Causality and the Cox regression model

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Abstract

This paper surveys results concerning the interpretation of the Cox hazard ratio in connection to causality in a randomized study with a time-to-event response. The Cox model is assumed to be correctly specified and we investigate whether the typical end product of such an analysis, the estimated hazard ratio, has a causal interpretation as a hazard ratio. Hernán (2010) pointed out that this is not possible due to selection, but without specific calculations. We provide more insight into the interpretation of hazard ratios and differences, investigating what can be learned about a treatment effect from the hazard ratio approaching unity after a certain period of time. The conclusion is that the Cox hazard ratio is not causally interpretable as a hazard ratio unless there is no treatment effect or an untestable and unrealistic assumption holds. We give a hazard ratio that has a causal interpretation and study its relationship to the Cox hazard ratio.

Contents

1. Introduction

We consider estimation of the causal effect of a randomized binary exposure variable A on a survival time; see Section 3 for a brief introduction to causal inference. The question is if we can use the hazard ratio (HR) to convey the result. We will sometimes refer to a HR calculated from a Cox model as a Cox HR if we wish to stress that it is calculated based on this model, i.e., it is independent of time. We imagine the situation where the Cox regression model or an extended version of the model is correctly specified, the latter leading to two hazard ratios, one in an initial time period and another thereafter. We show that the HR obtained cannot be given a causal interpretation when interpreted as a HR, except in the trivial case where there is no causal effect or an unrealistic and unverifiable condition holds. This was pointed out in Hernán (2010), but without any mathematical calculations. In this paper we explain this mathematically. The problem is not a matter of estimating the parameters of the Cox model inconsistently as they are estimated consistently using the standard analysis. The issue arises only when it comes to interpretation of the estimated HR. This is problematic as this quantity is often presented as the end-result of such an analysis. Nor is the problem due to unmeasured confounding, which we have guarded us against by the randomization.

Apart from providing explicit calculations showing that Hernán's warning is well-founded, we define a HR that can be given a causal interpretation. Such a HR is desirable, as it potentially allows a description of a treatment effect that changes with time. Aalen et al. (2015) re-iterated Hernán's warning, also giving specific calculations but focussing mostly on non-collapsibility of the Cox model, which is a well-known problem; see for instance Martinussen and Vansteelandt (2013), Sjölander et al. (2016), and Daniel et al. (2021). However, non-collapsibility does not sufficiently explain why we cannot understand a HR causally. Suppose an additional unobserved variable Z also affects the outcome T, i.e., Z is an unmeasured risk factor. If the Cox model is correct given A and Z, then the marginal model, conditioning only on A, is no longer a Cox model; this is the non-collapsibility of Cox model. The situation where a HR based on the marginal Cox regression analysis is reported should therefore not arise. Instead, we explore the situation where a piecewise constant Cox model is correctly specified, suggesting reporting results based on the corresponding Cox regression analysis. We pay special attention to what can be learned about the treatment effect from the hazard contrast vanishing after a certain point in time, i.e., the hazard ratio becoming unity or the hazard difference becoming zero. Time-changing hazard ratios are often interpreted as a change in treatment effect, see Lederle et al. (2019) and Primrose et al.

(2019) for recent examples, and a similar situation arises in the Women's Health Initiative study used as illustration by Hernán (2010). Recently a Cross-Pharma Non-proportional Hazards Working Group published their recommendations concerning analysis of time to event endpoints under non-proportional hazards, such as the situation with time changing hazard ratios (Lin et al. 2020a). The recommendations center around how to construct a hypothesis test that retains high power under non-proportional hazards, but it is also stated that 'Based on the observed data, the piecewise constant HRs could be used to describe the change in treatment effect over time.' We argue that there is no causal support for such reporting; see also Bartlett et al. (2020) and Lin et al. (2020b).

The paper is organized as follows. We first give brief introductions to survival analysis and causal inference in Sections 2 and 3. In Section 4 we show that the Cox HR is not causally interpretable as a hazard ratio unless there is no treatment effect or an unverifiable assumption is met. Section 5 gives measures that have a causal interpretation. In Section 6, we show that the same issues pertain for hazard differences. Section 7 gives a method to estimate the survival function contrast efficiently if there are predictive baseline covariates available, and Section 8 contains some concluding remarks.

2. Survival analysis

This paper focusses on the marginal Cox model but we begin with a brief account of survival analysis and the Cox model in general. We let T denote the event time, such as time to death if considering all-cause mortality. We will not deal with competing risks but, the problem pointed out in this paper for survival data surely persists for competing risk data. A common situation is that we also observe additional information about a given subject, comprised in the vector X. In most applications the survival time T is not observed for all individuals, as there is typically right-censoring. This means that, for a given individual, we observe

$$D = \{X, \Delta, \tilde{T} = \min(T, C)\},$$

where C is the censoring variable. We assume that T and C are conditionally independent given X. The proportional hazards model (Cox 1972)

$$\lambda_T(t; X) = \lambda_0(t) e^{X^T \theta}$$

is the default regression model in practice. There are several reasons for this. The hazard function

$$\lambda_T(t; X) = \lim_{h \to 0} P(t \leq T < t + h \mid T \geq t, X)/h$$

is attractive for theoretical purposes as it gives a link to counting processes via the intensity function $Y(t)\lambda_T(t; X)$, with $Y(t) = I(t \leq \tilde{T})$ the so-called at-risk indicator, which is unity at time t if the subject is still at risk at time t. The counting process is $N(t) = I(\tilde{T} \leq t, \Delta = 1)$ and a key result is that the process

$$M(t \mid X) = N(t) - \int_0^t Y(s)\lambda_T(s; X)ds \qquad 1.$$

is a martingale with respect to the filtration generated by $\{N(t), Y(t)\}$ and X. This has been an extremely useful tool in developing estimators and studying their large-sample properties, see Andersen et al. (1993), Martinussen and Scheike (2006), or Andersen et al.

(2021). Without censoring the counting process simplifies to $N(t) = I(T \leq t)$ and its intensity process to $I(t \leq T)\lambda_T(t; X)$, so it is seen that censoring is easily handled by changing the at-risk indicator. In this respect, the hazard function is a natural quantity to model.

There are many hazard regression models but the Cox proportional hazards model is by far the most popular, being seen as the null model, in that '...explicit excuses are now needed to use different models' (Keiding 1998). If X is comprised of a treatment indicator A and additional baseline information W, then one reason for the popularity of the Cox model is that

$$\frac{\lambda_T(t; A = 1, W)}{\lambda_T(t; A = 0, W)} = e^{\theta_A}, \qquad 2.$$

where θ_A is the coefficient corresponding to A (assuming no interaction between A and W). Hence the model provides a one-number summary of the effect of the treatment A. Further, the model is flexible, as the baseline hazard function $\lambda_0(t)$ need not be modeled. The model has been studied extensively and efficient estimation is possible in standard packages.

3. Causal inference

In this paper we will phrase causal quantities via potential outcomes, see Hernán (2004) and Hernán and Robins (2020). Let T^a denote the potential outcome, i.e., the waiting time we would see if the exposure A were set to a. We shall throughout assume that this intervention is meaningful (Hernán and Taubman 2008). We assume that $T^a = T$ if $A = a$ and also that T^a and A are independent. These two assumptions are referred to as consistency and exchangeability, respectively, with the latter being assured as the treatment is randomized. See Hernán (2004) for further discussion on ideal randomized experiments. Thus,

$$P(T > t \mid A = a) = P(T^a > t \mid A = a) = P(T^a > t),$$

from which it follows that

$$\lambda_{T^a}(t) = \lambda(t; a).$$

There is a population causal effect of the exposure A on the outcome T if the two distributions $P(T^1 > t)$ and $P(T^0 > t)$ differ, that is, the two counterfactual distributions of the outcome T, where everybody in the population has been exposed versus no one in the population has been exposed, differ.

4. Causal interpretation of the Cox hazard ratio?

We now focus on the situation with only the randomized treatment indicator A as explanatory variable. The Cox model in this simplified setting is

$$\lambda(t; A = a) = \lambda_0(t)e^{\beta a}, \qquad 3.$$

where we have changed notation for the regression parameter to β. We let $\Lambda_0(t) = \int_0^t \lambda_0(s)\, ds$ denote the cumulative baseline hazard function. As already mentioned, because of the randomization, $\lambda_{T^a}(t) = \lambda(t; a)$. Hence, if the Cox model is correctly specified then, Cox regression yields consistent estimates $\{\hat{\beta}, \hat{\Lambda}_0(t)\}$ of the parameters $\{\beta, \Lambda_0(t)\}$. Further, if $\beta \neq 0$ then, according to Section 3, there is a causal effect of the exposure on T, as the counterfactual distributions $P(T^1 > t)$ and $P(T^0 > t)$ differ. The Cox model can

thus be used to investigate if there is a causal exposure effect under the assumption that the model is correctly specified. However, we cannot interpret $\exp(\hat{\beta})$ as a causal HR at any $t > 0$, unless there is no exposure effect, $\beta = 0$; or unless the unrealistic and untestable assumption 12. holds. The HR we are in fact estimating by such an analysis is

$$\frac{\lambda(t; A=1)}{\lambda(t; A=0)} = \frac{\lim_{h\to 0} P(t \le T^1 < t+h \mid T^1 \ge t)/h}{\lim_{h\to 0} P(t \le T^0 < t+h \mid T^0 \ge t)/h} \qquad 4.$$

since, for $u > t$,

$$P(T > u \mid T \ge t, A = a) = P(T^a > u \mid T^a \ge t), \quad a = 0, 1,$$

and, for $t > 0$, the two groups given by $T^0 \ge t$ and $T^1 \ge t$, are no longer comparable if the treatment has an effect, thereby ruining a causal interpretation of the estimated HR from the Cox regression analysis.

That $T^0 \ge t$ and $T^1 \ge t$ are no longer comparable at $t > 0$ is due to selection if $\beta \neq 0$; see Hernán (2010). We illustrate this mathematically assuming a specific data generating process (DGP), where there is an unmeasured variable Z that also has an effect on T. The presence of Z reflects the situation where other things besides the treatment may affect the time to the specific event T we are studying, as is always the situation in real life. We again stress that this is not a matter of unmeasured confounders, as Z and the treatment variable A are independent due to the randomization of A. Our focus is on the situation where the marginal Cox model, conditioning only on A, is correctly specified. Thus, with sufficient amount of data, a thorough examination of the Cox model fit will show that there is no reason to believe that the model does not fit the data! However, we will consider a slightly more general setup using an extended Cox model with one HR initially and another thereafter: for example, a naive interpretation would lead to the conclusion that there is a beneficial effect of treatment (HR<1) in the initial period but not thereafter (HR=1). As mentioned in the Introduction, such situations arise in practice, and are often reported as a change in treatment effect. We seek a DGP, $\lambda(t; A, Z)$, so that

$$\frac{\lambda(t; A=1)}{\lambda(t; A=0)} = \begin{cases} e^{\beta}, & t \le \nu, \\ 1, & t > \nu, \end{cases} \qquad 5.$$

with $\beta < 0$. We may write 5. as

$$\lambda(t; A) = \{e^{\beta A} I(t \le \nu) + I(t > \nu)\}\lambda_0(t), \qquad 6.$$

where ν denotes the change point, and the baseline hazard function $\lambda_0(t)$ is not further specified. This setup includes the Cox model by taking ν equal to infinity, leading to only one HR, e^{β}. There are many possible $\lambda(t; A, Z)$ for which 6. is correctly specified, but for illustration we let $\lambda(t; a, z) = z\lambda^*(t; a)$ for some function $\lambda^*(t; a)$ and Z exponentially distributed with mean 1. Simple calculations (Martinussen et al. 2020) lead to

$$\lambda(t; A, Z) = \begin{cases} Z\lambda_0(t)e^{\beta A}\exp\{\Lambda_0(t)e^{\beta A}\}, & t \le \nu, \\ Z\lambda_0(t)\exp\left\{\Lambda_0(\nu)e^{\beta A} + \Lambda_0(\nu, t)\right\}, & t > \nu, \end{cases} \qquad 7.$$

where $\Lambda_0(\nu, t) = \int_\nu^t \lambda_0(s)\, ds$. Hence, if the DGP is given by 7. with Z exponentially distributed with mean 1, then model 6. is correctly specified and, as mentioned, with $\nu = \infty$ 6. simplifies to the marginal Cox model. Define

$$\mathrm{HR}_Z(t) = \frac{\lambda(t; A=1, Z)}{\lambda(t; A=0, Z)}$$

to be the HR we might calculate, had we had information about the hidden variable Z, to compare individuals on a more equal footing. It is seen from 7. that

$$\mathrm{HR}_Z(t) = \begin{cases} e^\beta \exp\left[\Lambda_0(t)\{e^\beta - 1\}\right], & t \leq \nu, \\ \exp\left[\Lambda_0(\nu)\{e^\beta - 1\}\right], & t > \nu, \end{cases}$$

and since $e^\beta < 1$ we see that $\mathrm{HR}_Z(t) < 1$ for all t. If one were willing to use HR's to convey the causal effect of the treatment then, based on $\mathrm{HR}_Z(t)$, there seems to be a beneficial effect of the treatment at all times. However, the naive conclusion based on the change point Cox model is that the treatment effect disappears after time ν. Thus using the HR's to argue about the treatment effect leads to contradictory conclusions, despite the estimates being consistent. Also, when the marginal Cox model is correctly specified, i.e. $\nu = \infty$, then

$$\mathrm{HR}_Z(t) = e^\beta \exp\left[\Lambda_0(t)\{e^\beta - 1\}\right] < e^\beta < 1, \quad t > 0,$$

so the $\mathrm{HR}_Z(t)$ points towards a stronger effect than does the Cox HR. Similar calculations and conclusions were made by Stensrud et al. (2019).

We get these contradictory conclusions because of selection, (Hernán 2010). In the specific setting, the selection can be quantified: while $E(Z \mid A = 1) = E(Z \mid A = 0)$ due to randomization, at later time points we have

$$\frac{E(Z \mid T > t, A = 1)}{E(Z \mid T > t, A = 0)} = \begin{cases} \exp\left\{\Lambda_0(t)(1 - e^\beta)\right\}, & t \leq \nu, \\ \frac{\exp\{\Lambda_0(\nu)\} + \Lambda_0(\nu,t)}{\exp\{\Lambda_0(\nu)e^\beta\} + \Lambda_0(\nu,t)}, & t > \nu, \end{cases}$$

so indeed

$$E(Z \mid T > t, A = 1) > E(Z \mid T > t, A = 0),$$

indicating that we are left with more frail subjects in the active treatment group.

Imagine the situation where we get access to the variable Z and also by some divine insight know that model 7. is correctly specified. It is then reasonable to ask if the seemingly more attractive $\mathrm{HR}_Z(t)$ can be interpreted causally as a hazard ratio. Unfortunately, the answer is no. To see why, note that

$$\mathrm{HR}_Z(t) = \frac{\lim_{h \to 0} P(t \leq T^1 < t + h \mid T^1 \geq t, Z)/h}{\lim_{h \to 0} P(t \leq T^0 < t + h \mid T^0 \geq t, Z)/h},$$

is only causally interpretable as a hazard ratio if T^0 and T^1 are conditionally independent given Z, which is untestable and biologically implausible. Indeed, we can construct a DGP $\lambda(t; A, Z, V)$ with V a new hidden variable so that $\lambda(t; A, Z, V)$ marginalizes to $\lambda(t; A, Z)$ that further marginalizes to $\lambda(t; A)$, the latter being the Cox model if $\nu = \infty$. Take V to be exponentially distributed with mean 1, and independent of Z and A, and let

$$\lambda(t; A, Z, V) = VZ\lambda_0(t)e^{\beta A} \exp\left[\Lambda_0(t)e^{\beta A} + Z\{\exp\left\{\Lambda_0(t)e^{\beta A} - 1\right\}\right] \tag{8.}$$

If the DGP is governed by 8. then the hazard ratio $\mathrm{HR}_{VZ}(t)$ derived from this model (keeping V and Z fixed), $\mathrm{HR}_Z(t)$ and the Cox HR will all be different, though all the models 8., 7. and 6. from which they are derived are correctly specified.

5. Effect measures that have a causal interpretation

If the Cox model 3. is correctly specified then, for all $t > 0$,

$$e^{\beta} = \frac{\log P(T^1 > t)}{\log P(T^0 > t)}, \qquad 9.$$

and $P(T^a > t)$ has a causal interpretation. Hence, in this way, the number e^{β} is a function of causal quantities. However, the relationship shown in 9. is hardly the reason why the Cox model is so popular, as it is difficult to appreciate what the right hand side of 9. really means. Instead one is tempted to appeal to the usual HR interpretation of e^{β}. However, as we have argued, e^{β} can only be interpreted as a causal HR in the trivial case of no treatment effect or if condition 12. below holds. There are other but not much used interpretations of e^{β}; see De Neve and Gerds (2020).

A hazard ratio that has a causal interpretation is

$$\mathrm{HR}(t) = \frac{\lim_{h\to 0} P(t \leq T^1 < t + h \mid T^0 \geq t, T^1 \geq t)}{\lim_{h\to 0} P(t \leq T^0 < t + h \mid T^0 \geq t, T^1 \geq t)}. \qquad 10.$$

since at time point t we compare individuals that would survive until time point t under both treatment regimes, hence preserving the balance we have at start of the study due to the randomization. Unfortunately, 10. is not identifiable without invoking untestable assumptions. A further drawback is that the individuals with $(T^0 \geq t, T^1 \geq t)$ are unknown to us. Nevertheless, due to its causal interpretation, $\mathrm{HR}(t)$ and its relationship to $e^{\beta} = \mathrm{HR}$ is of theoretical interest. If the Cox model is correctly specified with $e^{\beta} < 1$ and the joint distribution of T^0 and T^1 is governed by a copula (Nelsen 2006) induced by a frailty (Oakes 1989) then it is shown in Martinussen et al. (2020) that

$$\mathrm{HR}(t) < e^{\beta} < 1. \qquad 11.$$

This confirms the intuition of Hernán (2010), who argues based on the frailty setting. The causal effect of the treatment as conveyed by $\mathrm{HR}(t)$ is stronger than what should be believed from the ordinary Cox HR. Intuitively this makes sense because if there is beneficial effect of the treatment, $e^{\beta} < 1$, then there will be increasingly more frail subjects in the treated group compared to the untreated group as time passes by and yet the Cox model is correctly specified, which points to the stronger effect of the treatment that 11. suggests. However, it is also shown in Martinussen et al. (2020) that there exist joint distributions of T^0 and T^1 so that T^0 and T^1 are positively correlated and

$$e^{\beta} < 1, \quad e^{\beta} < \mathrm{HR}(t),$$

so, unfortunately, 11. is not a general result. Also, if

$$T^0 \text{ and } T^1 \text{ are independent} \qquad 12.$$

then $\mathrm{HR}(t) = e^{\beta}$, and the Cox HR is then causally interpretable as a hazard ratio. However, 12. is unrealistic and also untestable.

6. Hazard differences

It is tempting to think that hazard differences have a more appealing causal interpretation than hazard ratios, apart from them being collapsible (Martinussen and Vansteelandt 2013).

This is partly true, but of little practical use, as we shall now demonstrate. For an additive hazards model

$$\lambda(t; A, Z) = \psi(t)A + \omega(t, Z), \tag{13.}$$

conditioning on A and possibly unmeasured baseline covariates Z, the independence relation $A \perp\!\!\!\perp Z$ extends to all risk sets, in the sense that $A \perp\!\!\!\perp Z \mid T > t$ (Vansteelandt et al. 2014, Aalen et al. 2015). The previous concerns about selection may therefore appear of less relevance for time-varying hazard differences. If we further assume that $T^0 \perp\!\!\!\perp T^1 \mid Z$ then

$$\mathrm{HD}_Z(t) = \lim_{h\to 0} P(t \le T^1 < t + h \mid T^1 \ge t, Z)/h - \lim_{h\to 0} P(t \le T^0 < t + h \mid T^0 \ge t, Z)/h$$

has a causal interpretation, as the conditioning set $(T^a \ge t, Z)$ in the two terms on its right hand side can be replaced by $(T^0 \ge t, T^1 \ge t, Z)$. Furthermore

$$\mathrm{HD}_Z(t) = \psi(t) = \lambda(t; a = 1) - \lambda(t; a = 0),$$

where $\lambda(t; a)$ is obtained by marginalization using 13., and an Aalen additive hazard analysis (Aalen 1989), conditioning only on A, would thus provide a causally interpretable hazard difference. However, as the true $\lambda(t; A, Z)$ is not known to us this is of no practical use. Imagine instead that true DGP is given by 7.. Since A is binary, the additive hazards model

$$\lambda(t; A) = \lambda_0(t) + \psi(t)A \tag{14.}$$

remains correctly specified. However, the Aalen additive hazards analysis would now lead to the same misleading conclusion as was the case for the (extended) Cox regression analysis with a treatment-by-time interaction that we considered in Section 4. Indeed, the $\psi(t)$ in 14. has the explicit form

$$\psi(t) = \lambda_0(t)(e^{\beta} - 1)I(t \le \nu).$$

We see that $\psi(t) = 0$ for $t > \nu$ and an Aalen additive hazards analysis would therefore also indicate that the treatment effect vanishes after time ν, which we have seen is false. More details about causal interpretation of hazard differences are given in Martinussen et al. (2020).

7. Estimating the survival function efficiently

The survival function

$$P(T^a > t) = P(T > t \mid A = a)$$

is a meaningful causal quantity and one can contrast the two survival functions

$$\delta(t) = P(T^1 > t) - P(T^0 > t)$$

on the absolute scale to convey a potential causal effect of the treatment. In practice we can never be certain that the marginal Cox model is correctly specified, so one may prefer to estimate $\delta(t)$ using the contrast between the two corresponding Kaplan–Meier estimators if censoring does not depend on any baseline covariates W. However, one may use such baseline covariates to increase efficiency based on the corresponding efficient influence function, see for instance van der Vaart (1998). With n independent identically distributed

replicates of $D = \{W, A, \Delta, \tilde{T} = \min(T, C)\}$ so that T and C are conditionally independent given (A, W), the efficient influence function corresponding to $\delta(t)$ is

$$\tilde{\psi}(t, D; G) = \phi(t, D, G) - \delta(t), \tag{15.}$$

where

$$\begin{aligned}
\phi(t, D; G) =& \delta(t, W) + \int h(u, t, A, W) dM(u \mid A, W), \\
\delta(t, W) =& P(T > t \mid A = 1, W) - P(T > t \mid A = 0, W), \\
h(u, t, A, W) =& I(u \leq t) g(A, W) \frac{S(t \mid A, W)}{S(u \mid A, W) K_C(u \mid A, W)}, \\
g(A, W) =& \frac{A}{P(A = 1)} - \frac{1 - A}{P(A = 0)},
\end{aligned}$$

$S(u \mid A, W) = P(T > u \mid A, W)$ and $K_C(u \mid A, W) = P(C > u \mid A, W)$. Above, $G = \{S(\cdot \mid A, W), K_C(\cdot \mid A, W), P(A = 1)\}$ denotes the unknown parameters in the efficient influence function. In reality G is unknown and must be estimated, by G_n, say, leading to an estimator

$$\hat{\delta}(t) = n^{-1} \sum_{i=1}^{n} \phi(t, D_i; G_n)$$

that is semiparametrically efficient if the models used to obtain G_n are correctly specified and is consistent if either of $\{S(\cdot|A, W)\}$ or $\{K_C(\cdot|A, W), P(A = 1)\}$ are correctly specified; the estimator is said to be doubly robust. Hence, if the censoring does not depend on W then $\hat{\delta}(t)$ is consistent even if we misspecify $S(\cdot|A, W)$. The estimator $\hat{\delta}(t)$ is sometimes referred to as the one-step estimator (Benkeser et al. 2017). Alternatively, one may estimate $\delta(t)$ using Targeted Maximum Likelihood Estimation; see van der Laan and Rubin (2006), van der Laan and Rose (2011) and Díaz et al. (2019) for this specific target parameter in a discrete time setting. Ozenne et al. (2020) describe a similar approach for competing risk data focussing on the cumulative incidence function. Lu and Tsiatis (2008) describe how to use auxiliary covariates to increase efficiency if the marginal Cox regression model is correctly specified.

8. Concluding remarks

In this paper we have argued that neither a Cox HR nor time-varying hazard ratios are causally interpretable as hazard ratios. However, they may be used for descriptive purposes when addressing non-causal questions. For instance, suppose the outcome is time-to death after onset of a certain disease with two subclasses ($A = 1$ and $A = 0$) of the disease, and where we know from a previous study where model 5. was used, and was correctly specified, that $\exp(\beta) = 2$ with $\nu = 2$ years. Assume also that all other risk factors were equally balanced in the two subclasses at time 0 (onset of disease). Then, based on this analysis, we can say that patients in disease subclass 1 who survive the first two years from onset of the disease will have the same subsequent risk of dying as those in disease subclass 0 — information that may be useful for consulting patients at time ν =2 years, or later. Hence, even though the hazard ratio at any given time point mixes the differences between the two subclasses due to an overall different mortality risk and selection, this is irrelevant for the individual patient still at risk at that point in time.

It is of interest to be able to estimate a potential time-varying treatment effect. Imagine the effect of an implanted medical device, such as a stent, on survival for heart patients. Suppose that the medical device gradually deteriorates and stops being operational after some time ν. Is it possible to detect such a time-varying exposure effect based for instance on a study that randomises participants over this implanted medical device? We have shown that a piecewise constant Cox model is not appropriate for this purpose, as such an analysis mixes the treatment effect with selection.

SUMMARY POINTS

1. Cox regression analysis may be used for causal inference if the model is correctly specified.
2. The Cox hazard ratio is not causally interpretable as a hazard ratio, unless it is unity (no causal effect) or the unrealistic and untestable assumption 12. is met.
3. The Cox hazard ratio does not express, for instance, that treatment works equally effectively at all times, as the hazard ratio at a given time mixes differences between treatment arms due to treatment effect as well as selection.
4. The difficulties concerning the causal interpretation of hazard ratios pertain for hazard differences. The root cause of the problem is the interpretation of the hazard function itself, more than its particular structure.

FUTURE ISSUES

1. Estimation of time-varying treatment effects will require a precise formulation of what is meant by such, and also extensions to existing theory.
2. Further exploration concerning effect measures within survival analysis that have a causal interpretation and may give insight into time dynamics.

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