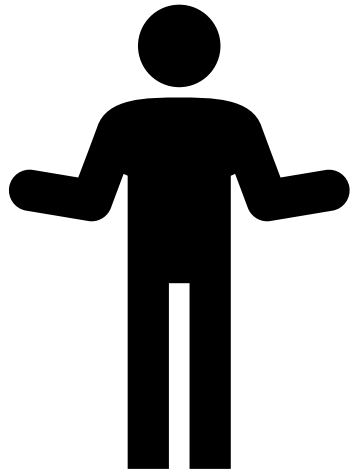
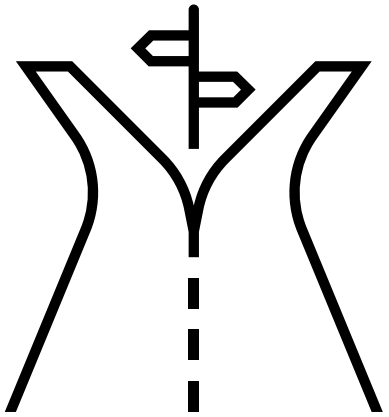
Causal prediction for medical decision making: Methods and practice



Advanced topics: Time-to-event outcomes and time-dependent strategies

Ruth Keogh

[Day 4, morning]



Outline

1. Extensions of estimands to time-to-event outcomes
2. Extensions to time-varying treatment strategies
3. Case-study: causal prediction in liver transplantation

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1. Extensions of estimands to time-to-event outcomes
2. Extensions to time-varying treatment strategies
3. Case-study: causal prediction in liver transplantation

Reminder of estimands for prediction under interventions

Prediction

$E(Y \mid X)$ risk of outcome conditional on X

X may include anything: no need to worry about confounding, mediation, colliders etc.

Causal inference

$E(Y^1 - Y^0)$ average treatment effect (ATE)

$E(Y^1 - Y^0 \mid M)$ conditional average treatment effect (CATE)

M effect modifiers; need to account for confounding and other potential biases

Prediction under interventions

$E(Y^1 \mid X)$ risk of outcome conditional on X if treatment would be 1

$E(Y^0 \mid X)$ risk of outcome conditional on X if treatment would be 0

X may include prognostic factors and effect modifiers; need to account for confounding and other potential biases

Reminder of estimands for prediction under interventions

Steno data example

Estimand element	Specification
Target population	Adults with type 1 diabetes who have not yet started using statins.
Time point of intended use	Attendance at a screening visit at the diabetes center
Outcome and prediction horizon	CVD death up to 5 years
Predictors	LDL, SBP, motion, polygenic risk score, sex, age, diabetes duration, smoking.
Treatment options	(i) Start using statins (ii) Do not start using statins

$E(Y^1|X^*) = \Pr(Y^1 = 1|X^*)$ Risk of CVD death up to 5 years conditional on X^* if a person were to start statins

$E(Y^0|X^*) = \Pr(Y^0 = 1|X^*)$ Risk of CVD death up to 5 years conditional on X^* if a person were NOT to start statins

Reminder of estimands for prediction under interventions

Steno data example

Suppose we have censored time-to-event data:
$\tilde{T}$: time to the event or censoring
D: event indicator

Estimand element	**Specification**
Target population	Adults with type 1 diabetes who have not yet started using statins.
Time point of intended use	Attendance at a screening visit at the diabetes center
Outcome and prediction horizon	CVD death up to 5 years $Y = 0,1$
Predictors	LDL, SBP, motion, polygenic risk score, sex, age, diabetes duration, smoking.
Treatment options	(i) Start using statins (ii) Do not start using statins

$E(Y^1|X^*) = \Pr(Y^1 = 1|X^*)$ Risk of CVD death up to 5 years conditional on X^* if a person were to start statins

$E(Y^0|X^*) = \Pr(Y^0 = 1|X^*)$ Risk of CVD death up to 5 years conditional on X^* if a person were NOT to start statins

Extension of estimands for time-to-event outcomes

Steno data example

Suppose we have censored time-to-event data:
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T^1: Counterfactual time to CVD death if a person starts statins
T^0: Counterfactual time to CVD death if a person does not start statins

Average treatment effect could be the risk difference: $\Pr(T^1 \leq 5) - \Pr(T^0 \leq 5)$

Extension of estimands for time-to-event outcomes

T^1: Counterfactual time to CVD death if a person starts statins
T^0: Counterfactual time to CVD death if a person does not start statins

Average treatment effect could be the risk difference:

$$\Pr(T^1 \leq 5) - \Pr(T^0 \leq 5)$$

Other causal estimands for time-to-event outcomes:

- Risk ratio
- Restricted mean survival time

Extension of estimands for time-to-event outcomes

T^1: Counterfactual time to CVD death if a person starts statins
T^0: Counterfactual time to CVD death if a person does not start statins

Average treatment effect could be the risk difference:

$$\Pr(T^1 \leq 5) - \Pr(T^0 \leq 5)$$

Other causal estimands for time-to-event outcomes:

- Risk ratio
- Restricted mean survival time

What about hazard ratios?

- Hazard ratios (and any measure based on hazards) have been shown to be lacking a clear causal interpretation, and estimands based on risks are preferable
- But models for hazards (e.g. the Cox model) can be used to obtain risks

Hernán MA. The hazards of hazard ratios. Epidemiology. 2010;21(1):13-5. doi: 10.1097/EDE.0b013e3181c1ea43.
Stensrud MJ, et al. Limitations of hazard ratios in clinical trials. European Heart Journal. 20191;40(17):1378–83.

Causal prediction for time-to-event outcomes

Steno data example

Suppose we have censored time-to-event data:
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Treatment options	(i) Start using statins (ii) Do not start using statins

T^1: Counterfactual time to CVD death if a person starts statins
T^0: Counterfactual time to CVD death if a person does not start statins

Estimands for causal prediction:

$$\Pr(T^1 \leq 5|X^*) \text{ and } \Pr(T^0 \leq 5|X^*)$$

Causal prediction for time-to-event outcomes

Estimands for causal prediction:

$$\Pr(T^1 \leq \tau | X^*) \text{ and } \Pr\left(T^0 \leq \tau | X^*\right)$$

Identification using observational data:

$$\Pr(T^1 \leq \tau | X^*) = \Pr(T \leq \tau | A = 1, X^*)$$

- ….if X^*includes all confounders, and under the consistency assumption
- To estimate this from censored time-to-event data we also need some assumptions about the censoring distribution
  - including that the event and censoring times are independent conditional on a set of covariates
- The g-formula and IPW methods covered yesterday can be modified to estimate these risks

Causal prediction for time-to-event outcomes

G-formula (regression) approach

```r
{r}
mod_A1<-glm(cvd_5year~LDL_0+motion+steno_prs+sex_male+age+diabetes_duration+smoking
+SBP_0,data=train[train$statin==1,],family="binomial")

summary(mod_A1)

mod_A0<-glm(cvd_5year~LDL_0+motion+steno_prs+sex_male+age+diabetes_duration+smoking
+SBP_0,data=train[train$statin==0,],family="binomial")

summary(mod_A0)
```

- The logistic regressions could be replaced by Cox regressions (for example)
- We can then obtain an estimate of the risks under the two interventions of interest
- Other methods/models can also be used

Causal prediction for time-to-event outcomes

IPW approach (if not all confounders are available in the deployment data)

```r
{r}
#fit the propensity score model
mod_ps<-glm(statin~LDL_0+motion+steno_prs,data=train,family="binomial")

#obtain weights
pi_L<-predict(mod_ps,newdata=train,type="response")
train$ipw<-ifelse(train$statin==1,1/pi_L,1/(1-pi_L))

#Fit weighted outcome model in those with A=1
mod_ipw_A1<-glm(cvd_5year~LDL_0+motion+sex_male+age+diabetes_duration+smoking+SBP_0
,data=train[train$statin==1,],family="binomial",weights=ipw)

#Fit weighted outcome model in those with A=0
mod_ipw_A0<-glm(cvd_5year~LDL_0+motion+sex_male+age+diabetes_duration+smoking+SBP_0
,data=train[train$statin==0,],family="binomial",weights=ipw)
```

- The weighted logistic regressions could be replaced by (e.g.) weighted Cox regressions
- We can then obtain an estimate of the risks under the two interventions of interest

Causal prediction for time-to-event outcomes: competing risks

Steno data example

$\tilde{T}$: time to the event or censoring
$D = 1$: event of interest
$D = 2$: competing event

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Target population	Adults with type 1 diabetes who have not yet started using statins.
Time point of intended use	Attendance at a screening visit at the diabetes center
Outcome and prediction horizon	CVD death up to 5 years
Predictors	LDL, SBP, motion, polygenic risk score, sex, age, diabetes duration, smoking.
Treatment options	(i) Start using statins (ii) Do not start using statins

Average treatment effect could be the difference in cumulative incidences:

$$\Pr(T^1 \leq 5, D = 1) - \Pr(T^0 \leq 5\ D = 1)$$

See Young et al. (2020) for a discussion of estimands in the competing events setting.

Young JG, Stensrud MJ, Tchetgen Tchetgen EJ, Hernán MA. A causal framework for classical statistical estimands in failure-time settings with competing events. Statistics in Medicine. 2020;39(8):1199–236.

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2. Extensions to time-varying treatment strategies
3. Case-study: causal prediction in liver transplantation

Time-varying treatment strategies

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"Point treatment" strategy

Time-varying treatment strategies

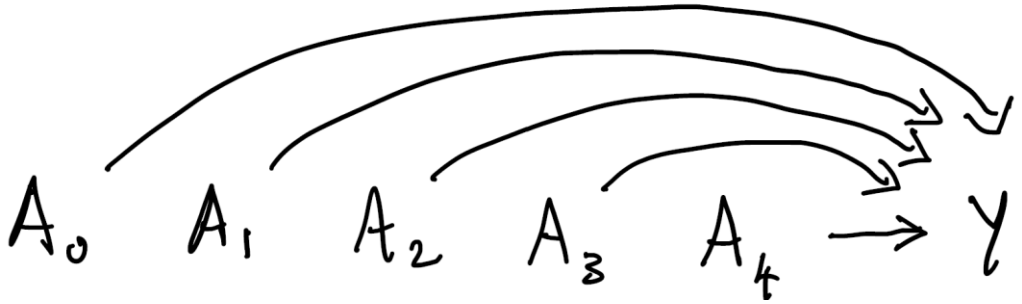
i. Start statins and continue for 5 years
ii. Do not start statins now or for the next 5 years
iii. Start statins within 3 months
iv. Start statins if your LDL cholesterol is above a threshold

Time-varying treatment strategies

Time-varying treatment strategies

i. Start statins and continue for 5 years
ii. Do not start statins now or for the next 5 years

We need some notation for treatment over time to state our causal estimand.



The history of treatment up to time 5 is denoted

$\overline{A}_T = \{A_0, A_1, A_2, A_3, A_4\}$

Time-varying treatment strategies

Time-varying treatment strategies

i. Start statins and continue for 5 years
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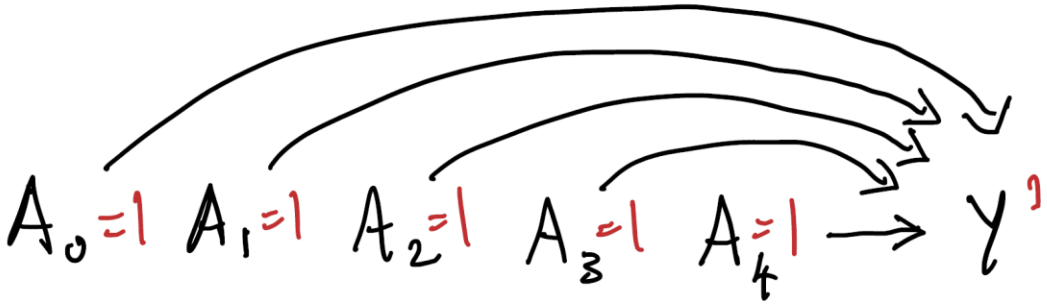
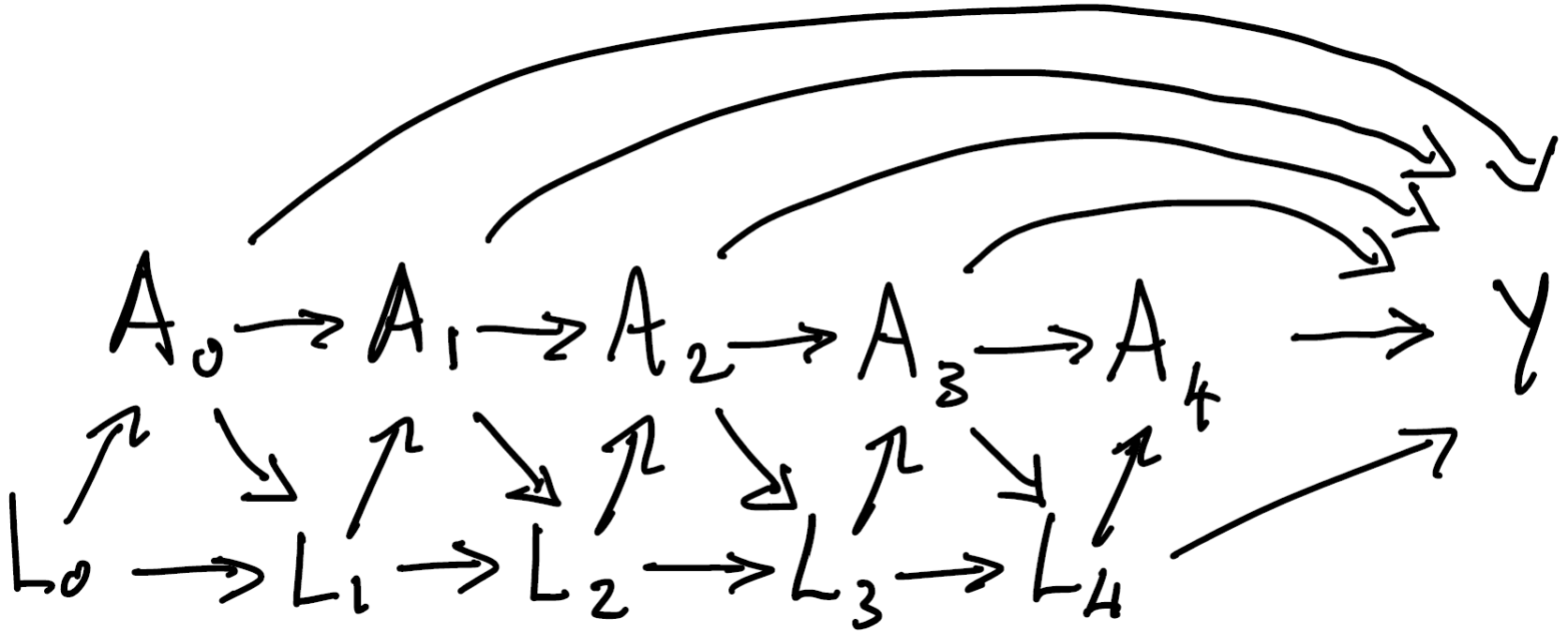


The history of treatment up to time 5 is denoted
$\overline{A}_T = \{A_0, A_1, A_2, A_3, A_4\}$

$Y^{\overline{A}_T=\{1,1,1,1,1\}} = Y^1$: counterfactual outcome if we were to set the sequence of treatment to be $\overline{A}_T = \{1,1,1,1,1\}$

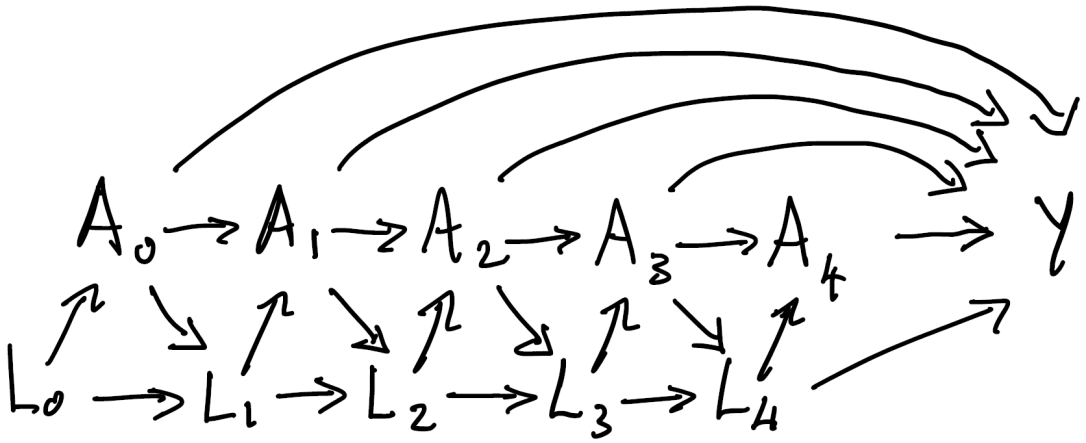
$Y^{\overline{A}_T=\{0,0,0,0,0\}} = Y^0$: counterfactual outcome if we wee to set the sequence of treatment to be $\overline{A}_T = \{0,0,0,0,0\}$

Time-varying treatment strategies: estimation using observed data



- To estimate $\mathrm{E}\left(Y^{\overline{A}_T=\{1,1,1,1,1\}}\right) - E(Y^{\overline{A}_T=\{0,0,0,0,0\}})$ from observed data is more challenging
- We now face the challenge of time-dependent confounding

Time-varying treatment strategies: estimation using observed data



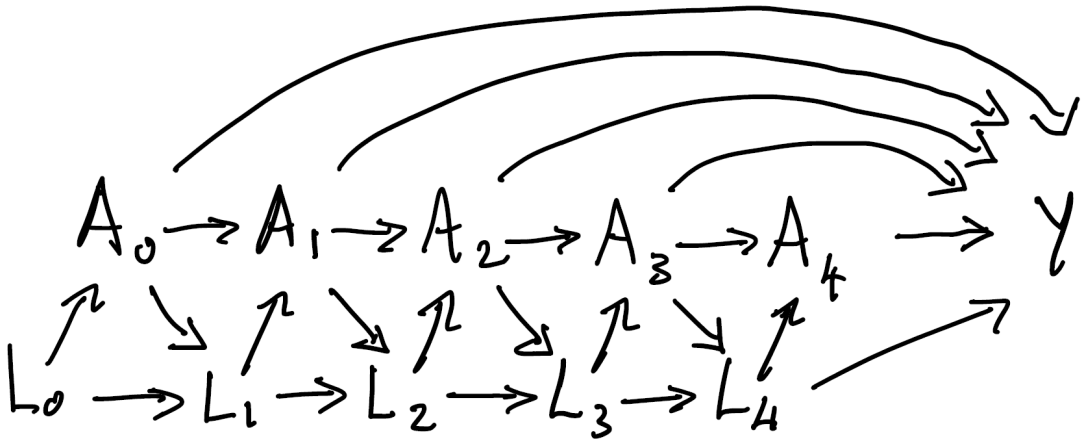
Daniel RM, Cousens SN, De Stavola BL, Kenward MG, Sterne JAC. Methods for dealing with time-dependent confounding. Statistics in Medicine. 2013;32(9):1584–618.

Hernan MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC. Part III

Estimation methods

- IPW using time-dependent weights
- Longitudinal g-formula
- Doubly-robust extensions

Time-varying treatment strategies: estimation using observed data



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What about causal prediction in this setting?

- We may be interested in

$$\Pr\left(Y^{\overline{A}_T=\{1,1,1,1,1\}} = 1|X^*\right) \text{ and } \Pr\left(Y^{\overline{A}_T=\{0,0,0,0,0\}} = 1|X^*\right)$$

- The analysis needs to account for time-dependent confounding while also giving us estimates that are conditional on the baseline predictors X^*

Time-varying treatment strategies: estimation using observed data

Lin et al. (2021) **A scoping review of causal methods enabling predictions under hypothetical interventions.** *Diagnostic and Prognostic Research* 5; 3.

- 3: Using observational data combined with estimates of treatment effects from trials
- 10: Using longitudinal observational data

Time-varying treatment strategies: estimation using observed data

Lin et al. (2021) **A scoping review of causal methods enabling predictions under hypothetical interventions.** *Diagnostic and Prognostic Research* 5; 3.

- 3: Using observational data combined with estimates of treatment effects from trials
- 10: Using longitudinal observational data

"Offset" method

Xu, Arnold, Stevens, …, Wood. **Prediction of Cardiovascular Disease Risk Accounting for Future Initiation of Statin Treatment.** American Journal of Epidemiology 2021; 190: 2000–2014.

Marginal structural models estimated using IPW

Sperrin, Martin, Pate, et al. **Using marginal structural models to adjust for treatment drop-in when developing clinical prediction models.** Statistics in Medicine. 2018; 37: 4142– 4154. https://doi.org/10.1002/sim.7913

Outline

1. Extensions of estimands to time-to-event outcomes
2. Extensions to time-varying treatment strategies
3. Case-study: causal prediction in liver transplantation

Keogh RH, Van Geloven N. **Prediction Under Interventions: Evaluation of Counterfactual Performance Using Longitudinal Observational Data.** *Epidemiology.* 2024;35(3):329.

Case study: Liver transplantation

For people on the liver transplant waitlist, at a given moment when a transplant becomes available:

- what would their survival be if they received the transplant?
- what would their survival be if the do not receive the transplant?

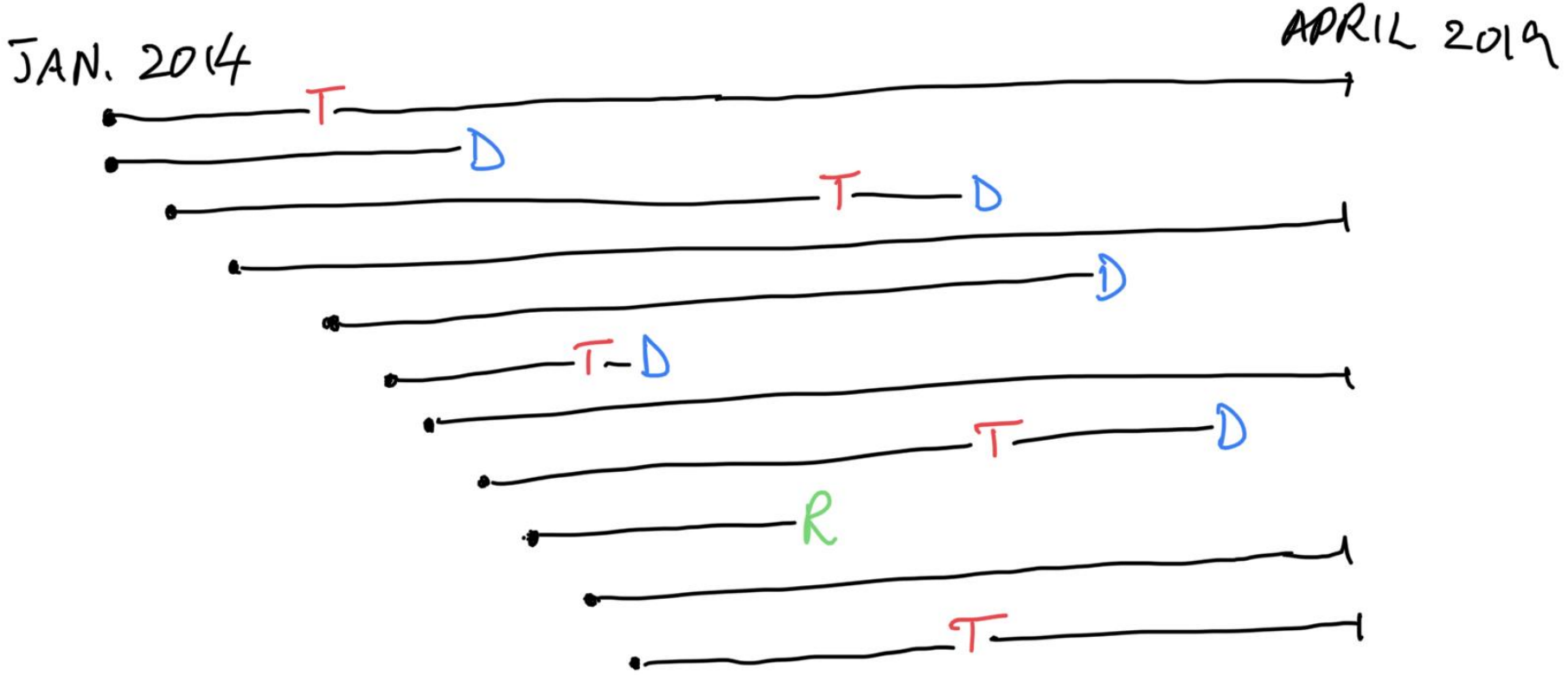
Data from the Scientific Registry of Transplant Recipients:

- People joining the liver transplant waitlist in the US from January 2014 to April 2019: n=43,190
- Information on date of transplant, removal from wait list, death (pre- or post transplant)
- Individual characteristics recorded longitudinally

Case study: Liver transplantation

Population	People on the waiting list for a liver transplant
Moment(s) of intended use	Any moment a new donor organ becomes available
Intervention options	(1) Receive a liver transplant at that time; (2) Not receiving a transplant at that time or in the future.
Outcome and prediction horizon	Death or removal from the transplant waitlist due to worsening health status, up to 3 years.
Predictors	22 individual characteristics: demographics, disease characteristics, biomarkers, co-morbidities

Case study: causal prediction in liver transplantation



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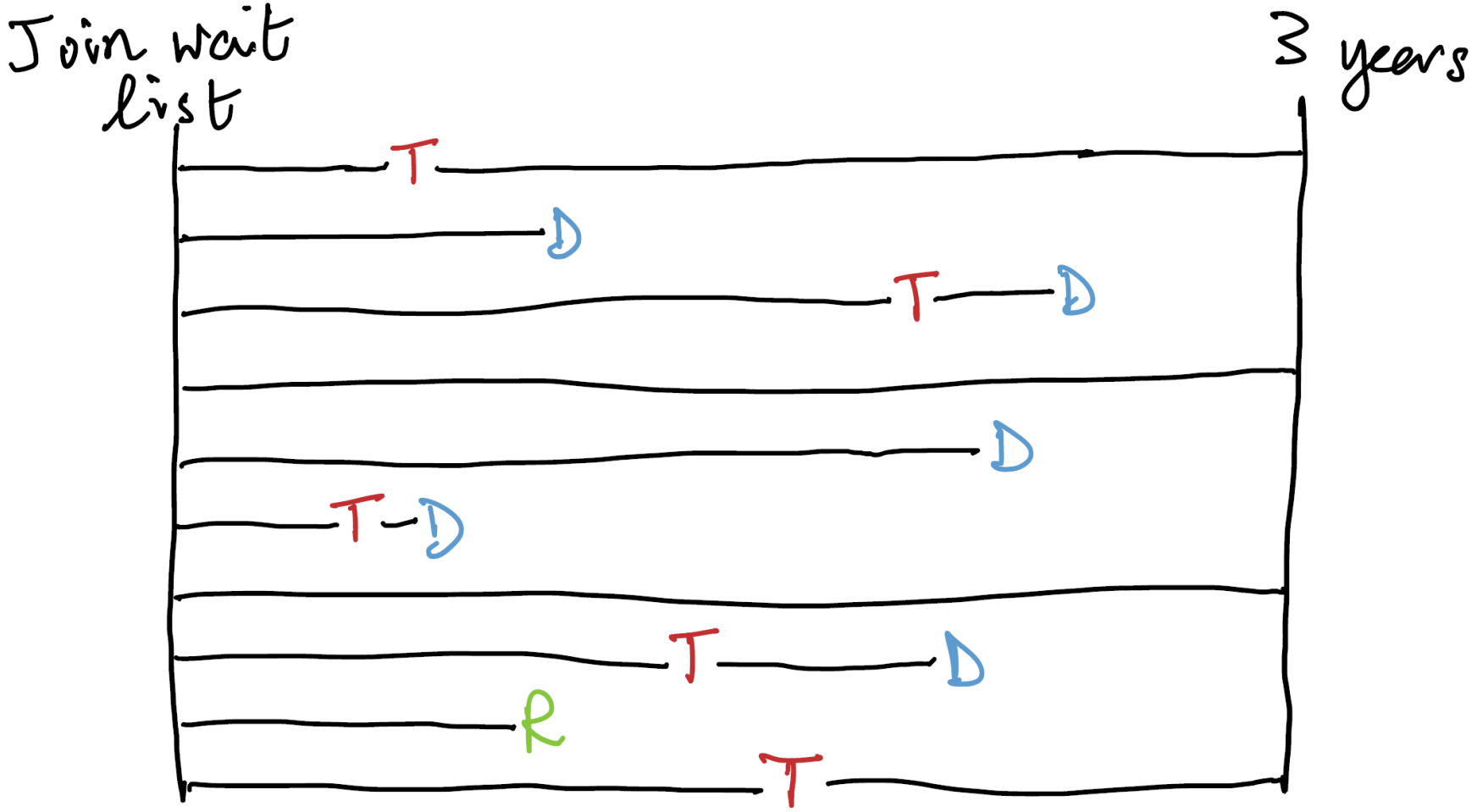

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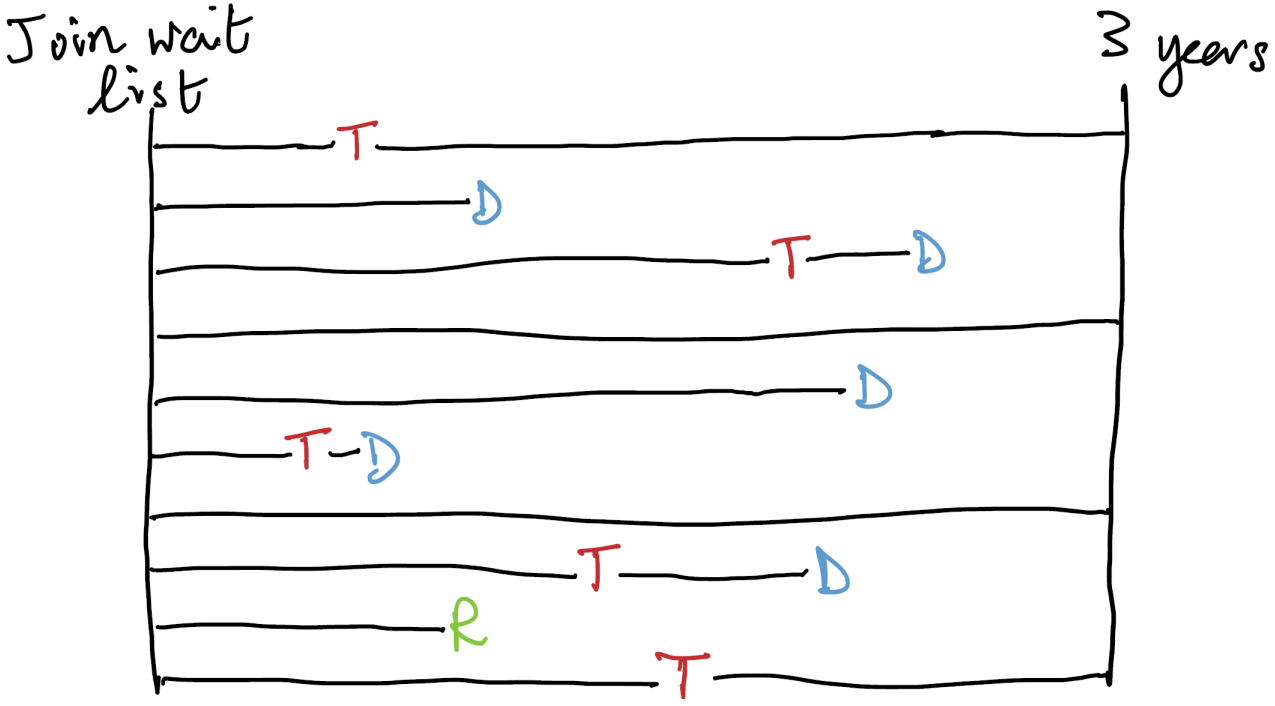
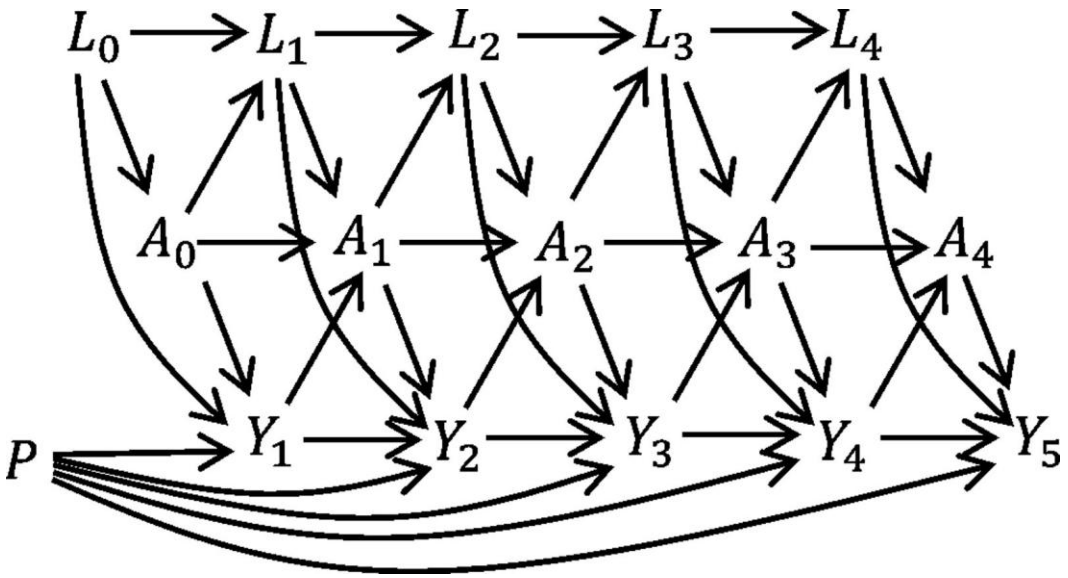


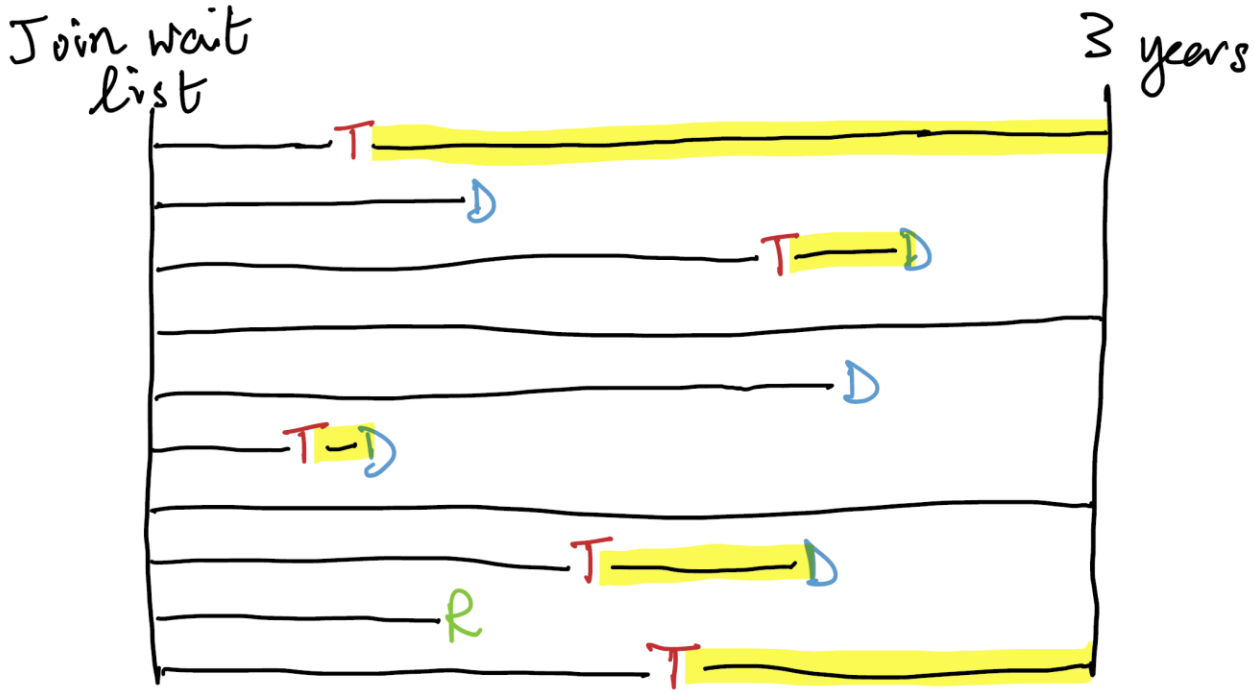


Case study: causal prediction in liver transplantation

Intervention options	(1) Receive a liver transplant at that time; (2) Not receiving a transplant at that time or in the future.

Causal prediction model

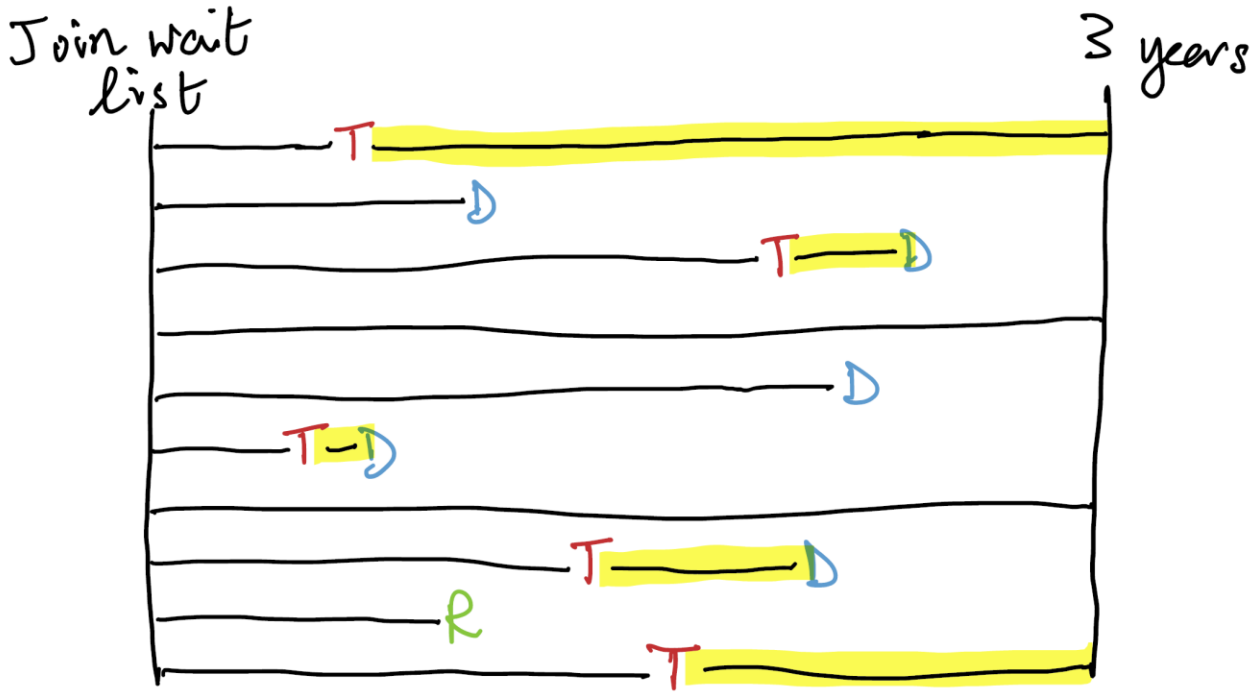
- Developed using post-transplant survival data, using predictors measured just before transplant
- We can use this model to obtain predictions of post-transplant survival, even for people who do not receive a transplant



Case study: causal prediction in liver transplantation

Intervention options	(1) Receive a liver transplant at that time; (2) Not receiving a transplant at that time or in the future.

Person ID	Time of death/ censoring	Death	Covariates at transplant
1			
2			
3			
Etc …			



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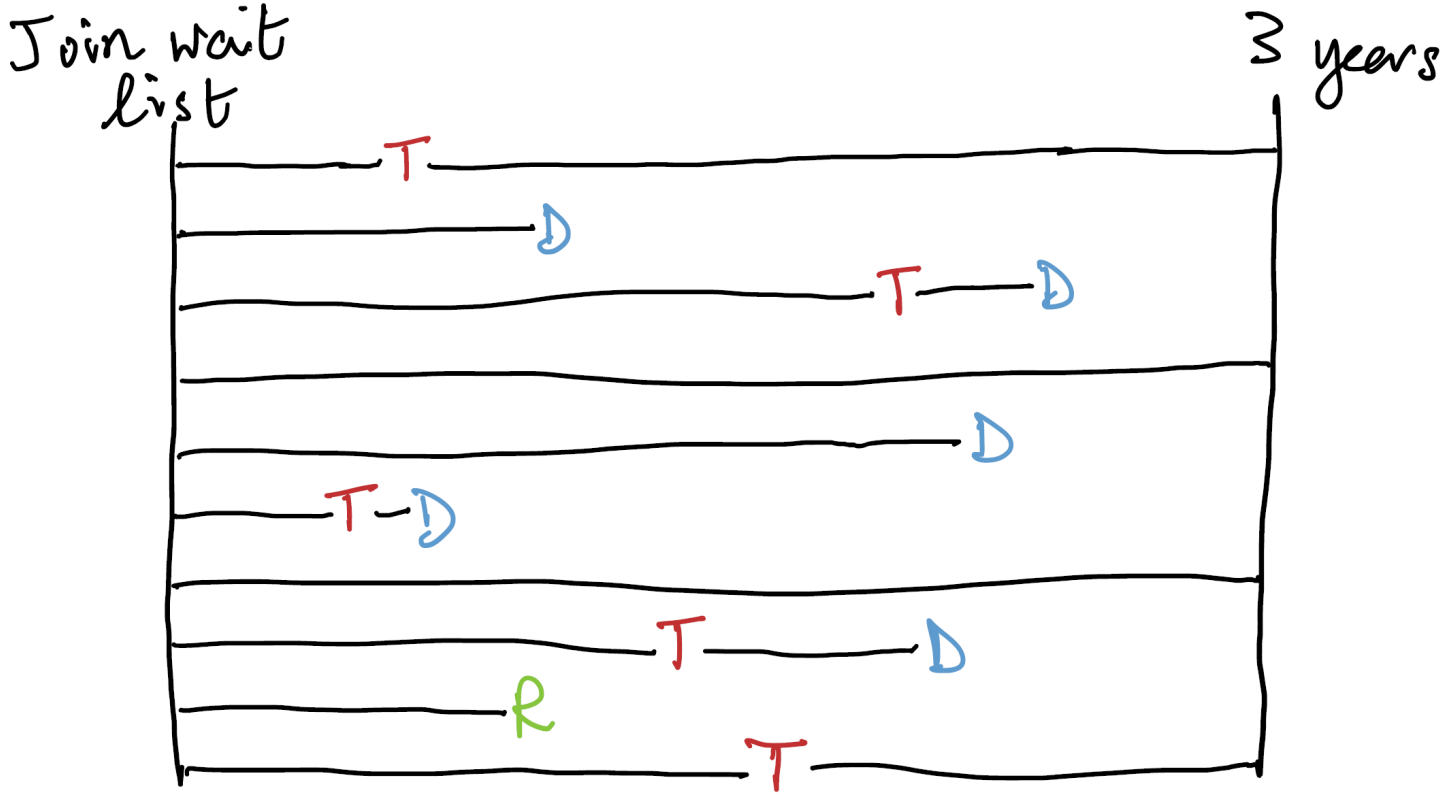

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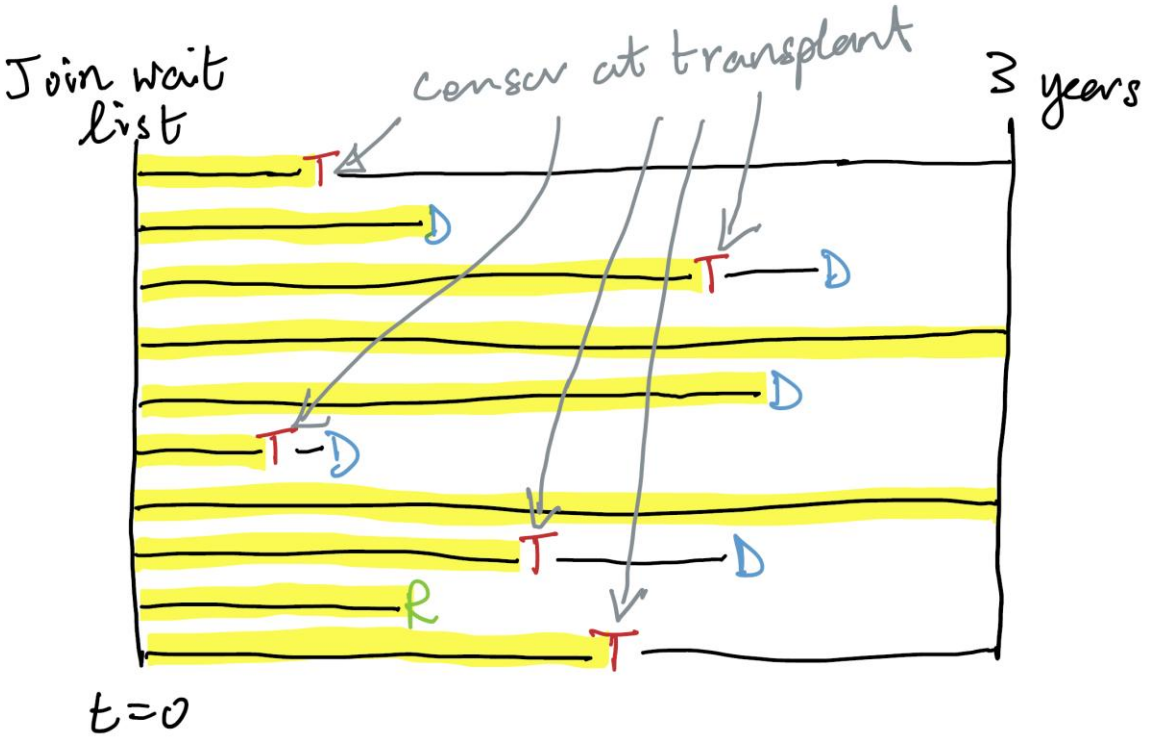

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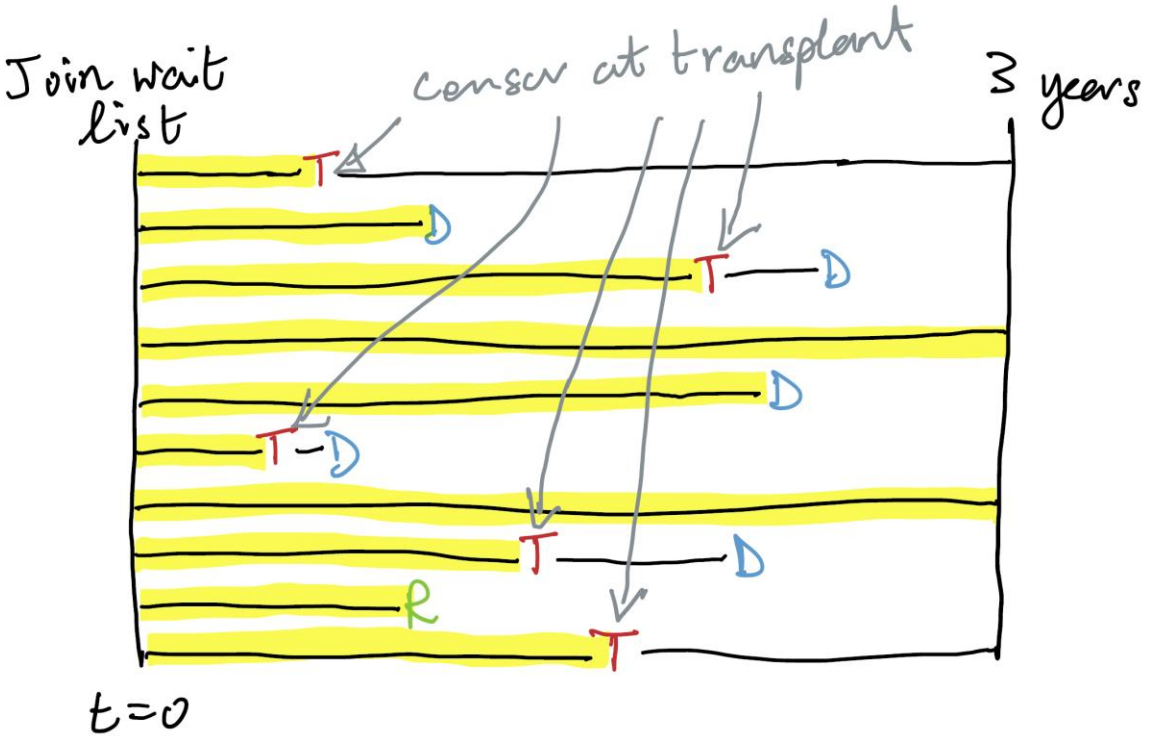

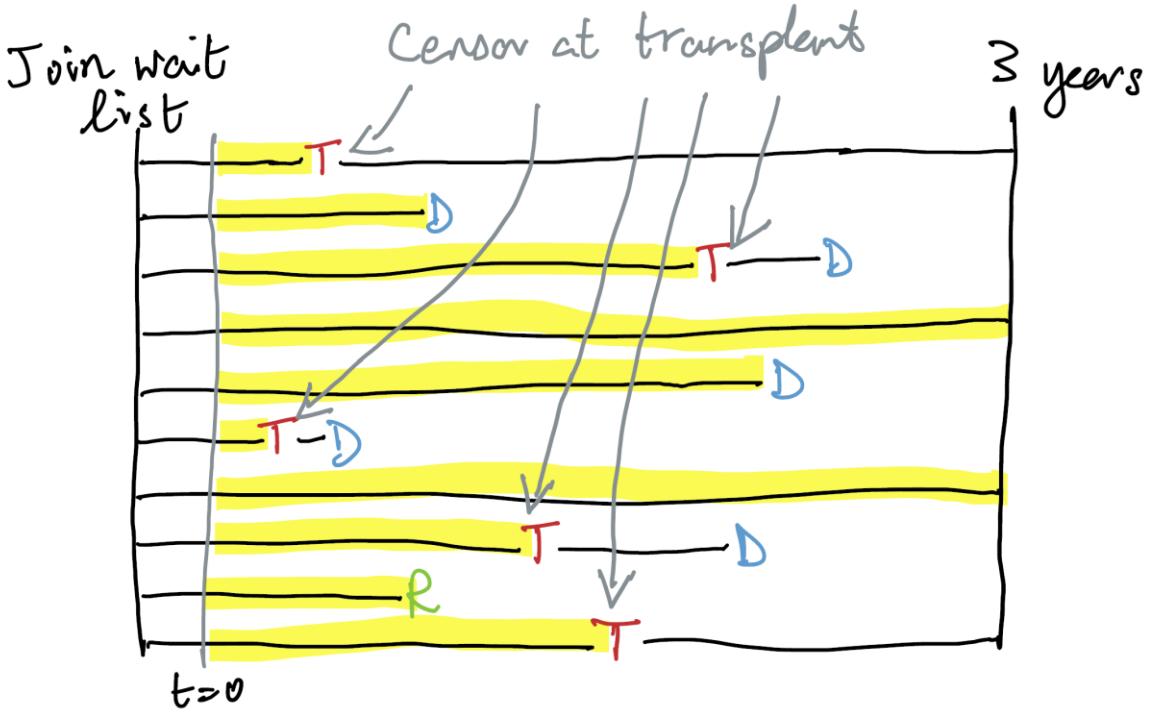

Case study: causal prediction in liver transplantation

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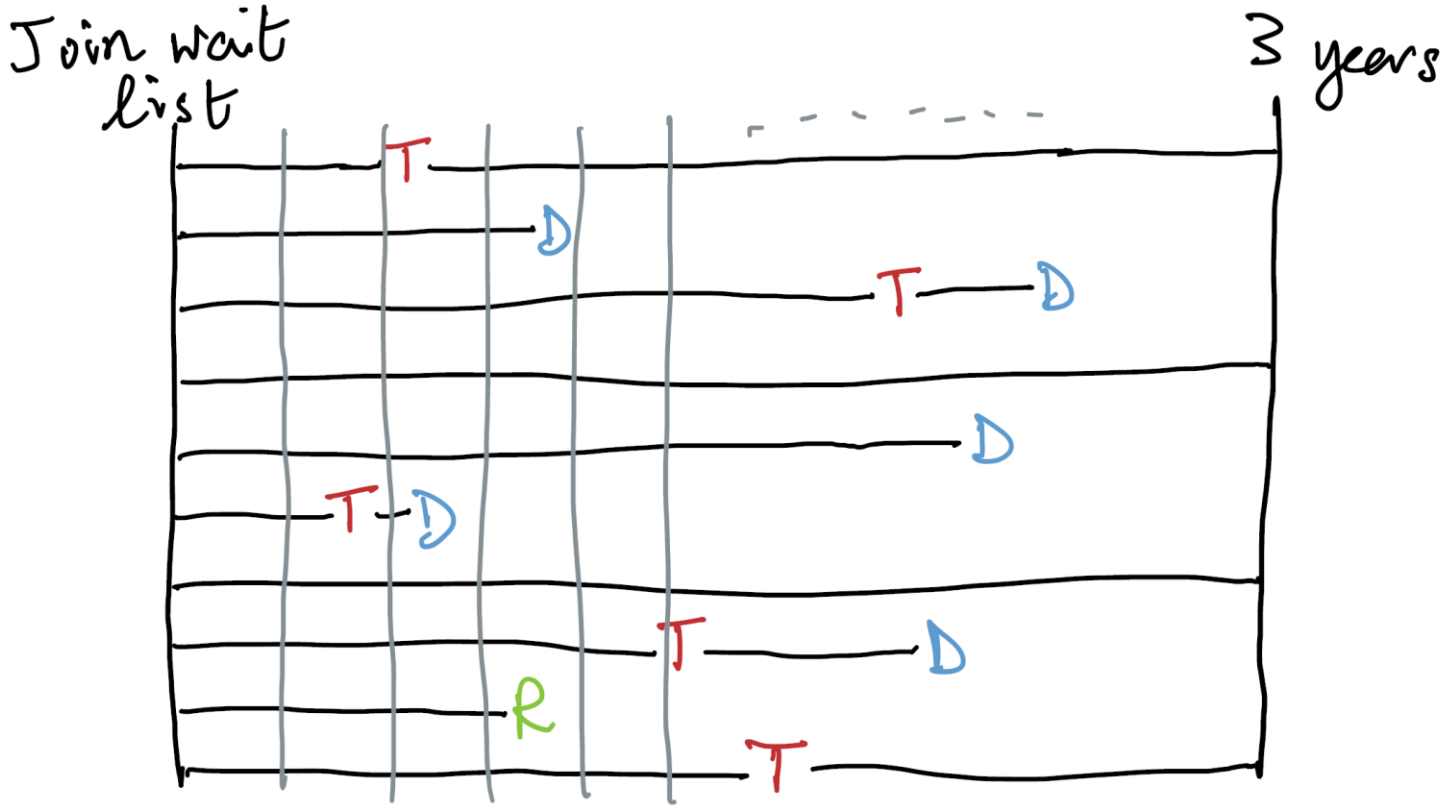


Case study: causal prediction in liver transplantation

Intervention options	(1) Receive a liver transplant at that time; (2) Not receiving a transplant at that time or in the future.

Person ID	Start time	Stop time	Transplant	Removal	Death	Covariates
1						
1						
1						
2						
2						
Etc						

Person ID	Start time	Stop time	Transplant	Removal	Death	Covariates
1						
1						
1						
2						
2						
Etc						

Person ID	Start time	Stop time	Transplant	Removal	Death	Covariates
1						
1						
1						
2						
2						
Etc						

Case study: causal prediction in liver transplantation

Intervention options	(1) Receive a liver transplant at that time; (2) Not receiving a transplant at that time or in the future.

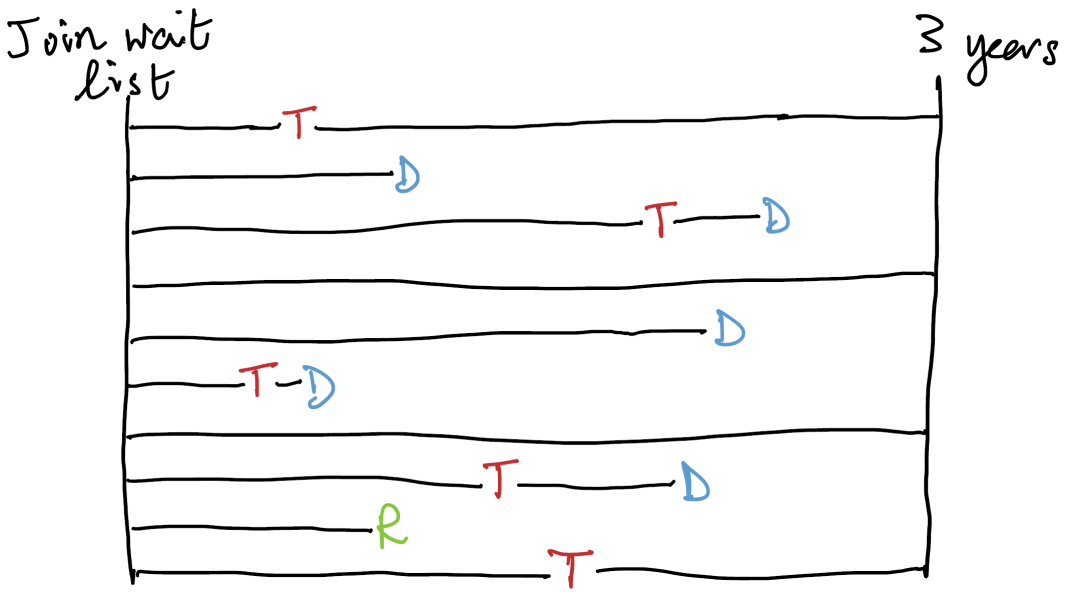
Causal prediction model for survival without transplant

1. Estimate inverse probability of censoring weights (IPCW) to address censoring at transplant – pooled logistic regression model using baseline and time-updated covariates
2. Fit a Cox model to the stacked data:
   - Using predictors measured at 'baseline'
   - Using time-updated IPCW

Gong, Schaubel. Estimating the average treatment effect on survival based on observational data ands using partly conditional modeling. Biometrics 2017; 73: 134-144.

Van Houwelingen. Dynamic Prediction by Landmarking in Event History Analysis.

Case study: causal prediction in liver transplantation



Training data (70% sample)

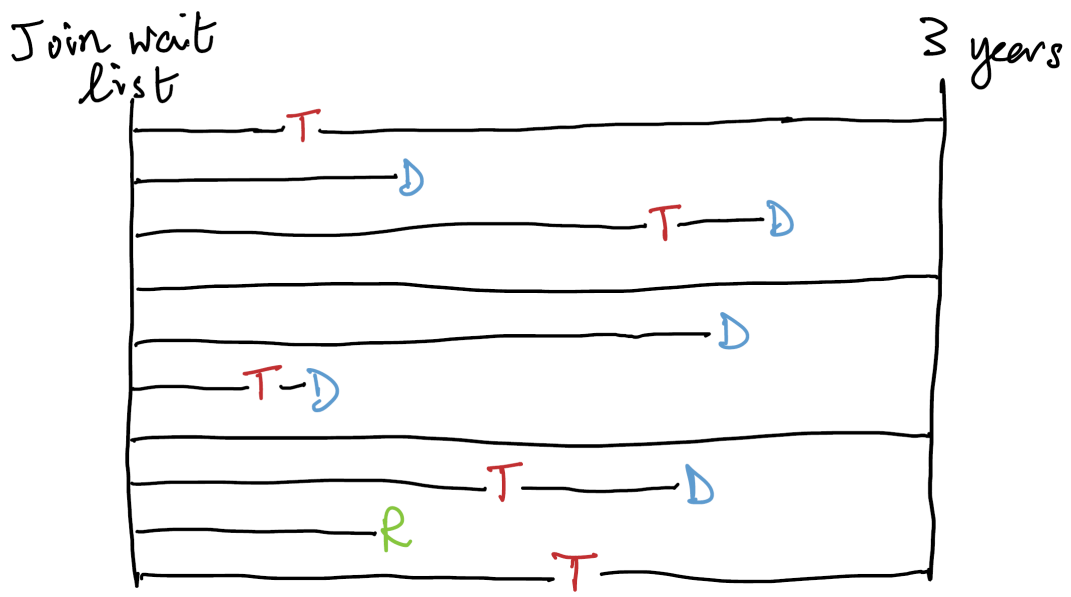
- Developed models for estimating risk under the two transplant strategies

Test data (30% sample)

- Estimate the predictive performance of our causal prediction models.

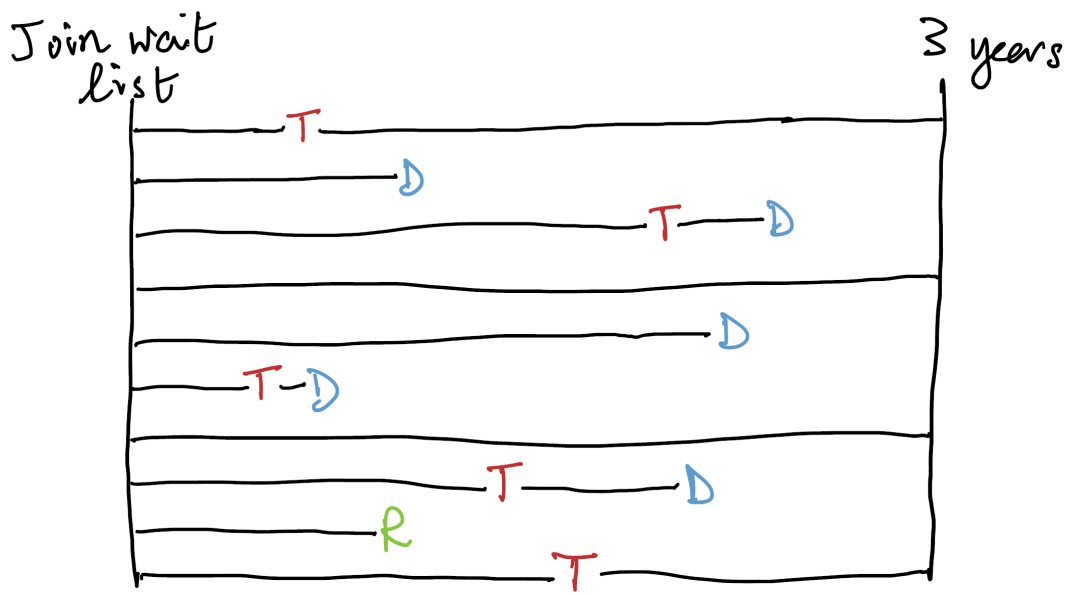
Fundamental problem: We cannot directly compare each person's predicted risk under a given treatment strategy with their observed outcome under that strategy

Case study: causal prediction in liver transplantation



- In the test data we obtain predictions under the two interventions for each individual based on the model developed in the training data
- These are compared with estimates of the ‘observed’ outcomes under each strategy – these are estimated using similar causal methods as are used in the training step

Case study: causal prediction in liver transplantation



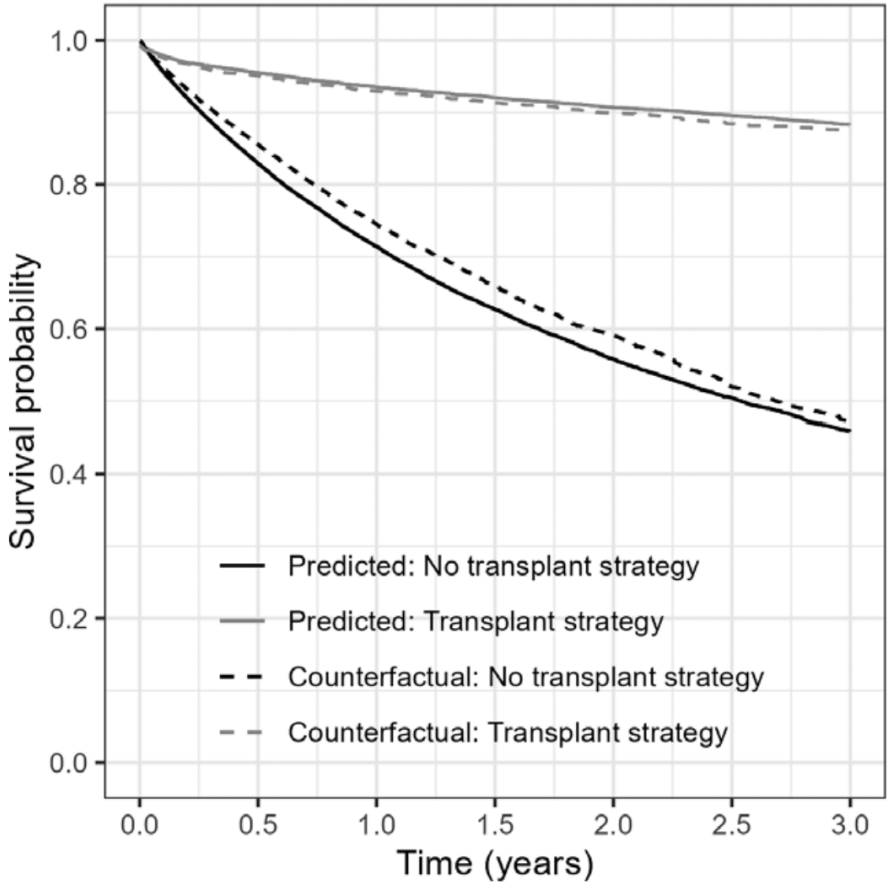
- In the test data we obtain predictions under the two interventions for each individual based on the model developed in the training data
- These are compared with estimates of the 'observed' outcomes under each strategy – these are estimated using similar causal methods as are used in the training step

We showed how a set of validation measures can be estimated in this setting:

- Calibration
- Discrimination (C-index, AUC)
- Overall performance (Brier score)

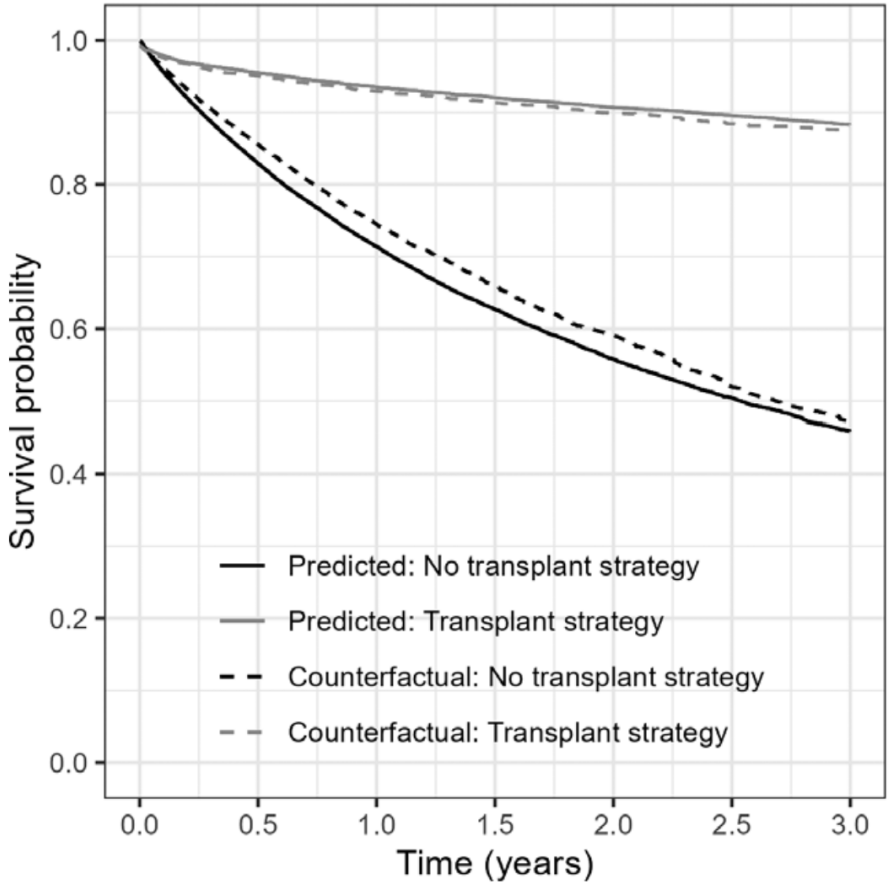
Case study: causal prediction in liver transplantation

Mean calibration

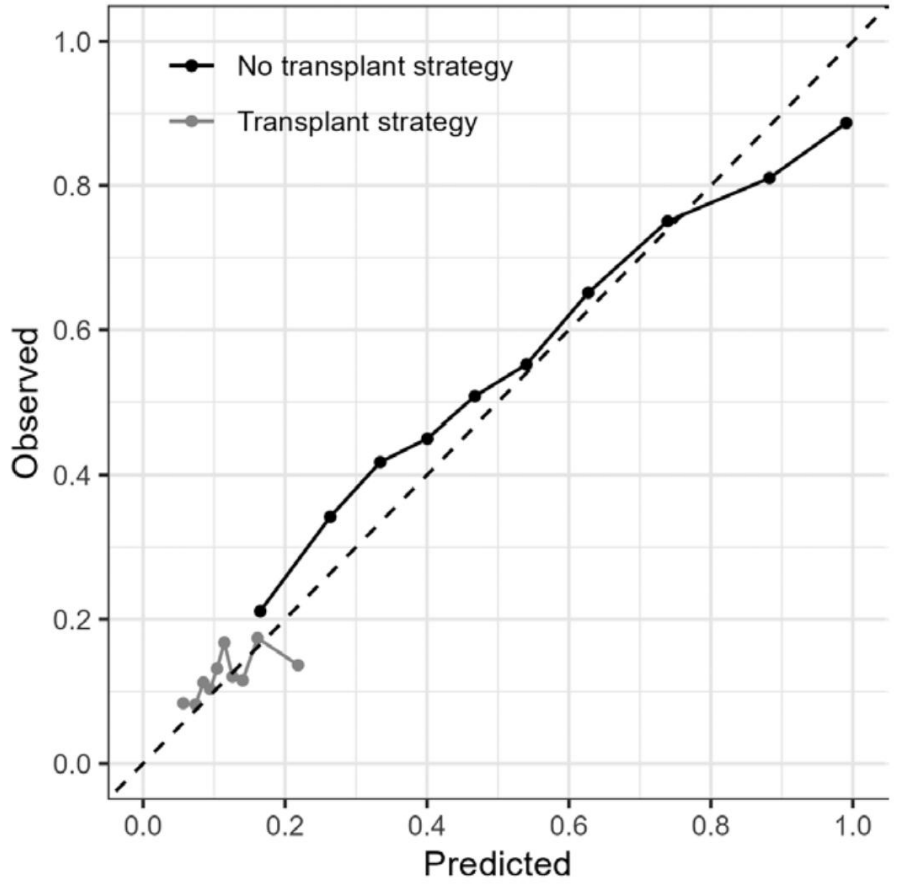


Case study: causal prediction in liver transplantation

Mean calibration



Calibration



Case study: causal prediction in liver transplantation

Other measures of predictive performance

TABLE. Liver Transplant Application: Evaluation of Counterfactual Performance

	Strategy	
	No Transplant	**Transplant**
Calibration: observed/expected ratio based on risk by 3 years	0.983	1.060
Discrimination: C-index up to 3 years	0.749	0.561
Discrimination: AUCt at 3 years	0.781	0.552
Prediction error: scaled Brier score (%) at 3 years	66.8	12.0

AUCt, cumulative/dynamic area under the receiver operating characteristic curve.

Case study: causal prediction in liver transplantation

Population	People on the waiting list for a liver transplant
Moment(s) of intended use	Any moment a new donor organ becomes available
Intervention options	(1) Receive a liver transplant at that time; (2) Not receiving a transplant at that time or in the future.
Outcome and prediction horizon	Death or removal from the transplant waitlist due to worsening health status, up to 3 years.
Predictors	22 individual characteristics: demographics, disease characteristics, biomarkers, co-morbidities

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Case study: causal prediction in liver transplantation

Population	People on the waiting list for a liver transplant
Moment(s) of intended use	Any moment a new donor organ becomes available
Intervention options	(1) Receive a liver transplant at that time; (2) Do not receive this liver, but remain on the wait list and can receive a transplant in the future
Outcome and prediction horizon	Death or removal from the transplant waitlist due to worsening health status, up to 3 years.
Predictors	22 individual characteristics: demographics, disease characteristics, biomarkers, co-morbidities