Letter to the Editor

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RE: Novel Application of Quantitative Single-Photon Emission Computed Tomography/Computed Tomography to Predict Early Response to Methimazole in Graves' Disease

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Dear Editor,

We read with great interest the article by Kim et al. (1), "Novel application of quantitative single-photon emission computed tomography/computed tomography to predict early response to methimazole in Graves' disease?" In the present article, the authors developed Cox regression prediction models to investigate the independent predictive factors associated with achievement of euthyroidism after methimazole treatment in Graves' disease. Clinical prediction models allow clinicians to evaluate patient prognosis quantitatively and permit effective risk stratification of patients (2). The Cox proportional hazards regression model is the method most frequently used to evaluate the effect of patient characteristics on the risk of occurrence of a time-to-event outcome (3). We would like to thank the authors for this highly interesting work. In this study, model predictors included 14 variables (univariate Cox analysis) and 3 variables (multivariate Cox analysis). The full dataset (euthyroidism was achieved: n = 14, euthyroidism was not achieved: n = 22) had far fewer events than the recommended number of 10 or more per variable. Too many variables in a Cox proportional hazards regression model may cause an overfitting problem. It should be noted that a low-event-per-predictor rate may bias correlation coefficients (both negatively and positively) of the model (events-per-variable-rule). In addition, well-known factors from the literature found to be associated with an early response to methimazole in Graves' disease should be included in Cox prediction models, even if they are not significant following screening by univariate analysis, as this is usually due to lack of statistical power (4). The results must be interpreted with caution. We recommend further study with a larger sample size.

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Response

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To the Editor,

We appreciate Zhang's raising the issue of statistical analysis.

It is generally true that it may be inappropriate to conduct multivariate analysis with a few number of events and many variables. Over-fitting may have happened in terms of statistics. However, we think statistical analysis is not sufficient but necessary. Truth in scientific studies may be explained by a variety of observations that translate to graphs, figures, numbers, etc. We think that statistical analysis is just one of such numerical demonstrations.

However, we endeavored to be as comprehensive as possible and adhered to the general rule of statistical analysis. For the univariate Cox's model, 14 variables are listed in Table 3 of the study (1). The variables have been tested several times, which is not effectively reflected in Table 3. Variables can have different scales. For example, the initial MMI dose, the significant predictor for prognosis prediction in univariate and multivariate analyses, has been tested in a ratio scale (absolute dose itself) and an interval scale (less than 10 mg, 10–20 mg, more than 20 mg). Other variables were tested in a similar way. For the multivariate analysis, there are several methods of data input (i.e., enter, forward, backward, and stepwise) We have innumerous combinations of statistical analyses, as well as variables. Table 3 is a summarized display of our comprehensive statistical investigation. Too many rounds of statistical analyses may be subject to certain error from the perspective of statisticians. With a small number of events, those kinds of concerns may be difficult to avoid, which is stated in the Limitation section.

We are grateful to the statisticians for feedback that will enrich our knowledge and consolidate our research design in the future. At the same time, we hope that the value of the scientific study is seen within the context of variable disciplines.

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