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Explicit inclusion of treatment in prognostic modeling was recommended in observational and randomized settings

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Abstract

Objectives: To compare different methods to handle treatment when developing a prognostic model that aims to produce accurate probabilities of the outcome of individuals if left untreated.

Study Design and Setting: Simulations were performed based on two normally distributed predictors, a binary outcome, and a binary treatment, mimicking a randomized trial or an observational study. Comparison was made between simply ignoring treatment (SIT), restricting the analytical data set to untreated individuals (AUT), inverse probability weighting (IPW), and explicit modeling of treatment (MT). Methods were compared in terms of predictive performance of the model and the proportion of incorrect treatment decisions.

Results: Omitting a genuine predictor of the outcome from the prognostic model decreased model performance, in both an observational study and a randomized trial. In randomized trials, the proportion of incorrect treatment decisions was smaller when applying AUT or MT, compared to SIT and IPW. In observational studies, MT was superior to all other methods regarding the proportion of incorrect treatment decisions.

Conclusion: If a prognostic model aims to produce correct probabilities of the outcome in the absence of treatment, ignoring treatments that affect that outcome can lead to suboptimal model performance and incorrect treatment decisions. Explicitly, modeling treatment is recommended.

Keywords: Prognosis; Models; Statistical; Computer simulation; Decision support techniques; Calibration

1. Introduction

Prognostic models (or risk scores) are increasingly important for clinical decision making [1,2]. For example, the predicted probability of an outcome, obtained through a prognostic model, may serve as the starting point for considerations of treatment initiation: high risks may lead to starting treatment, whereas in the case of low risks, treatments may be withheld or delayed. For example, in the guideline of the European Society of Cardiology [3], it is mentioned that "at risk levels $>10\%$, drug treatment is more frequently required," although the authors caution that "no threshold is universally applicable." To guide individual treatment decisions, prognostic outcome predictions should ideally reflect the predicted course or outcome risk of disease if a patient were to remain untreated [2,4].

Prognostic models are often developed using data from a randomized trial or an observational study, in which (at least part of the) individuals are treated [5]. If treatments are effective in reducing the risk of the predicted outcomes, simply ignoring

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What is new?

Key findings

- When developing a prognostic model using data from observational studies with treated patients, restricting the analysis to untreated individuals is not appropriate if treatment status depends on patient characteristics, including the predictors of the developed model.

What this adds to what was known?

- When developing a prognostic model (that aims to produce accurate probabilities of the outcome in case the patient is not treated) using data from a randomized trial in which individuals from one arm do not receive treatment, restricting the analysis to untreated individuals may be a suitable strategy. However, removing all patients in the treatment group will reduce the sample size, leading to greater uncertainty around predictions and also to prognostic models that are more prone to overfitting.

What is the implication and what should change now?

- For either randomized or observational studies, it is preferable to explicitly model treatment when developing a prognostic model.

those treatments in the development of a prognostic model may result in incorrect predictor–outcome associations and hence incorrect risk predictions of the natural history when used in new individuals [6]. Although predictions are correct for those among whom the model was developed (the ''derivation set''), they may not generalize to future individuals who may be treated differently. In other words, there is a danger of risk predictions being confounded by treatment: risk predictions appear low because of treatment, but in future patients, the true risk might be substantially higher if they remain untreated. Further complications arise when treatment decisions in the data available were already being based on the values of the predictors in the model. For example, in patients with hypertension, the observed predictive effect of blood pressure for cardiovascular outcomes is likely to be diluted, as those with high blood pressure will receive antihypertensive treatment, based on the observed high blood pressure, in turn lowering their predicted risk. Thus, if a prognostic model is developed using these data, the effect of blood pressure is likely to be downwardly biased, and therefore, risk predictions may be too low in future untreated individuals.

Methods to account for treatments in the development of a prognostic model to be used for predicting the health course of individuals in the absence of treatment include simply ignoring treatment (SIT) [5], restricting the development set to untreated individuals [6], censoring observations after treatment has started [7], and explicit modeling of the treatment [8]. In addition, in the TRIPOD statement, there is an item on the reporting of treatment received among participants of a study developing or validating a multivariable prediction model for diagnosis or prognosis [9].

In this article, we evaluate these different methods in situations that aim to develop a prognostic model–generating predictions in case individuals were to remain untreated, which serve as input for treatment decisions. In particular, we examine how the methods impact on the predictive performance and proportion of correct indications of treatment of a prognostic model being developed using data from a randomized or observational study.

2. Consequences of ignoring treatment in different phases of model development

The development and introduction of a new prognostic model comprises four distinct phases: derivation, validation, impact assessment, and implementation of the model [1]. As indicated above, for a model to be used to guide treatment decisions, the predictions made by the model should be the outcome risks of individuals if no treatment were to be given. This implies that such models should be developed in untreated populations. Nevertheless, in all phases of prognostic modeling research, some portion of the study population may actually be treated by an effective treatment.

When deriving a model in a treatment-naïve population, the model will indeed provide risk predictions that reflect what will happen if a future, but similar individual remains untreated. However, when part of the population is treated and treatment is ignored in the model derivation phase, the risk predictions from the model will be too low when validated or applied in individuals who are yet untreated. To what extent the predictions will be too low likely depends on the proportion of treated individuals in the derivation set and the magnitude of the treatment effect. Fig. 1 illustrates this impact of ignoring treatment in the development of a prognostic model.

The impact of ignoring treatment when validating the developed model in new individuals obviously depends on what cohort of patients have been used in the derivation phase. If the model was derived in a treatment-naïve population, the model will provide correct predictions if the individuals in the validation set are all untreated too; the predicted risks will correspond reasonably well with the observed risks. However, if such a developed model is validated in a (partly) treated population, the predicted risks will appear to be too high, if treatment is simply ignored in the validation phase.

When a model is derived in a (partly) treated population and this treatment is ignored in the development, the predicted risk will be too low, when validating the model in