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Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes

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Abstract

Objective: Cox proportional hazards regression models are frequently used to determine the association between exposure and time-to-event outcomes in both randomized controlled trials and in observational cohort studies. The resultant hazard ratio is a relative measure of effect that provides limited clinical information.

Study Design and Setting: A method is described for deriving absolute reductions in the risk of an event occurring within a given duration of follow-up time from a Cox regression model. The associated number needed to treat can be derived from this quantity. The method involves determining the probability of the outcome occurring within the specified duration of follow-up if each subject in the cohort was treated and if each subject was untreated, based on the covariates in the regression model. These probabilities are then averaged across the study population to determine the average probability of the occurrence of an event within a specific duration of follow-up in the population if all subjects were treated and if all subjects were untreated.

Results: Risk differences and numbers needed to treat.

Conclusions: Absolute measures of treatment effect can be derived in prospective studies when Cox regression is used to adjust for possible imbalance in prognostically important baseline covariates.

Keywords: Risk differences; Numbers needed to treat; Survival analysis; Cox proportional hazards regression model; Measures of treatment effect; Absolute risk reduction; Observational study; Randomized controlled trial

1. Introduction

In randomized controlled trials, the effect of treatment on dichotomous outcomes can be reported using a variety of measures of treatment effect: absolute risk reduction, relative risk, relative risk reduction, the number needed to treat (NNT), and the odds ratio. Schechtman argues that both relative and absolute measures should be reported [1]. Cook and Sackett argue that for clinical decision making the NNT is more meaningful than the relative risk, the relative risk reduction, or the odds ratio [2]. Jaeschke et al. suggest that the odds ratio and the relative risk provide limited information [3]. Finally, Sinclair and Bracken argue that clinically important questions are best addressed using relative risks, relative risk reductions, risk differences, and the NNT [4]. Common to all of these perspectives is the notion that relative measures of treatment effect provided limited clinical information, and that absolute measures of treatment effect (or measures derived from them such as the NNT) are more relevant for clinical decision making. In the face of these proposals, some medical journals require that absolute risk reductions and the associated NNT be reported for any randomized controlled trial with a dichotomous outcome [5].

In many randomized controlled trials, the outcome is time-to-event in nature. In such settings, Kaplan−Meier survival curves are often used to compare survival times among the different arms of the trial. When Kaplan−Meier survival curves are used to estimate the effect of treatment on survival, the difference in survival probabilities between treated and untreated subjects can be estimated for different durations of follow-up. This difference in survival probabilities provides an estimate at the population level of the effect of treatment on the probability of survival over a specified duration of time. Some statisticians have advocated that adjusted estimates of treatment effect be reported in randomized controlled trials [6−9]. This allows one to

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What is new?

Key finding

- In observational cohort studies and in randomized controlled trials, absolute risk reductions and numbers needed to treat (NNTs) can be derived from an adjusted Cox proportional hazards regression model or an accelerated failure time parametric survival model.

What this adds to what was known?

- The use of the hazard ratio as a measure of association between treatment and outcome can be supplemented by the absolute risk reduction and the NNT in observational cohort studies and randomized controlled trials with dichotomous exposures and time-to-event outcomes.

What is the implication, what should change now?

- When using a survival regression model in an observational cohort study or randomized controlled trial with a binary exposure and time-to-even outcome, authors should supplement the reporting of the hazard ratio with that of the absolute risk reduction and the NNT for clinically meaningful durations of follow-up time.

adjust for potential residual imbalance in prognostically important baseline covariates between treatment arms. For this reason, Cox proportional hazards regression models have been used to estimate adjusted hazard ratios in randomized controlled trials. In this context, adjusted hazard ratios are reported to quantify the magnitude of the treatment effect. The hazard ratio provides a relative measure of treatment effect. Unfortunately, neither the absolute reduction in the probability of an event occurring during a specific length of follow-up nor the NNT to avoid one such event are conveyed by the hazard ratio.

Although time-to-event outcomes are common in randomized controlled studies, they also occur frequently in observational studies. Researchers are increasingly using observational studies to estimate the effect of treatment on outcomes. In nonrandomized studies, unlike in randomized trials, treated subjects often differ systematically from untreated subjects. Therefore, outcomes cannot be compared directly between treated and untreated subjects. Statistical methods must be used to adjust for systematic differences between treated and untreated subjects when estimating the effect of treatment on outcomes. A commonly used method in the medical literature for this purpose is the Cox proportional hazards regression model. The use of this model allows investigators to estimate the effect of treatment on survival after adjusting for baseline covariates. As in the case of randomized controlled trials, the use of Cox regression models allows one to estimate the relative impact of treatment on survival. However, the hazard ratio does not allow one to infer the absolute reduction in the probability of the outcome occurring during a specified duration of follow-up, nor the number of subjects that must be treated to avoid one event over a specified duration of follow-up.

Several authors have described methods to derive relative risks, relative risk reductions, absolute risk reductions, and NNTs from a logistic regression model in either a randomized controlled trial or in an observational study [10–13]. Many of these methods are based on estimating the marginal (or population-average) probability of the outcome if all subjects in the population were treated, and the marginal probability of the outcome if all subjects were untreated. The use of these methods allows for reporting of more clinically meaningful measures of treatment effect when logistic regression is used to estimate adjusted odds ratios.

The objective of this paper was to describe how risk differences and NTTs can be derived from a Cox proportional hazards model in either a randomized controlled trial or in an observational study with time-to-event outcomes. I also demonstrate that this method can be used with parametric accelerated failure time (AFT) survival models. The paper is organized as follows: In Section 2, I describe how absolute measures of treatment effect can be derived from a time-to-event regression model. In Section 3, a case study is presented in which the utility of the proposed methods is demonstrated. Finally, in Section 4, I summarize my findings.

2. Estimating clinically meaningful measures of treatment effect from survival models

In this section, we describe how to estimate absolute reductions in the risk of an event occurring within a specific duration of follow-up using both Cox proportional hazards regression models and parametric AFT survival models. The NNT to avoid one event within the specified duration of follow-up can be calculated as the reciprocal of the absolute risk reduction.

Let us assume that in a randomized controlled trial or an observational study, a time-to-event outcome variable T_i is observed for the ith subject. Furthermore, let Z_i denote the treatment status of the ith subject (with $Z = 1$ denoting treatment and $Z = 0$ denoting no treatment), while $X_{1i}, X_{2i}, \ldots, X_{ki}$ denote the value of k baseline covariates measured on this subject.

2.1. Cox proportional hazards model

The use of the Cox proportional hazards regression model is pervasive in modern medical research. The Cox proportional hazards regression model relates the hazard of the outcome to treatment status and baseline covariates: