Identifying risk factors: Challenges of separating signal from noise

Jeevanantham Rajeswaran, PhD,^a and Eugene H. Blackstone, MD^{a,b}

From the Departments of ^aQuantitative Health Sciences and ^bThoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio.

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Address for reprints: Eugene H. Blackstone, MD, Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, 9500 Euclid Ave, Desk JJ-4, Cleveland, OH 44195 (E-mail: blackse@ccf.org).

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Identifying risk factors from a possibly large number of candidate variables—variable selection—is key in clinical outcomes studies. However, different persons analyzing the same dataset often identify different risk factors.¹ Making variable selection more reproducible is the challenge addressed by Karim and colleagues in this issue of the *Journal*.²

BAGGING PREDICTORS³

The approach taken by Karim and colleagues is based on resampling (Figure 1).⁴ Observations in a dataset of size *n* are selected randomly with replacement to populate a new analysis dataset of equal size (a bootstrap sample). Many such datasets are generated, and each is analyzed.^{3,5} It is rare that the identical risk factors are found,⁶ confirming the suspicion that analysis of a single dataset produces unstable (unreproducible) results. However, if one aggregates results of these many analyses, signal separates from noise. A macro library is available from the authors for regression procedures in SAS (SAS Institute, Cary, NC).

PREPARING THE DATASET FOR ANALYSIS

Not discussed by Karim and colleagues are some challenges of preparing the dataset for such an analysis, because one does not want to repeat 1000 analyses due to a mistake!

Missing Data

Screen all covariables and discard those with a large amount of data missing. How much is too much depends on the degree of redundancy within available variables; perhaps 25% is reasonable for conventional missing data methods. For remaining variables having missing data, statistically acceptable approaches include multiple imputation,⁷ as used by Karim and colleagues, although interesting new machine-learning methods are being developed. Analyzing only patients with complete data for all variables is generally unacceptable.

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Central Message

Variable selection is important for identifying risk factors. Combining parametric and machine-learning nonparametric methods using resampling may provide the most reproducible risk factor models.

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Sufficient Data

Screen categorical covariables in relationship to categorical endpoints, such as death. The effective sample size for such analyses is number of observed events.⁸ When few endpoints are available for a categorical variable (5-10 or less), any analysis with such a variable will be unstable, and it should be eliminated from consideration.

Continuous Variables

Use continuous variables as such in models, rather than arbitrarily categorizing them. Recognize, however, that a continuous variable may have a nonlinear relationship with the endpoint. After sensitivity analysis, Karim and colleagues decided to use no transformations of scale for continuous variables. However, the main reason for using transformations or spline representations for continuous variables is to meet model assumptions. For example, logistic regression assumes that continuous variables are associated linearly with the logit of the binary response. Alternatively, the multivariable analysis can be supplemented by a completely nonparametric analysis, eg, random forests⁹; partial dependency plots will illuminate the risk-adjusted shape of a continuous variable vis-a-vis outcome to guide model development (Figure 2).^{10,11}

FIGURE 1. Example of automated variable selection by bootstrap aggregation (bagging), depicting the advantage of averaging. Fifteen variables labeled A through O are depicted as potential predictors of death after mitral valve surgery. In A, analyses of 5 bootstrap samples are shown. Tall bars indicate the variable was selected at $P < .05$, and gaps represent variables not selected. B and C show running averages as the bootstrap samples increased from 1 to 1000. Notice that no variable was selected 100% of the time, and all 15 were selected at one time or another. From Blackstone and colleagues.⁴

FIGURE 2. Random forest for survival partial dependency plot depicts the nonlinear relationship between albumin and 1-year predicted survival.¹⁰ Graph presents a risk-adjusted estimate of the effect of albumin on survival after aortic valve replacement. Circles and solid lines represent risk-adjusted estimates, and dashed lines indicate 68% confidence band. From Szeto and colleagues.¹¹

Selecting Candidate Variables for Multivariable Analysis

The final step in preparing for analysis is to compile the list of candidate variables. Karim and colleagues used expert opinion and current literature to compile “plausible predictors,” an approach that may preclude addition of new knowledge. Others use *P* values based on a series of univariable models, selecting candidates that are statistically significant. This approach ignores lurking variables, ie, variables that are not statistically significant until another variable is taken into account.^{12,13} We recommend incorporating all available and well-vetted variables in model building, coupled with full exploitation of the machine-learning aspect of bootstrap methods that can efficiently and effectively identify the most reliable variables (signal).

VARIABLE SELECTION PROCESS

The result of analyzing data may depend on the variable selection strategy, which is explored by Karim and colleagues. We only caution that backward selection starts with all variables forced into the model, generally requiring a large effective sample size, such as available in the study of Karim and colleagues. This can be achieved in a machine-learning environment by incorporating random subsets of variables instead.¹⁰

Are We There Yet?

Not discussed by Karim and colleagues is the matter of collinearity—high correlation among variables. Examples

are creatinine, blood urea nitrogen, and estimated glomerular filtration rate; height, weight, and body surface area; and multiple candidate transformations of scale for continuous variables. Thus, another step is clustering of highly correlated variables. After bagging is completed, calculate how often the cluster of variables has been selected. The most commonly selected or informative representative of the cluster may be identified as a risk factor. This same counting process will indicate how many terms are needed to represent a nonlinear relationship of a continuous variable.

ALTERNATIVES

Karim and colleagues note in their Discussion that machine-learning approaches open up new methods,¹⁴ such as random forests,^{9,10} for identifying important variables related to outcome without need for *P* values, superior ways to model continuous variables, and ways to account for complex interrelations among variables. These methods, being rapidly developed and used by the Microsofts, Amazons, and Googles of the world, will, we believe, replace many traditional statistical methods¹⁵ and provide better predictive models, yielding superior insight into the data.

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