space, independence of observations, and a fixed parametric form. Biological data frequently violates these assumptions through cyclical patterns, interaction effects, time-dependent variations, and multiple response thresholds. These violations are not merely theoretical concerns; they can lead to significant distortions in the analysis.

These distortions manifest in several ways: underestimation of extreme probabilities, failure to detect important interaction effects, inability to capture threshold effects, and smoothing out of local patterns. In the context of asthma research, treatment responses might display sudden improvements, plateau effects, complex immune system interactions, and individual variability patterns: none of which are adequately captured by logistic regression's rigid structure.

The impact on research conclusions can be substantial. Critical response patterns might be missed, treatment effects could be underestimated, and there is a significant risk of both false-negatives and false-positives. The model's tendency to oversimplify relationships can lead to misleading conclusions about treatment efficacy and patient outcomes. Alternative approaches, such as generalised additive models [5], would provide more accurate insights into treatment response patterns in biological systems.

Shareable abstract (@ERSpublications)
Hamada *et al.* used logistic regression to analyse treatment responses to mepolizumab in severe eosinophilic asthma. To better capture complex biological patterns and enhance predictive accuracy, they should have utilised generalised additive models. https://bit.ly/4bXM4Aa

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