Hazard ratios from randomised trials are causal

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30th May 2019

Acknowledgement

Thanks to Rhian Daniel and Stijn Vansteelandt for helpful discussions.

Motivation

Hazard and the Cox model

Aalen et al (2015)

The HR is a causal effect

Conclusions

Outline

Motivation - Aalen et al 2015 [3]

Lifetime Data Anal (2015) 21:579–593
DOI 10.1007/s10985-015-9335-y

CrossMark

Does Cox analysis of a randomized survival study yield a causal treatment effect?

Odd O. Aalen[1] · Richard J. Cook[2] · Kjetil Røysland[1]

Aalen et al 2015

"Despite the fact that treatment assignment is randomized, the hazard ratio is not a quantity which admits a causal interpretation in the case of unmodelled heterogeneity."

"This makes it unclear what the hazard ratio computed for a randomized survival study really means. Note, that this has nothing to do with the fit of the Cox model. The model may fit perfectly in the marginal case with X as the only covariate, but the present problem remains."

Implications

Most people (I think) interpret the HR from a randomised trial as the causal effect of treatment.

Are they wrong to do so?

If they are, this is a serious problem which people should be more aware of.

My case

I will argue:

- the HR in an RCT is a valid causal effect
- but that it's interpretation indeed requires care, and it is likely often misinterpreted as something it's not

I will **not** argue that a Cox model / HR is the best way to quantify the effect of treatment on a time to event endpoint

Outline

Setup

A randomised trial is conducted.

Patients are randomised to active $X = 1$ or control $X = 0$.

Followed-up for time to event T, subject to censoring.

We let Z denote **all** baseline ($t = 0$) patient characteristics which are prognostic for T.

The hazard function and Cox model

The hazard function is

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T \leq t + \Delta t | T \geq t)}{\Delta t}$$

The hazard ratio comparing active to control treatment at time t is

$$HR(t) = \frac{\lambda(t|X = 1)}{\lambda(t|X = 0)}$$

Cox's model with treatment group as covariate assumes that

$$HR(t) = \frac{\lambda(t|X = 1)}{\lambda(t|X = 0)} = \exp(\beta)$$

Outline

Aalen et al 's critique - part 1

Aalen *et al* gives a number of perspectives for why the HR is not a valid causal effect.

Aalen *et al* show that survivors in two treatment groups are balanced w.r.t. baseline variables, i.e. $X \perp\!\!\!\perp Z | T > t$ only if

$$\lambda(t|X, Z) = a(t, X) + b(t, Z)$$

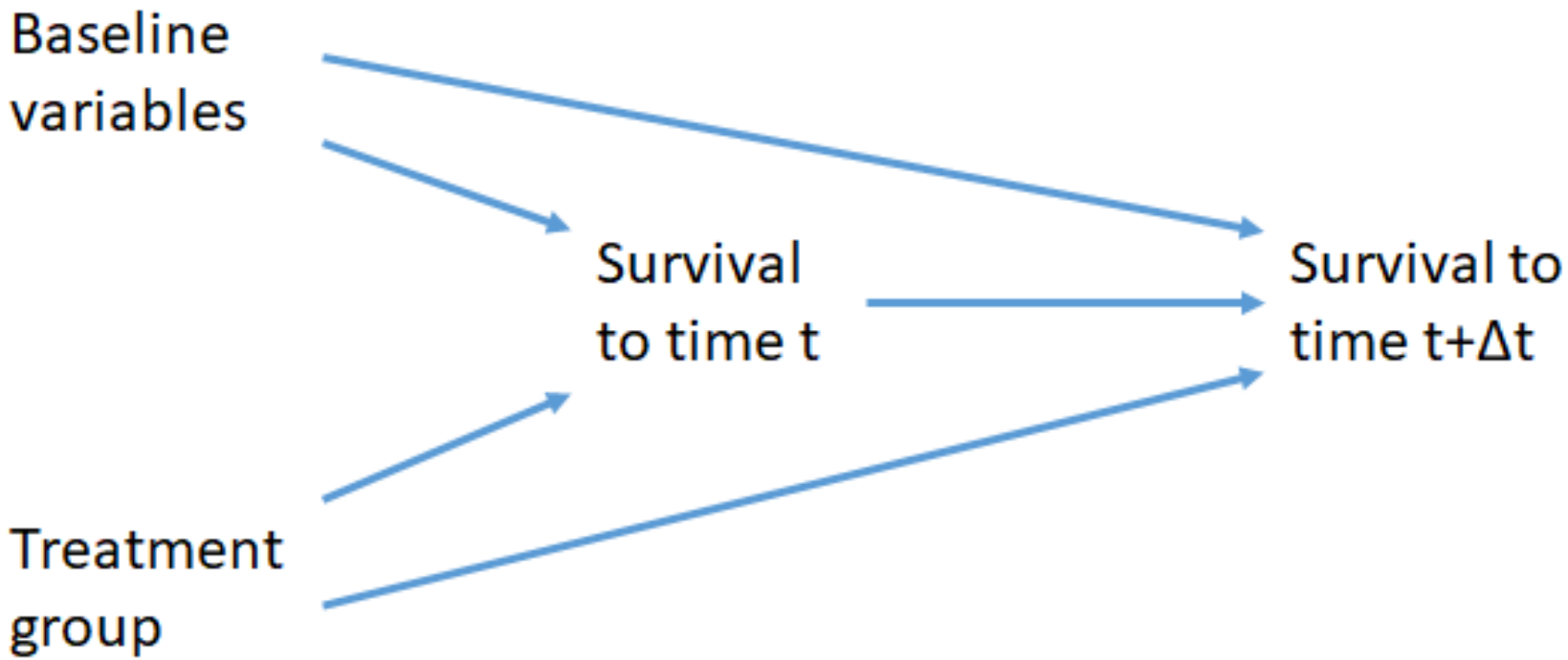
for functions $a(.,.)$ and $b(.,.)$.

A Cox model which includes X and Z as covariates does not satisfy this.

And if the above relation were satisfied, the marginal model given only X would not be a Cox model.

Aalen et al 's critique - part 2

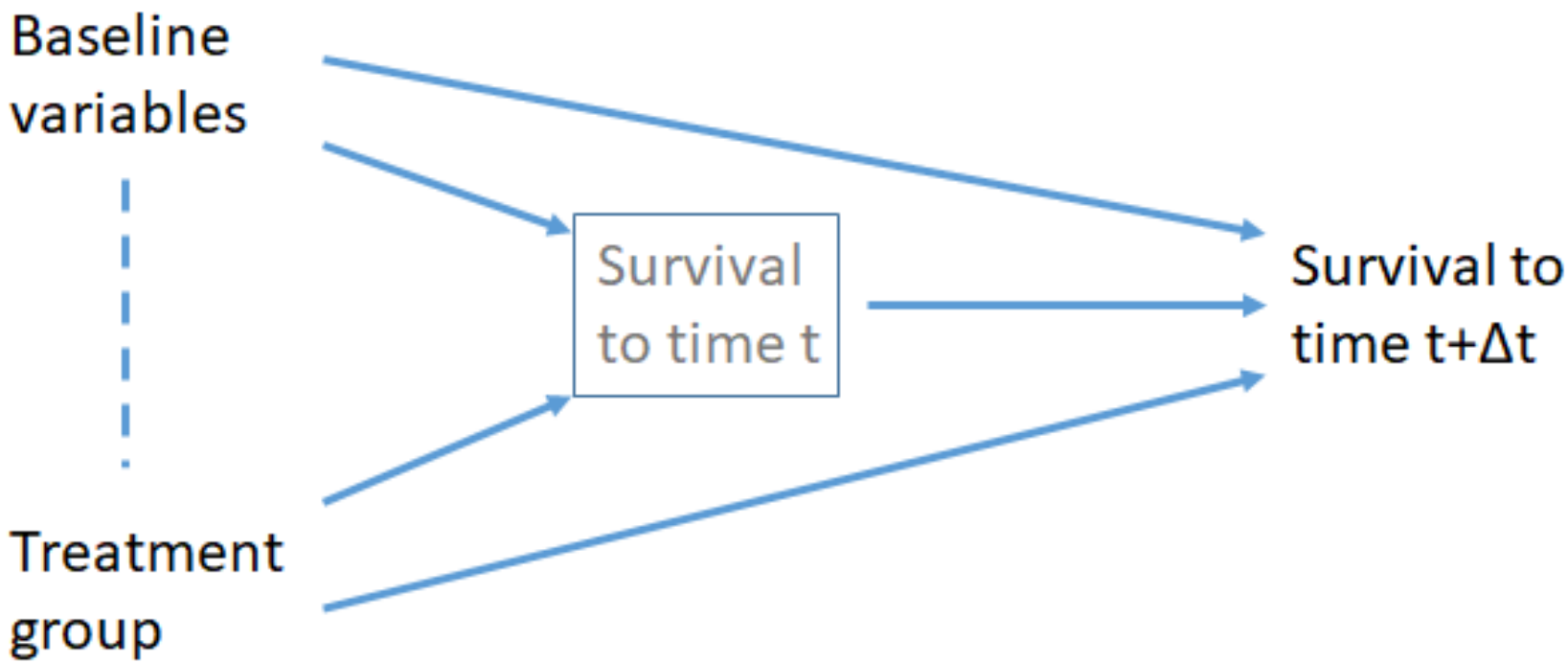
This issue can also be viewed via **directed acyclic graphs** (DAGs).



Aalen et al 's critique - part 2

The hazard ratio conditions on survival to t.

We are conditioning on a **collider**, and open up a path between baseline variables and treatment group.



Aalen et al 's critique - part 3

Aalen *et al* then consider an analysis based on the notion of an **individual level hazard** function.

This assumes individual level outcomes are inherently random, rather than deterministic.

Let $\lambda_i^0(t)$ and $\lambda_i^1(t)$ denote patient i's hazard under control and active treatments, and suppose:

$$\begin{aligned} \lambda_i^0(t) &= g(Z_i, t) \\ \lambda_i^1(t) &= g(Z_i, t)\exp(\beta) \end{aligned}$$

for baseline variables Z and function $g(.,.)$.

Then $\exp(\beta)$ represents the (common) individual level effect of treatment

Aalen et al 's critique - part 3 continued

In practice you can never hope to measure all the components of Z.

Like logistic regression, the Cox model is not **collapsible**.

If you marginalise over Z, you lose proportional hazards (in general), and the resulting HR coefficient for treatment X you estimate is not equal to $\exp(\beta)$.

Hence you can never hope to estimate the assumed common individual level effect $\exp(\beta)$ from the trial.

Outline

Counterfactuals

Following Hernán and Robins' [1], let T_i^0 and T_i^1 be counterfactual/potential times to event under control and active treatments, for a randomly selected individual i.

T_i^0 and T_i^1 could be deterministic or stochastic.

Individual level causal effects

Deterministic counterfactuals

A causal effect for individual i is some contrast of T_i^0 with T_i^1.

But since we only get to observe one of these, such effects are not identifiable.

Stochastic counterfactuals

A causal effect for individual i is some contrast of $\lambda_i^1(t)$ and $\lambda_i^0(t)$

But again for a given individual these are not identifiable, unless we make strong implausible assumptions, like e.g. that these individual level hazard functions are common across i.

Population or marginal causal effects

Hernán and Robins:

> *a population causal effect may also be defined as a contrast of, say, medians, variances, hazards, or cdfs of counterfactual outcomes. A causal effect can be defined as a contrast of any functional of the distributions of counterfactual outcomes under different actions or treatment values.*

Martinussen et al

Martinussen *et al* [2] note that

$$HR(t) = \frac{\lim_{\Delta t \to 0} P(t \leq T^1 \leq t + \Delta t | T^1 \geq t)/\Delta t}{\lim_{\Delta t \to 0} P(t \leq T^0 \leq t + \Delta t | T^0 \geq t)/\Delta t}$$

Those with $T^1 \geq t$ are not in general comparable with those with $T^0 \geq t$. Thus they conclude:

> *When viewed as a hazard ratio,* $\exp(\beta)$ *therefore does not represent a causal contrast.*

Hazard is a functional of population distribution

We can express the population/marginal hazard as

$$\lambda(t) = \frac{f(t)}{S(t)}$$

where $f(t)$ is the population density function of T and $S(t) = \int_t^\infty f(u)du$ is the survival function.

$\Rightarrow \lambda(t)$ is a function of the population density $f(t)$.

$HR(t)$ is a valid causal effect

Let $f^0(t)$ and $f^1(t)$ denote the population/marginal densities of the counterfactual failure times T^0 and T^1, and $S^0(t)$ and $S^1(t)$ the corresponding survival functions. Then

$$HR(t) = \frac{f^0(t)/S^0(t)}{f^1(t)/S^1(t)}$$

Thus $HR(t)$ is a contrast of a function of the two population densities $f^0(t)$ and $f^1(t)$, and **is** a valid population level causal effect.

$HR(t)$

$HR(t)$ **is** a population level causal effect.

$HR(t)$ is the ratio of instantaneous event rates in the survivors at time t if we assign the population to level 1 vs. level 0 of the treatment.

Interpreting changes in $HR(t)$

Suppose we assume T_i^0 and T_i^1 are stochastic.

Then in agreement with Aalen *et al* , I agree $HR(t)$ is **not** an individual level effect at time t, except under strong implausible assumptions.

Consequently, changes in $HR(t)$ **should not** be interpreted as representing solely changes in individual level treatment effect over time.

What if $HR(t)$ is constant over time?

If $HR(t)$ is constant over time, can we say more?

$HR(t) = \exp(\beta)$ a constant implies $S^1(t) = S^0(t)^{\exp(\beta)}$, and so

$$\exp(\beta) = \frac{\log\{S^1(t)\}}{\log\{S^0(t)\}}$$

But this interpretation is not nice nor easy to communicate.

Constant HR does not imply individual level effects are constant over time.

But is HR a useful causal effect measure?

$HR(t)$ is a valid population causal effect measure, but is it answering a useful question?

$\Rightarrow$ For individuals, the answer seems no in general. For policy makers at the population level, maybe.

If hazards are proportional, is HR useful?

$\Rightarrow$ For individuals and policy makers, maybe. But even here, important to note HR is not a risk ratio, as is sometimes implied [4].

In either case, other measures are arguably preferable. E.g. showing survival functions $S^0(t)$ and $S^1(t)$ and contrasts of these.

Outline

Conclusions

- $HR(t)$ **is a valid population level** causal effect, but its interpretation is subtle.
- $HR(t)$ is not an individual level causal effect, except under strong implausible assumptions.
- Changes in $HR(t)$ cannot legitimately be interpreted as changes in individual level treatment effect over time.
- It is likely that the HR and changes in $HR(t)$ are often not being interpreted correctly in practice.
- Even when $HR(t)$ is constant, alternatives to Cox's model may be preferable for quantifying causal effects.

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