Time-dependent confounders: Structural nested failure time models

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J.M. Robins: Structural nested failure time models

Ex. 1 *Alpha-tocopherol/beta-carotene study in Finland*

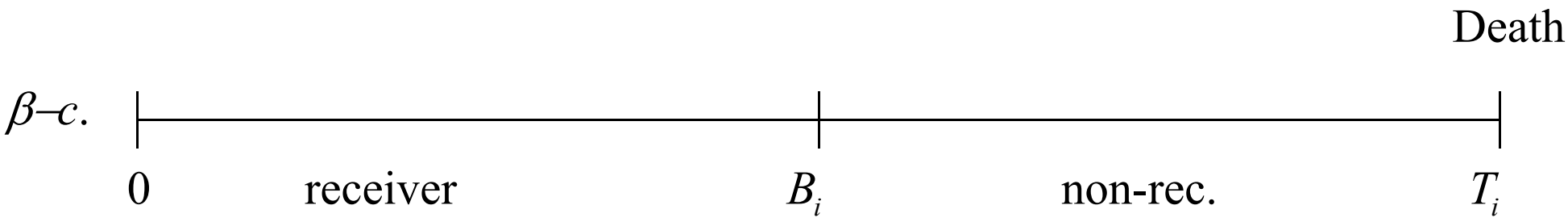
Main publication N Engl J Med **330**, 1020-1035, 1994

2 × 2 factorial design AT no effect vs. placebo
BC bad vs. placebo

by intention-to-treat

Reanalysis incorporating compliance:

P.A. Korhonen, N.M. Laird, J. Palmgren (1999). Statist.Med. **18**, 2879-2897.



U_i: survival time of person i if no $\beta - c.$

Model:

$U_i = T_i$ in placebo group

$U_i = \int_0^{Bi} e^{\psi_0} ds + \left(T_i - B_i\right)$ in $\beta - c.$ group

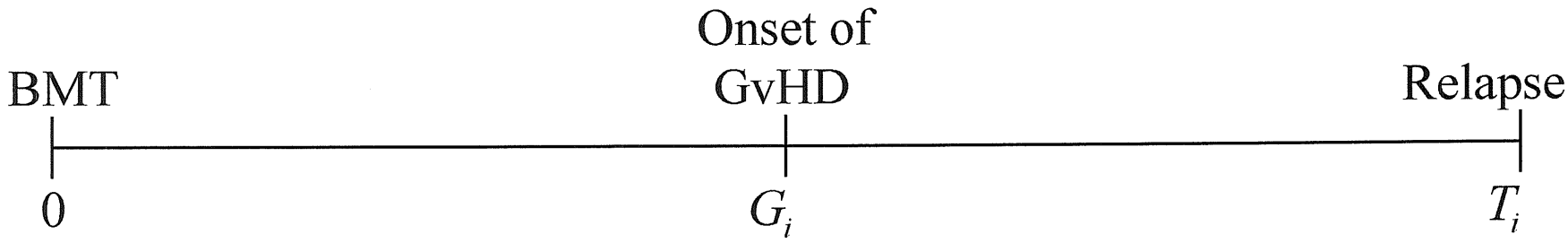
By randomisation, distribution of U_i should be the same in both groups: Note: U_i is counterfactual in the $\beta - c.$ group.

Estimate ψ_0 by requiring distr. U_i in plac. group = distr. U_i in $\beta - c.$ group.

Several complications re competing risk, censoring.

Ex. 2 Graft vs. Leukaemia Effect after Bone Marrow Transplantation using Structural Nested Failure Time Models

Keiding, Filiberti, Esbjerg, Robins, Jacobsen (1999). Biometrics **55**, 23-28.



$T_{G-,i}$ time to relapse if no GvHD

$T_{G+,i}$ time to relapse if always GvHD

Model:

$$T_{G-,i}(\psi_0) = \begin{cases} T_i & T_i \le G_i \\ G_i + (T_i - G_i)e^{\psi_0} & T_i > G_i \end{cases}$$

No randomisation!

Instead assume that we have measured all relevant (possibly time-dependent) confounders.

Conditional on these, nature does a sequential randomized experiment deciding whether or not to allocate GvHD.

$\Rightarrow$ estimate ψ_0 by requiring

$$\lambda_G(t|\mathcal{H}_t) = \lambda_G(t|\mathcal{H}_t, T_{G-}(\psi_0))$$

Details on Bone Marrow Transplantation example

163 pts DK, S, SF

AML = acute myeloid leukaemia
ALL = acute lymphoblastic leukaemia
CMU = cytomegalovirus infection

$$\text{CMV} \rightarrow \text{GvHD} \rightarrow \text{Relapse}$$
$$\searrow \text{CMV} \nearrow$$

Basic question: does GvHD decrease Relapse risk?

GvHD → Relapse

Estimated regression coefficients in Cox regression model for development of relapse

Covariate	$\hat{\beta}$	s.d.$(\hat{\beta})$	$\hat{\beta}$/s.d. $(\hat{\beta})$	exp $(\hat{\beta})$
Transplantation during				
Relapse	0.9644	0.4756	2.0277	2.6232
Remission	0	-	-	-
Donor CMV immunity at transplantation				
Yes	-1.3241	0.4271	-3.1005	0.2660
No	0	-	-	-
Transplantation during				
After 1^{o} Remission	2.0683	0.4950	4.1786	7.9111
Otherwise	0	-	-	-
Donor age				
> 20	1.4014	0.4075	3.4386	4.0609
≤ 20	0	-	-	-
GvHD (*t*)				
Yes at t	-1.1033	0.4134	-2.6687	0.3318
No at t	0	-	-	-

It seems that GvHD reduces risk to 1/3.

But what is the role of CMV?

CMV → GvHD

Estimated regression coefficients in model for development of GvHD with CMV as time-dependent covariate

Covariate	$\hat{\beta}$	s.d. $\left(\hat{\beta}\right)$	$\hat{\beta}$/s.d. $\left(\hat{\beta}\right)$	exp $\left(\hat{\beta}\right)$
Patient CMV immunity at transplantation				
Yes	0.7808	0.2598	3.0049	2.1833
No	0	-	-	-
Mismatch				
Yes	0.7796	0.2788	2.7958	2.1805
No	0	-	-	-
Transplantation during				
Relapse	0.9778	0.3318	2.9468	2.6587
Remission	0	-	-	-
CMV (*t*)				
Yes at t	1.0225	0.3681	2.7778	2.7803
No at t	0	-	-	-

CMV is associated with *increased* risk of later development of GvHD (estimated rate ratio = 2.8).

GvHD → Relapse

CMV ↗

Estimated regression coefficients in model for development of relapse with CMV as time-dependent covariate

Covariate	$\hat{\beta}$	s.d. $\left(\hat{\beta}\right)$	$\hat{\beta}$/s.d. $\left(\hat{\beta}\right)$	$\exp\left(\hat{\beta}\right)$
Transplantation during				
Relapse	0.9807	0.4780	2.0517	2.6664
Remission	0	-	-	-
Donor CMV immunity at transplantation				
Yes	-1.1989	0.4280	-2.8011	0.3015
No	0	-	-	-
Transplantation				
After 1^{o} Remission	2.1373	0.5014	4.2623	8.4765
Otherwise	0	-	-	-
Donor age				
> 20	1.9811	0.4914	4.0313	7.2509
≤ 20	0	-	-	-
GvHD (*t*)				
Yes at t	-1.1057	0.4184	-2.6429	0.3410
No at t	0	-	-	-
CMV (*t*)				
Yes at t	-1.0507	0.5437	-1.9326	0.3497
No at t	0	-	-	-

CMV decrases relapse risk (RR = 0.35)

GvHD

↘ CMV

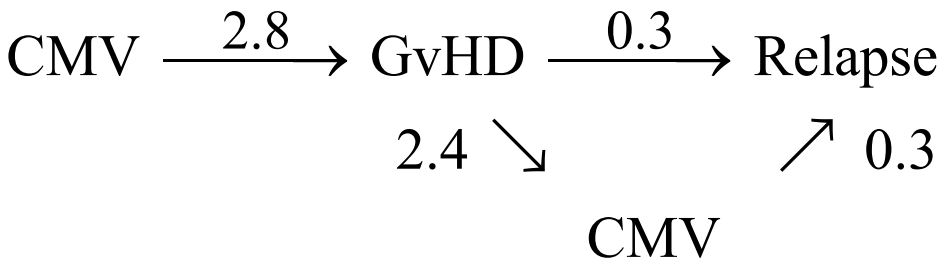
Estimated regression coefficients in model for development of CMV with GvHD as time-dependent covariate

Covariate	$\hat{\beta}$	s.d. $\left(\hat{\beta}\right)$	$\hat{\beta}$/s.d. $\left(\hat{\beta}\right)$	exp $\left(\hat{\beta}\right)$
CMV1 (*t*)				
Yes at t	0.8757	0.2993	2.9258	2.4007
No at t	0	-	-	-

GvHD increases risk of transition to CMV

Summary of effects

expressed as RR excluding time-fixed covariates



G-estimation approach

T_i: actual time to relapse for pt. i (could be censored due to death in remission or end of follow-up)

$T_{G-,i}$ counterfactual time to relapse for pt. i if GvHD did not exist

$T_{G+,i}$ counterfactual time to relapse for pt. i if i contracted GvHD immediately after transplantation

Assumption of no unmeasured counfounders:

$$\text{Onset of GvHD} \quad \frac{\perp\!\!\!\perp}{\mathcal{H}_t} \quad T_{G+,i} \;,\; T_{G-,i}$$

(covariate history at t)

Sharp null hypothesis of no effect of GvHD: $\forall_i : T_i = T_{G+,i} = T_{G-,i}$

Null hypothesis

Sharp: $T_i = T_{G+,i} = T_{G-,i}$ pointwise

Ordinary: $T_i = T_{G+,i} = T_{G-,i}$ in distribution

may be tested by testing

$$\lambda_G\left(t \middle| H(t)\right) = \lambda_G\left(t \middle| H(t), T\right)$$

: does intensity of GvHD depend also on relapse time T

$\lambda_G\left(t \middle| H(t)\right)$: intensity of onset of "treatment" GvHD

Modelling of effect of GvHD: time-dependent accelerated failure time model

G: time of GvHD T: relapse time

Assume acceleration parameter ψ:

$$T_{G-}(\psi) = \int_0^T e^{\psi I\{t>G\}} dt = \begin{cases} T & \text{for } T \le G \\ G + (T-G)e^{\psi} & \text{for } T > G \end{cases}$$

$\psi > 0$: $T_{G-} > T$ treatment harmful

$\psi < 0$: $T_{G-} < T$ treatment beneficial

$\psi = 0$: $T_{G-} = T$ treatment neutral

Note: T_{G+} corresponds to T for $G = 0$

so under this model $T_{G-}(\psi) = T_{G+}(\psi)e^{\psi}$

Censoring problems

End of follow-up: Assume potential censoring time C known;
reduce to $T \wedge C$, suitably accelerated for $\psi \neq 0$:

$T \wedge C_t(\psi)$ where for $t \leq G \quad C_t(\psi) = C,\ \psi \geq 0 \qquad C_t(\psi) = t + (C - t)e^{\psi},\ \psi \leq 0.$

Death in remission (competing risk)

$$\text{weight } W_i = \begin{cases} 0 & \text{if } i \text{ died in remission} \\ 1/P(\text{not dying in remission}) & \text{if not} \end{cases}$$

Inverse Probability of Censoring Weighted (IPCW) estimating equation
~ Horvitz-Thompson estimator in sampling

P (not dying in remission) estimated from Cox model with time-dependent covariates, allowing for some forms of dependent censoring.

Estimation of ψ

Estimate ψ by requiring

$$\lambda_G\left(t \middle| \mathcal{H}(t)\right) = \lambda_G\left(t \middle| \mathcal{H}(t),\ T_{G-}(\psi)\right)$$

Point estimate: the ψ yielding the least significant test statistic

Confidence interval: all ψ yielding acceptance

Score test using some suitable score function, here we use

$A_t(\psi) = I\left(T(\psi) < C_t(\psi)\right) I$ (not died in remission) W

Result

Cox regression of occurrence of GvHD

Covariate	$\hat{\beta}$	s.d.$(\hat{\beta})$	$\hat{\beta}$/s.d.$(\hat{\beta})$	exp $(\hat{\beta})$
Transplantation during				
Relapse	1.015	0.345	2.942	2.759
Remission	0	-	-	-
C_i (in days)	-0.000100	0.000215	-0.465	1.000
Patient CMV immunity at transplantation				
Yes	0.810	0.261	3.103	2.249
No	0	-	-	-
Mismatch				
Yes	0.882	0.280	3.150	2.416
No	0	-	-	-
CMV(*t*)				
Yes at *t*	0.630	0.350	1.800	1.877
No at *t*	0	-	-	-
A_t (0)	-0.00087	0.105	-0.0829	0.991

$\hat{\psi}_0 = -0.80$ 95% conf. iv. (–2.60, 0.90)

Interpretation

$\hat{\psi}_0 = -0.80$ insignificant tendency that GvHD *decelerates* time to relapse.

Relative increase in lifetime by getting GvHD immediately versus never getting it:

$$\frac{T_{G+} - T_{G-}}{T_{G-}} = e^{-\psi_0} - 1 \simeq 2.2 - 1 = 1.2$$

so that GvHD implies 120% increase in relapse-free time. This is in qualitative agreement with earlier analyses.