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Beyond linear assumptions in pulmonary function analysis: a methodological critique of veteran health outcome models

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To the Editor:
Zeng et al. conducted a comprehensive analysis investigating the clinical utility of pulmonary function testing (PFT) in evaluating long-term outcomes among deployed veterans who maintained preserved spirometry.[1] They employed sophisticated statistical methods, including adjusted mixed-effects regression models and advanced machine learning algorithms, to systematically evaluate how various PFT parameters could predict clinically significant outcomes in this population. Furthermore, they meticulously tracked the longitudinal evolution of PFT patterns in deployed veterans using interval-censored Cox proportional-hazards regression analysis, which allowed for precise temporal assessment of pulmonary function changes despite irregular testing intervals.[1] This methodologically rigorous approach provided valuable insights into the prognostic capabilities of PFT parameters beyond standard spirometric measurements in monitoring respiratory health among veterans with deployment-related exposures.

However, this paper raises critical theoretical and empirical concerns regarding the application of adjusted mixed-effects regression models and Cox proportional-hazards regression. The linear parametric nature of mixed-effects models and the semiparametric structure of Cox regression may be fundamentally misaligned with the inherently nonlinear and nonparametric characteristics of biological respiratory data, leading to erroneous conclusions.[2-6] While these statistical tools are widely used, Zeng et al. should acknowledge that their reliability hinges on meeting specific underlying assumptions that may not hold in complex biological systems. When linear methods are applied to nonlinear biological relationships, or when parametric/semiparametric approaches are used with data that follows no particular distribution, the resulting interpretations may be significantly distorted.

Supervised models like those employed in their study generate two distinct types of performance metrics: direct prediction accuracy and model-fit metrics. While prediction accuracy can be rigorously validated against ground truth labels from clinical outcomes, other statistical metrics lack corresponding ground truth for validation. These unverifiable assessment metrics—including AIC, BIC, likelihood ratio statistics, intraclass correlation coefficients, Schoenfeld residuals, and proportional hazards assumptions—are internally calculated constructs without external validation anchors. The reliance on these unanchored metrics can lead to overconfidence in model performance despite potential misspecification of the underlying data structure.

To strengthen their analysis, Zeng et al. should consider implementing complementary nonlinear and nonparametric methodologies to validate their findings, providing a more robust framework that acknowledges the complex, nonlinear nature of pulmonary function and its relationship to clinical outcomes in veterans with deployment-related exposures. This approach advocates for nonlinear nonparametric methods such as Gaussian Process Regression as an alternative to mixed-effects models and Random Survival Forests instead of Cox proportional-hazards regression, potentially revealing patterns that conventional parametric approaches might miss.

Author contributions

Yoshiyasu Takefuji completed this research and wrote this article.

Supplementary material

Supplementary material is available at *Annals of the American Thoracic Society* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material.

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