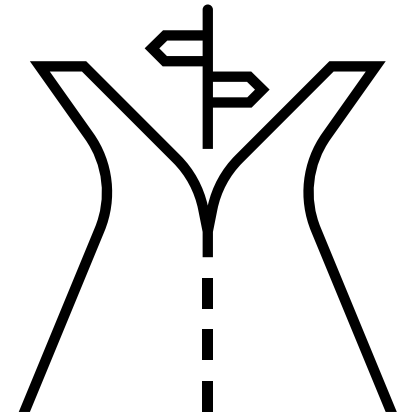
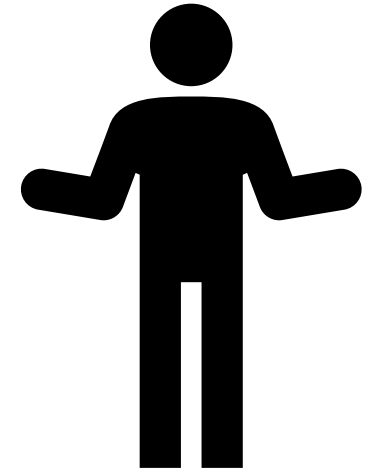


Causal prediction for medical decision making: Methods and practice

Case study: platelet transfusion
Nan van Geloven

[Day 4, morning]

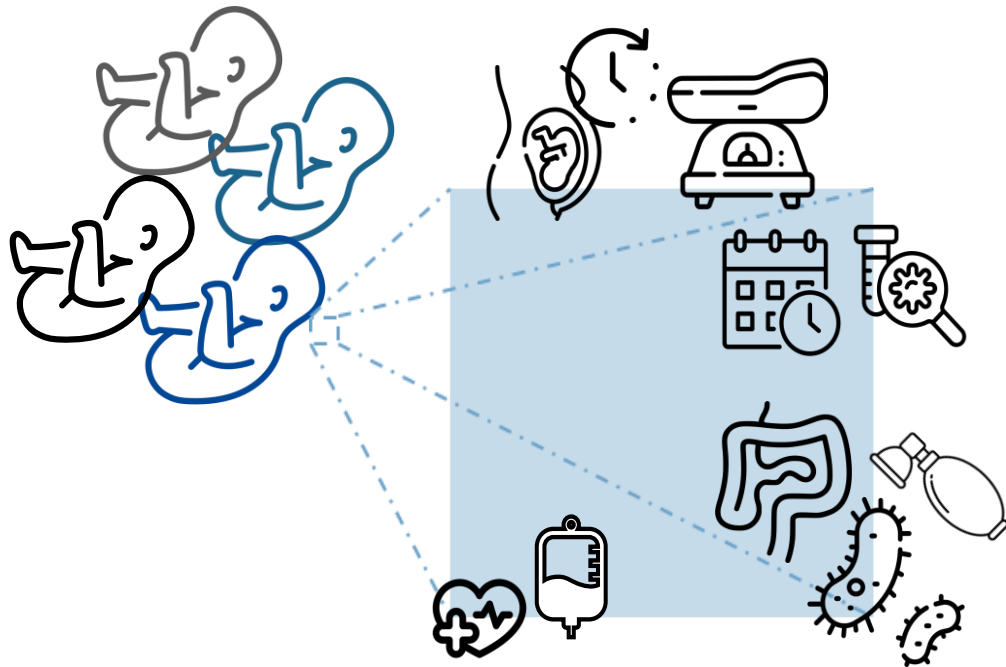


Case study: prophylactic platelet transfusions in the NICU

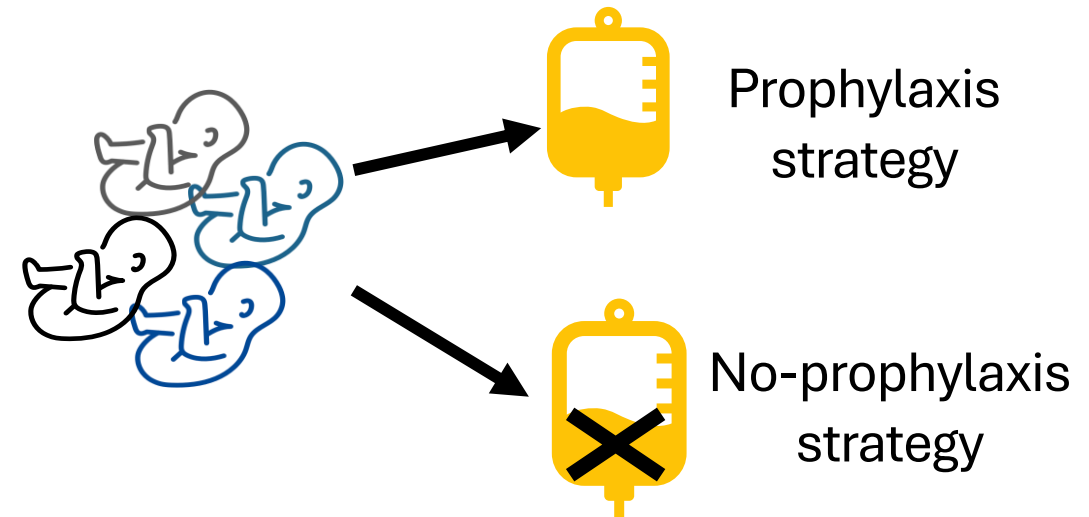
- Unknown which (and when) preterm infants with severe thrombocytopenia benefit from prophylactic transfusions
- Current guidelines only based on platelet count

Aim: develop a prediction model that can support individual transfusion decisions

Clinical factors in addition to platelet count



Prediction of 3-day risk of major bleeding or death under two transfusion strategies:



PROSPECT study:

Model development



International multicenter cohort study (14 NICUs)



Jan 2017 – Dec 2021



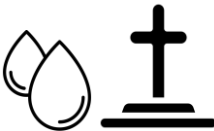
1042 infants with severe thrombocytopenia



Gestational age & birth weight:
28 weeks (IQR 26-30)
900 grams (IQR 698-1230)



65% received ≥ 1 transfusion



23% major bleeding or death within 10 days

MONET study:

Model validation

National multicenter cohort study (7 NICUs)

Jan 2010 – Dec 2015

637 infants with severe thrombocytopenia

Gestational age & birth weight:
28 weeks (IQR 26-30)
900 grams (IQR 710-1177)

73% received ≥ 1 transfusion

21% major bleeding or death within 10 days

Data

id	from	to	t_pc	c_plt_tx	c_majbl	c_death	f_age
4	0	1	9	0	0	0	2.1
4	1	2	9	0	0	0	2.1
4	2	3	9	0	0	0	2.1
4	3	4	9	0	0	0	2.1
4	4	5	16	0	0	0	2.1
4	5	6	16	0	0	0	2.1
4	6	7	16	0	0	0	2.1
4	7	8	16	1	0	0	2.1
4	8	9	16	1	0	0	2.1
4	9	10	16	1	0	0	2.1
4	10	11	16	1	0	0	2.1
4	11	12	16	1	0	0	2.1
4	12	13	16	1	0	0	2.1
4	13	14	16	1	0	0	2.1
4	14	15	16	1	0	0	2.1
4	15	16	16	1	0	0	2.1
4	16	17	16	1	0	0	2.1
4	17	18	16	1	0	0	2.1
4	18	19	203	1	0	0	2.1
4	19	20	203	1	0	0	2.1

Hourly status from birth up to 21 days

Time-fixed and time-varying predictors

+ time-varying confounders:
perinatal asphyxia, planned invasive procedures, IV bolus therapy, PDA treatment

Transfusions

Time-related challenges

1. Infants may receive more than one transfusion over time
→ how to define the prophylaxis and no-prophylaxis treatment strategies?
2. Later transfusion decisions are based on parameters (eg platelet count) affected by earlier transfusion decisions
→ time-varying confounding
3. Model should be applicable repeatedly over time
→ multiple prediction moments

1. Defining the treatment strategies



No-prophylaxis strategy: if an infant were not to receive a platelet transfusion for the next 3 days



Prophylaxis strategy: if an infant were to receive a prophylactic platelet transfusion within 6 hours (and possibly again later)

Considerations:

- What is relevant to the decision?
- Time between decision making, ordering and applying transfusion
- How much evidence in the data on these strategies?

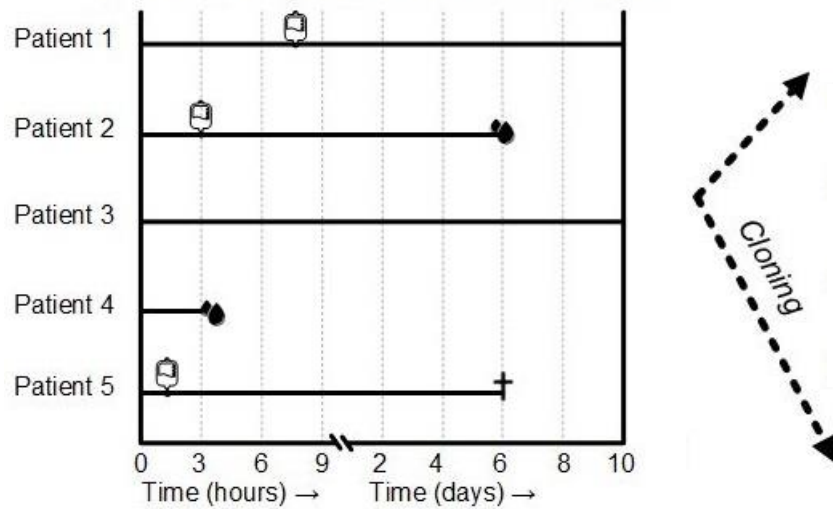
Estimand

Target population	Preterm neonates with a gestational age <34 weeks and severe thrombocytopenia defined as platelet count $<50 \times 10^9/L$, admitted to a tertiary care NICU in Western Europe
Time point(s) of intended use	At any timepoint during the first week after the onset of severe thrombocytopenia
Outcome and prediction horizon	Major bleeding or death; primary time horizon 3 days
Predictors	Time fixed: gestational age, small-for-gestational age. Time varying: mechanical ventilation, platelet count, cumulative number of previous platelet transfusions, necrotizing enterocolitis, sepsis, inotropes, postnatal age
Treatment option(s)	<i>No-prophylaxis strategy</i> : no platelet transfusion during 72 hours after the prediction time point. <i>Prophylaxis strategy</i> : administering one or more platelet transfusions within 6 hours after the prediction time point

2. Adjusting for time-varying confounding

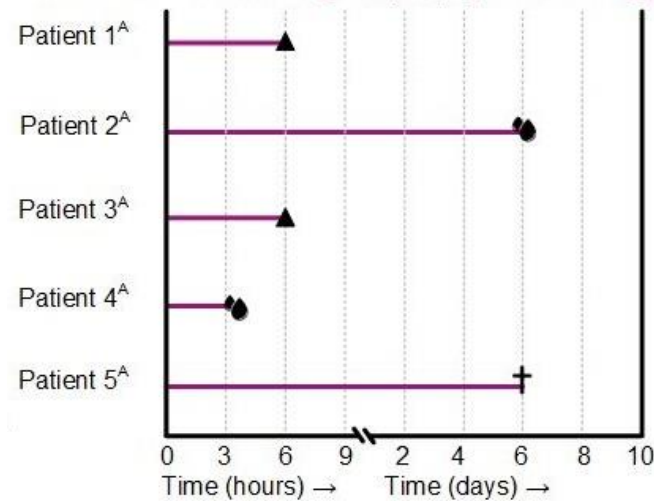
Step 1: Cloning

Dataset D: longitudinal observational data

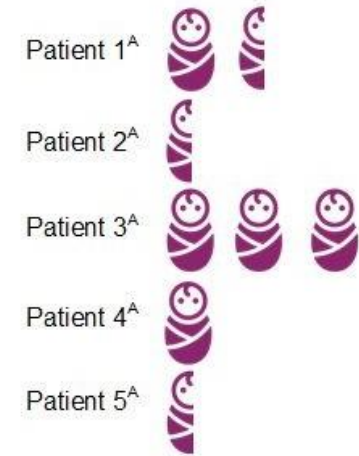


Step 2: Censoring

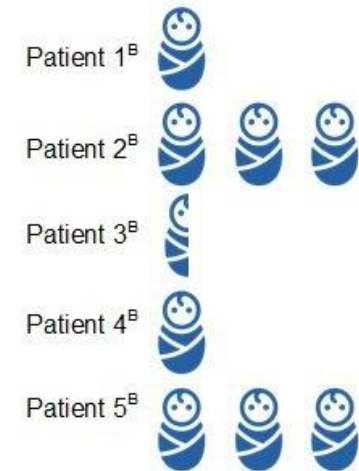
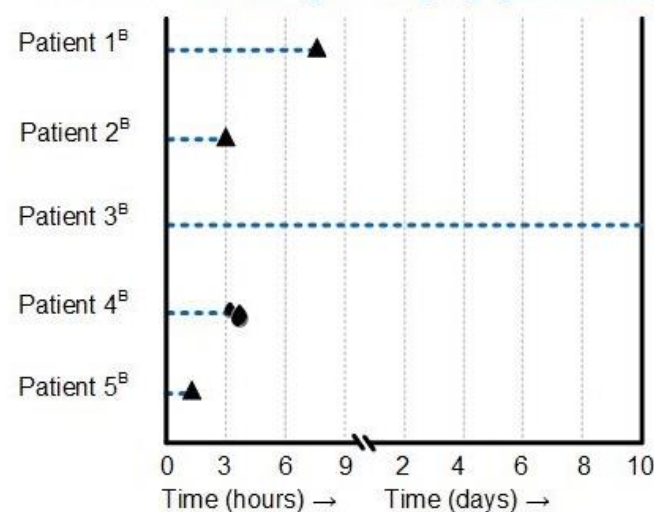
Dataset D^A: mimicking the prophylaxis strategy



Step 3: Weighting



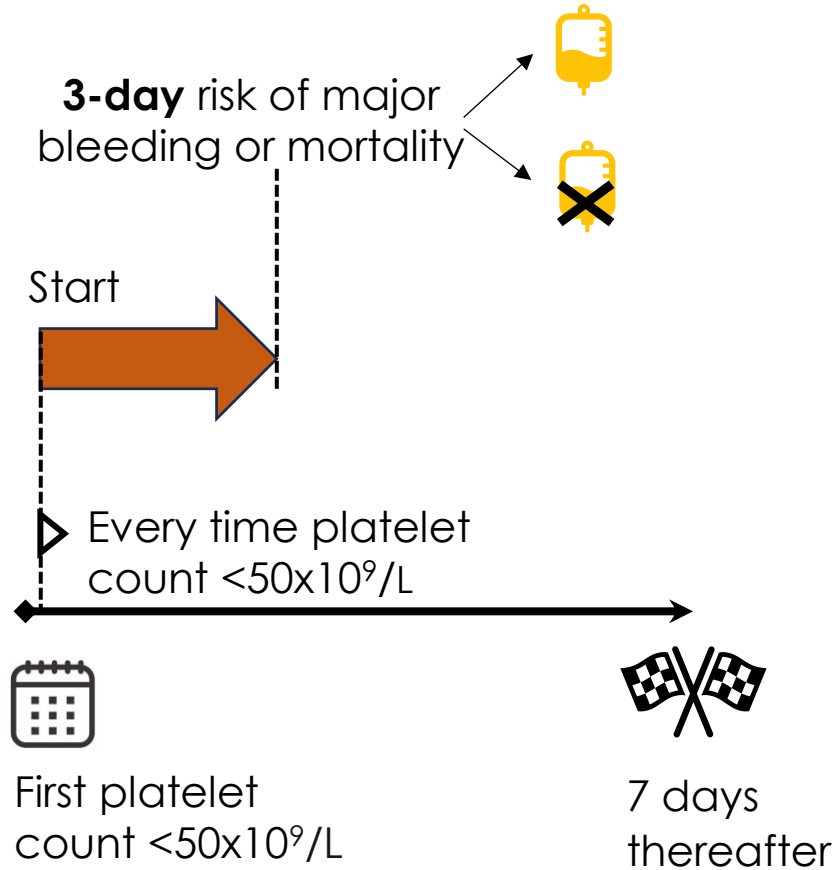
Dataset D^B: mimicking the no-prophylaxis strategy



Legend

- Administration of platelet transfusion
- Follow-up of patient
- Prophylaxis (if platelet transfusion within 6h)
- No-prophylaxis (if no platelet transfusion for 72h)
- Major bleeding
- Death
- Artificial censoring (if non-adherent to strategy)
- Reweighting using inverse probability of censoring weighting (IPCW)

3. Ensuring model can be used repeatedly



3. Landmarking

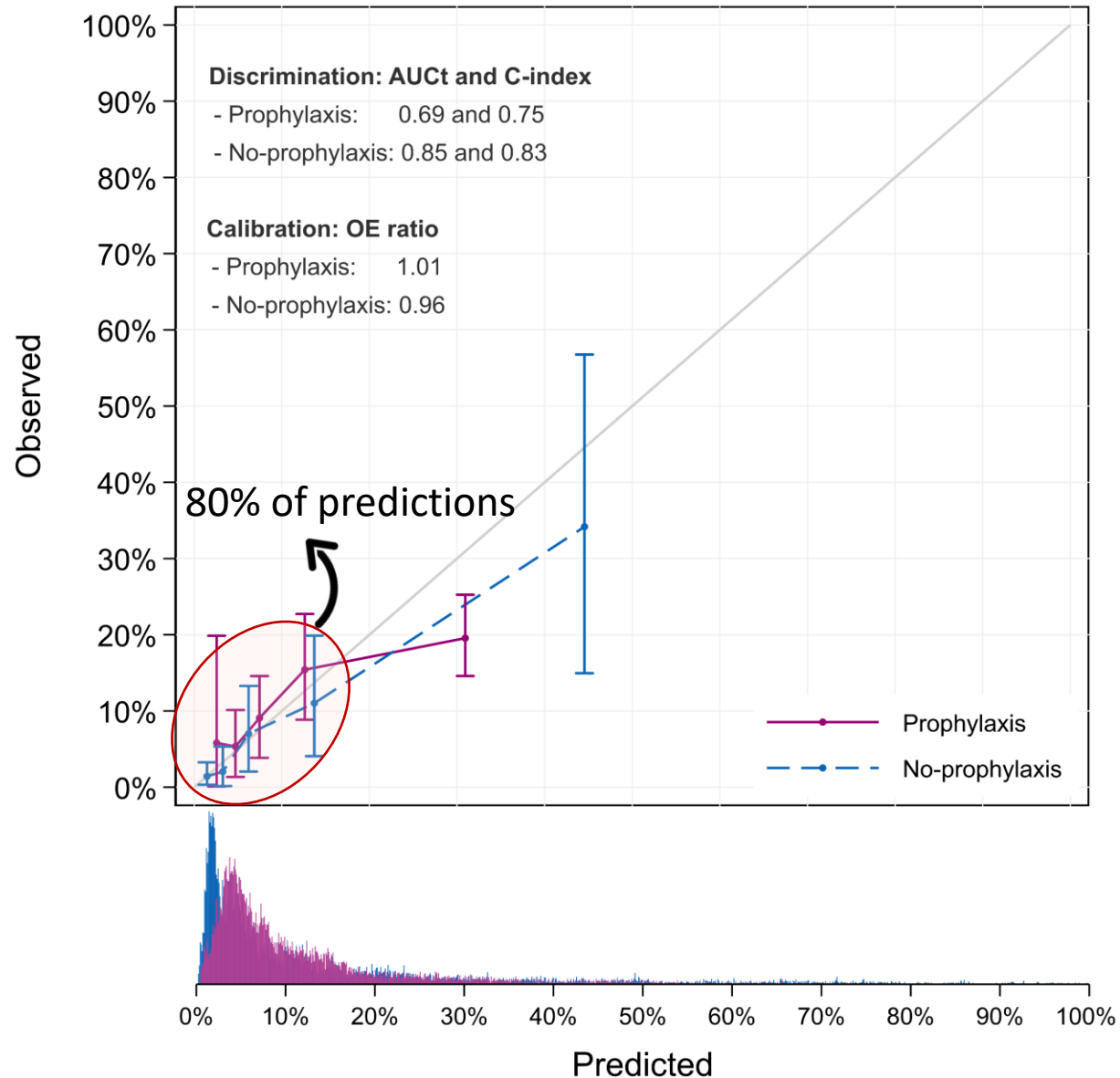
id	from	to	t_pc	c_plt_tx	c_majbl	c_death	f_age
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4	5	6	16	0	0	0	2.1
4	6	7	16	0	0	0	2.1
4	7	8	16	1	0	0	2.1
4	8	9	16	1	0	0	2.1
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4	12	13	16	1	0	0	2.1
4	13	14	16	1	0	0	2.1
4	14	15	16	1	0	0	2.1
4	15	16	16	1	0	0	2.1
4	16	17	16	1	0	0	2.1
4	17	18	16	1	0	0	2.1
4	18	19	203	1	0	0	2.1
4	19	20	203	1	0	0	2.1

two weighted Cox
proportional hazards pooled
over all landmark datasets

landmark time added as
predictor

Van Houwelingen. “Dynamic Prediction by Landmarking
in Event History Analysis.” *Scandinavian Journal of
Statistics* 2007

Results validation dataset



Keogh and Van Geloven. Prediction under interventions: Evaluation of **Counterfactual** Performance Using Longitudinal Observational Data. Epidemiology 2024

Example patients

Predictors	Patient 1	Patient 2
Gestational age (weeks + days)	28+0	28+0
Postnatal age (days)	7	1
Platelet count ($\times 10^9/\text{L}$)	25	25
Time since first platelet count $< 50 \times 10^9/\text{L}$ (hr)	0	0
No. of previous platelet transfusions	0	0
SGA (birth weight $< p10$)	No	Yes
Inotropes	No	No
Mechanical ventilation	Yes	No
Antibiotic treatment for (suspected) sepsis	Yes	No
Necrotizing enterocolitis	Yes	No

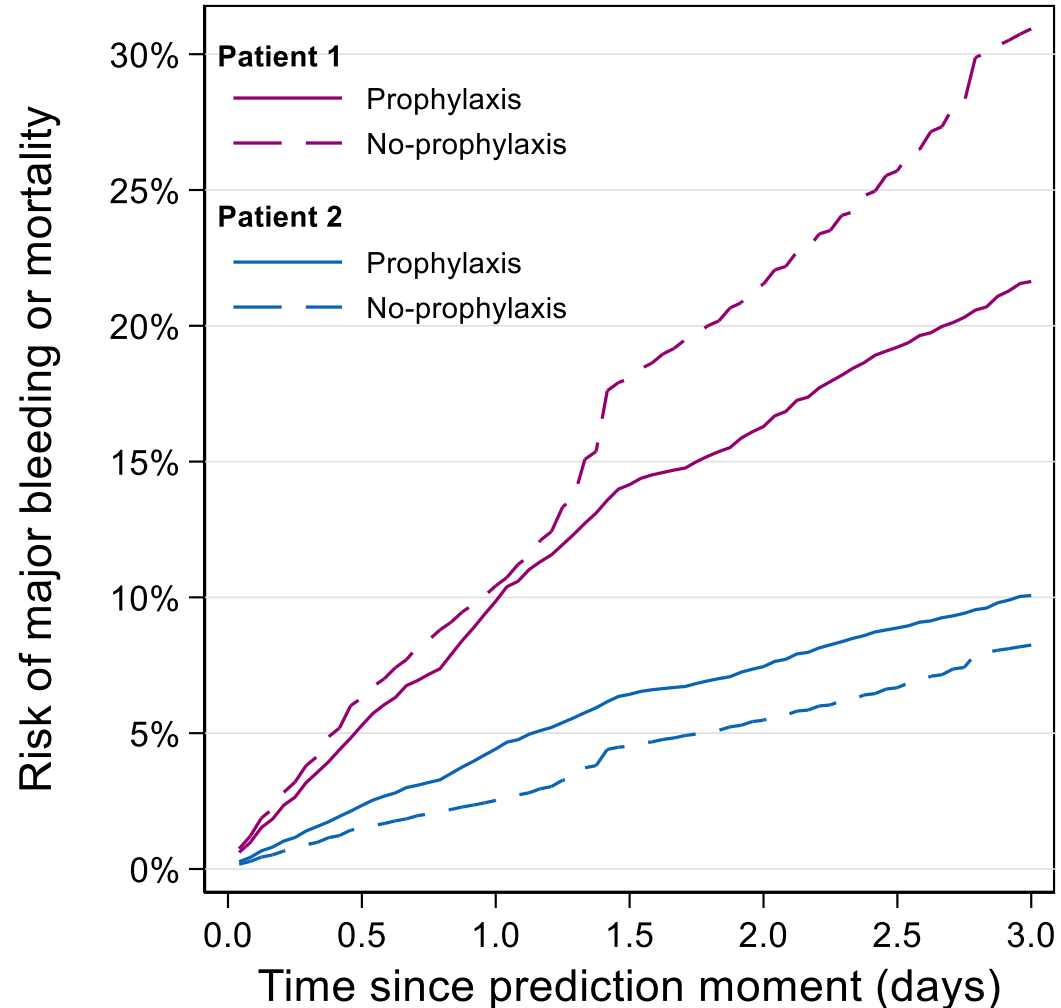
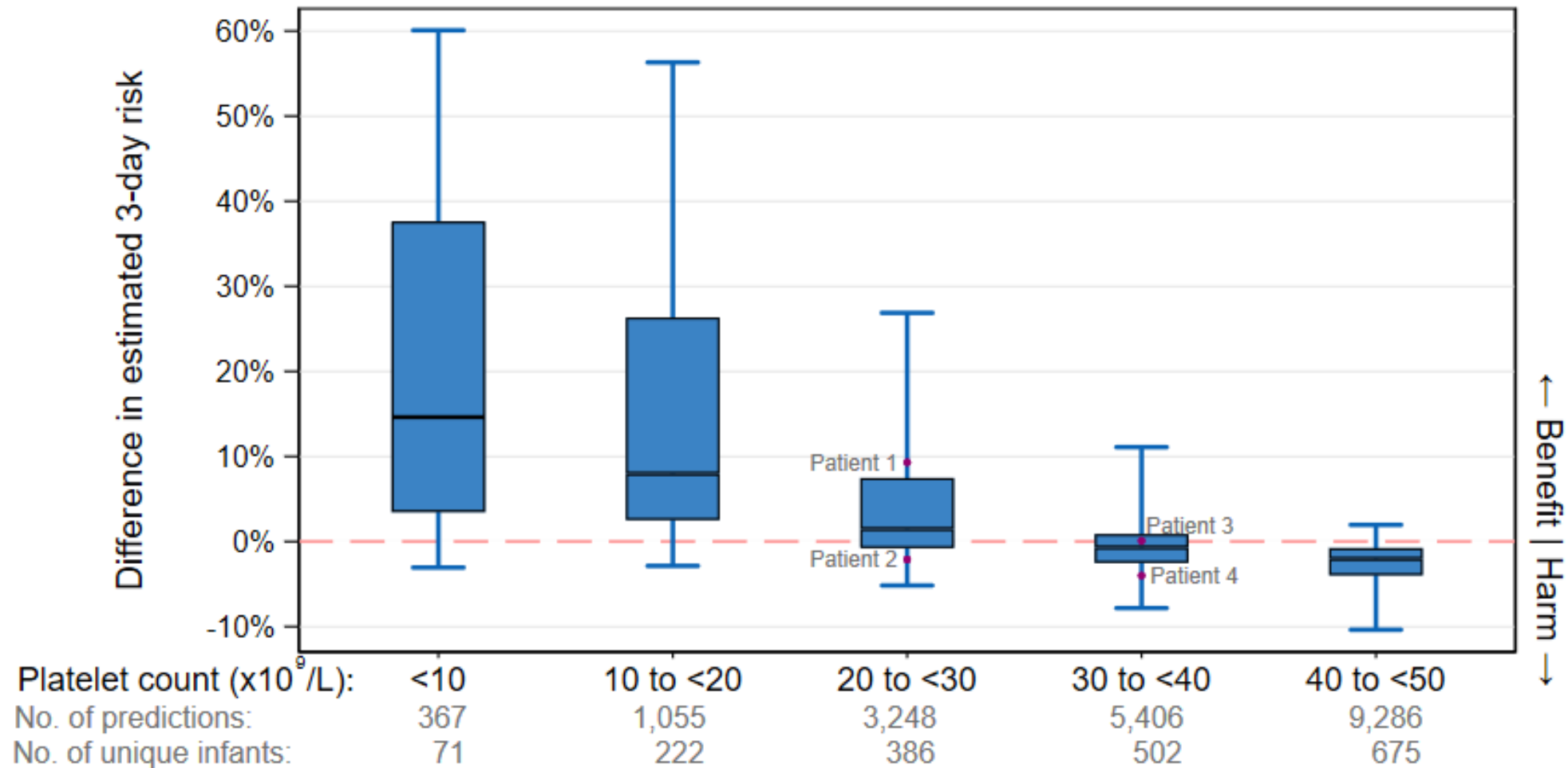


Illustration of the model's predictions by platelet count



Next steps

Determine meaningful risk cut-offs for performing transfusion (interviews with clinicians and patient representatives)

Compare expected outcomes under a prediction-driven transfusion strategy to outcomes under current care

- in observational data
- in a randomized trial

<- clinical utility
(this afternoon!)

Reflections

Successful collaboration of clinicians, epidemiologists and biostatisticians

Additional funding obtained for statistical analysis

Extensive SAP made up front (31 pages in total)

Still data showed some unexpected things: 8 changes to plan explained in SAP

- E.g. one center followed different transfusion strategy than others
- Some babies with poor outcome went without platelet measurement for long time
- Truncation of weights

Acknowledgments



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