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Introduction

- **Morphine** is commonly used as maintenance and rescue analgesic in children after cardiac surgery.
- Rescue morphine doses are often assumed to be independent, but under this assumption, studies¹ showed an unexpected positive relationship between morphine concentration and requirement for rescue morphine.

Aims

- **Quantify the need for rescue morphine** doses for postoperative pain treatment in children under three years of age after cardiac surgery

Methods

Patients (0-3 years) after cardiac surgery²

- received 100 mcg/kg morphine loading dose
- were randomized to either receive morphine or paracetamol maintenance treatment.

Rescue morphine dosing was analysed through **repeated time-to-event analysis** driven by morphine pharmacokinetics in the paracetamol arm (n=92)^{3,4}.

Analysis was performed in NONMEM (v7.5, ICON PLC) and R. The assumption of independence of events was assessed by testing the influence of 'time since previous rescue morphine event' as an increasing factor on the hazard.

Results

Events and duration of trial per patient

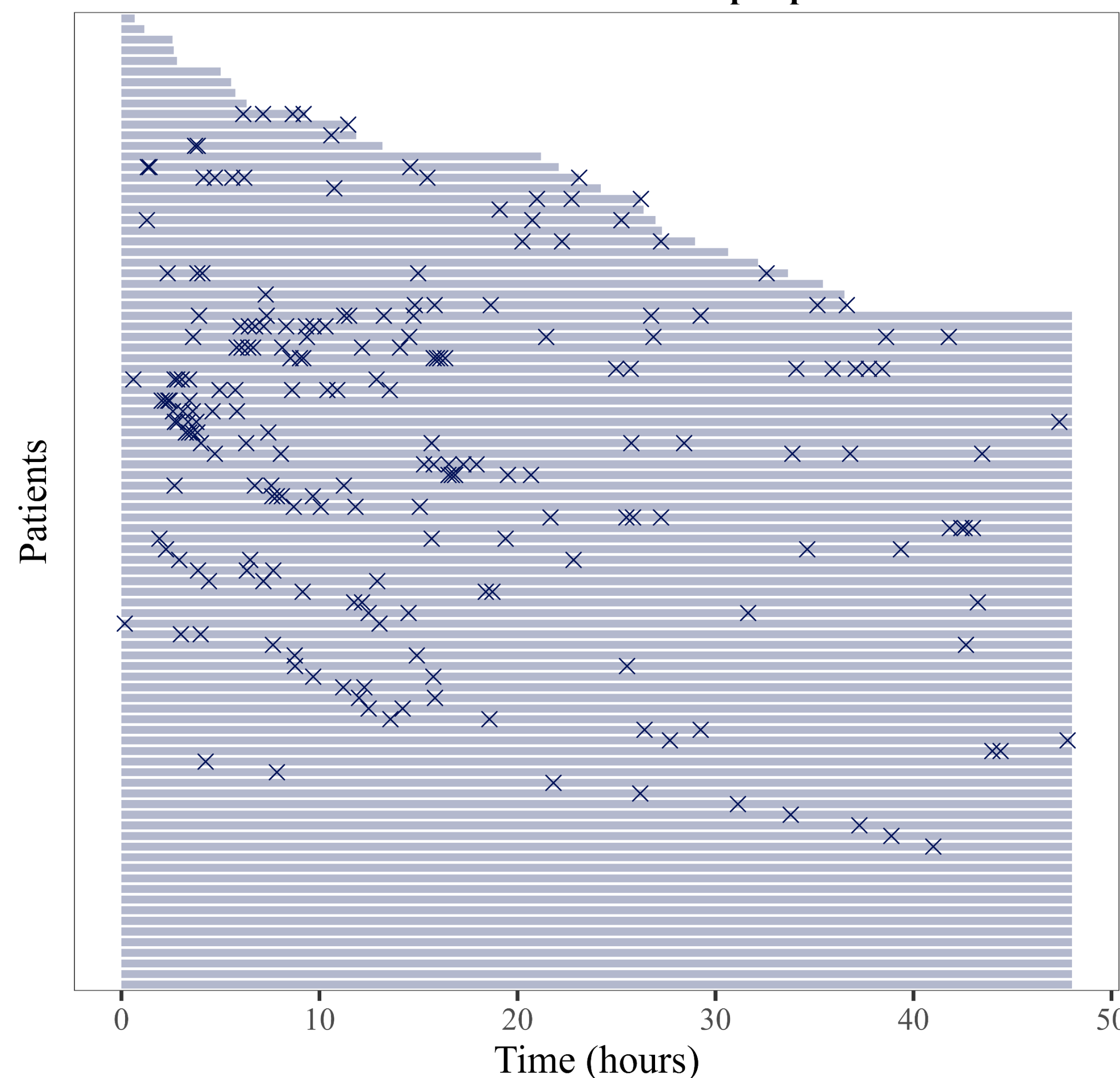


Figure 1: Overview of rescue morphine event data. Horizontal blue lines are the follow up times, and the blue crosses are the rescue morphine administration.

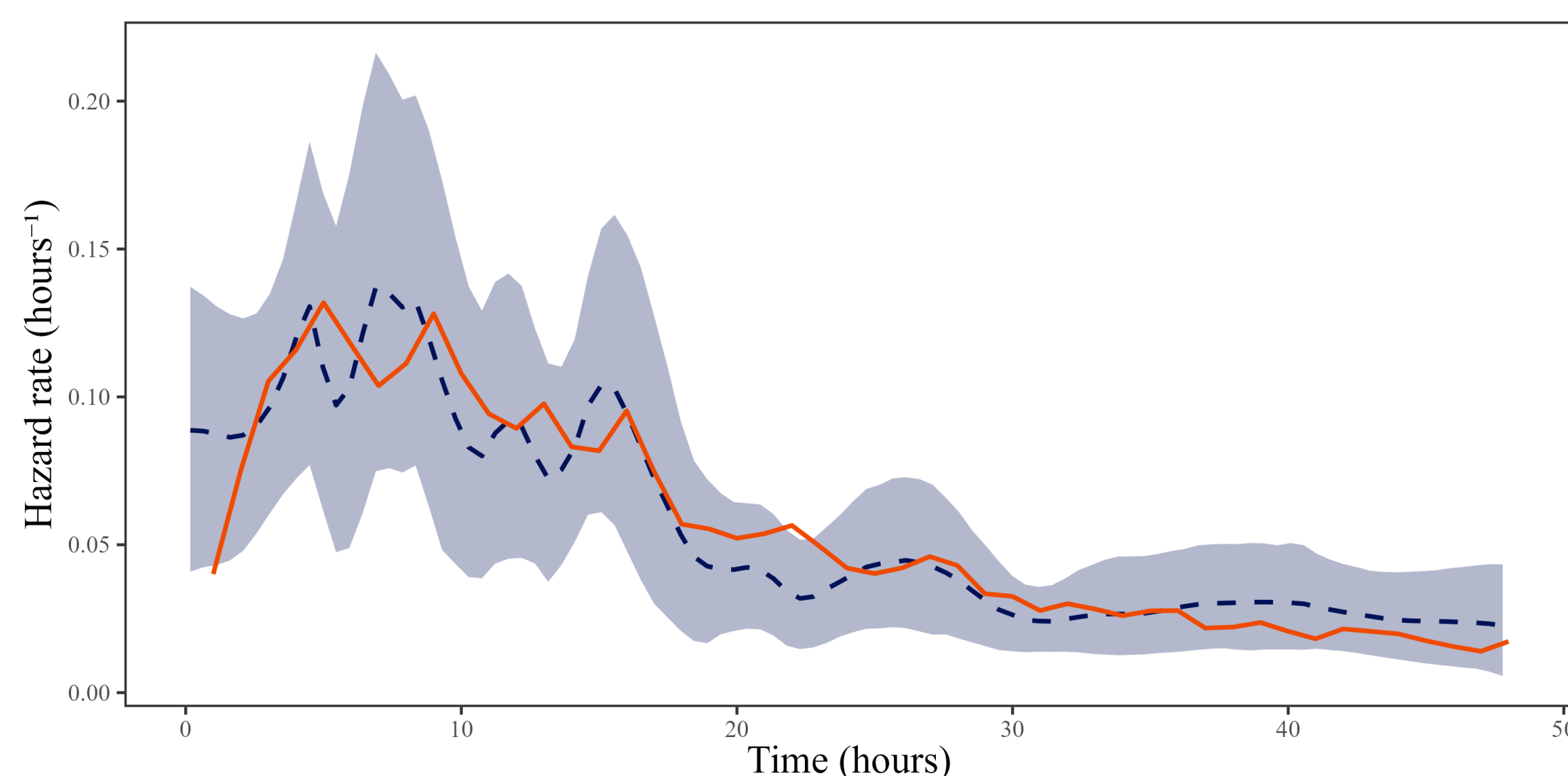


Figure 2: Model evaluation of the PKPD model using the kbVHC. The orange solid line depicts the mean of the model-predicted individual hazard estimates, while the dashed line and the shaded area depict the kernel estimate of the hazard rate in the data and its 95% confidence interval.

Representative example of hazard over time

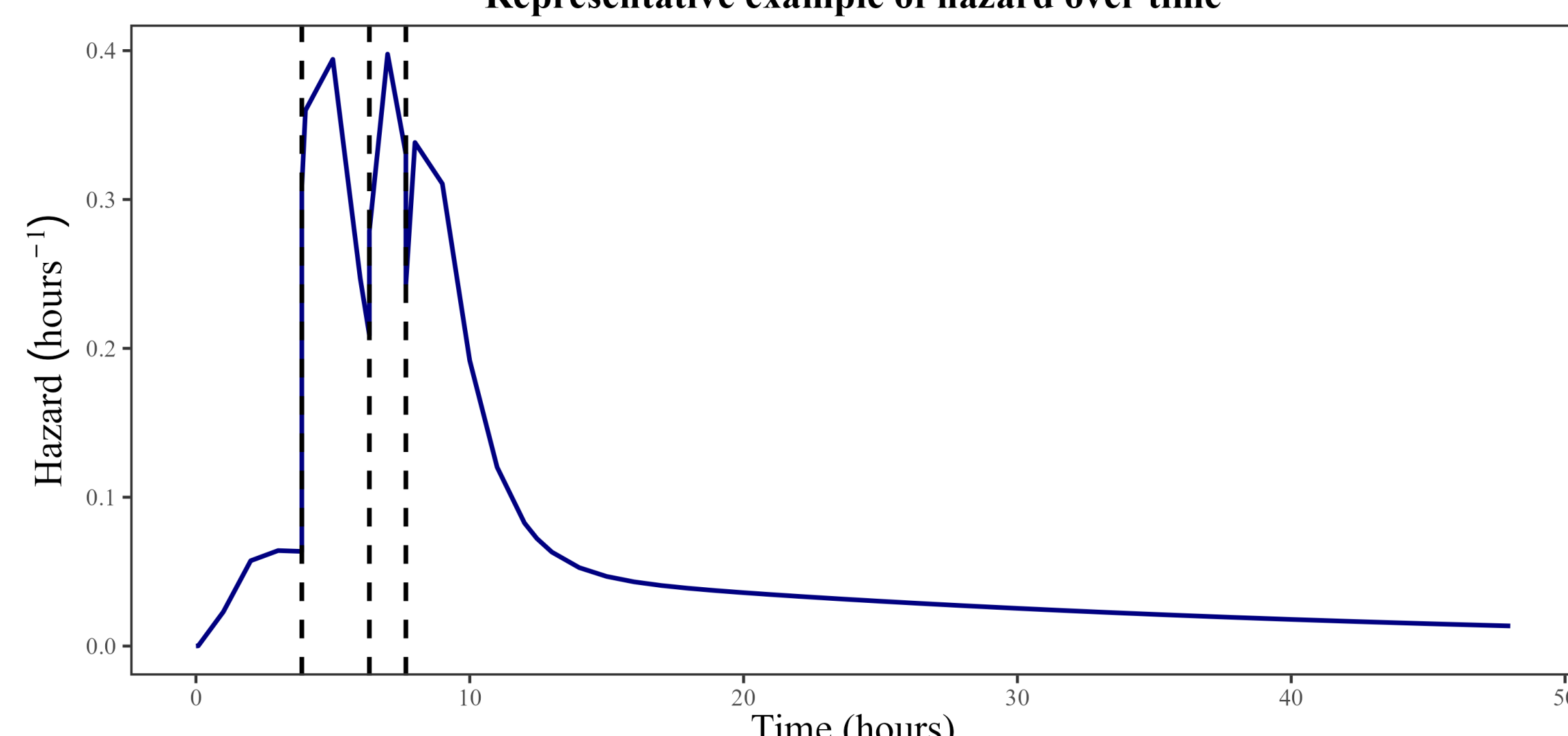
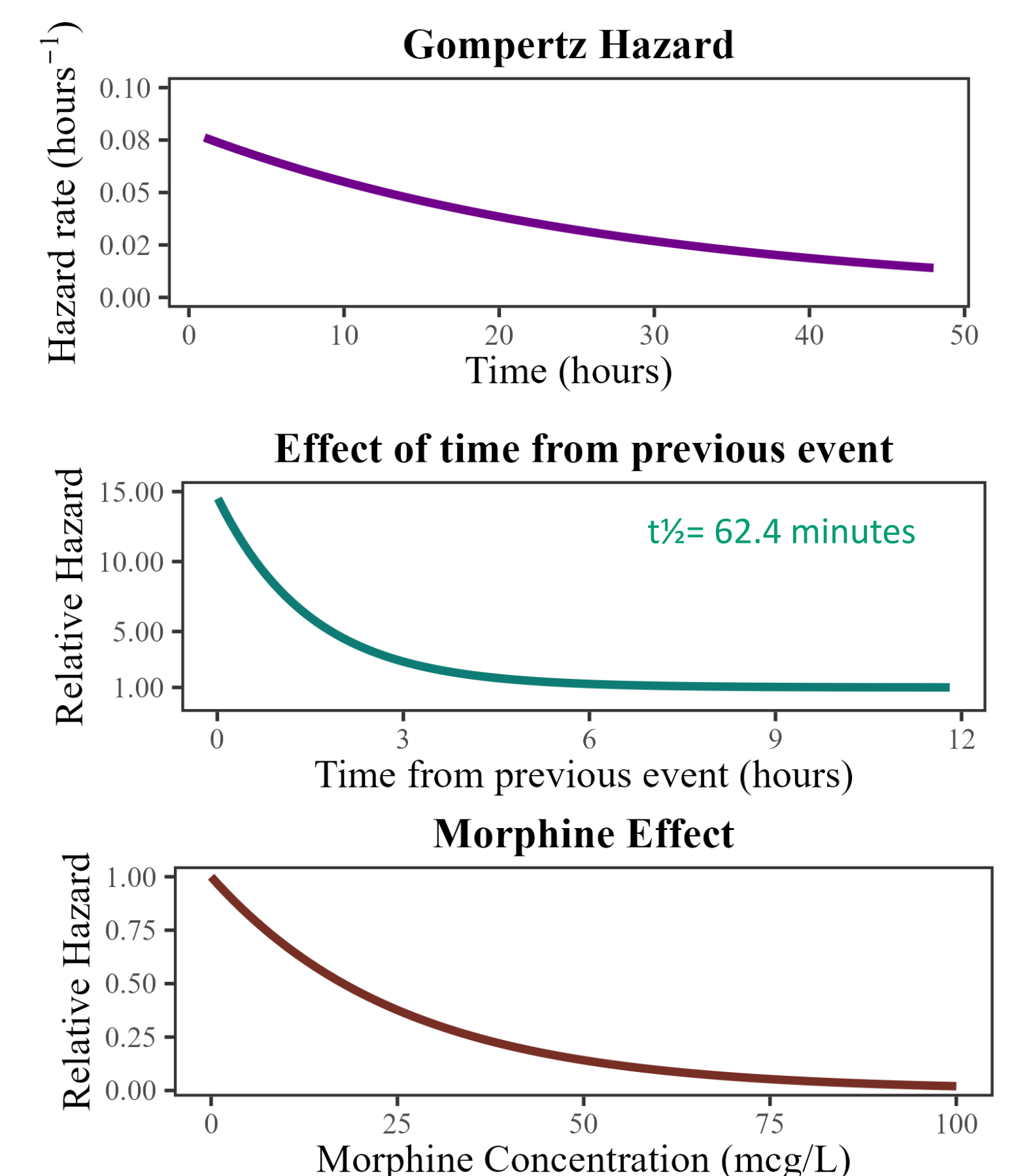


Figure 3: Individual hazard over time (solid line) of a representative example with rescue morphine events depicted with dashed lines.

Table 1: Parameter estimates and relative standard error (RSE) of pharmacokinetic-pharmacodynamic model with visual illustration of the different sub-models. H = Base Hazard, T = Time, H_{SLOPE} = Slope base hazard, I = Increase previous event, TE = Previous event time, E_{SLOPE} = Slope effect previous event, M_{SLOPE} = slope exponential morphine effect, C_{MORPHINE} = morphine concentration, CV = Coefficient of variation, t_{1/2} = Half-life

Parameters	Estimate (RSE%)
Base hazard = $H \cdot e^{(H_{SLOPE} \cdot T)}$	
Base Hazard (hour ⁻¹)	0.079 (16%)
H _{SLOPE} (hour ⁻¹)	-0.036 (17%)
Effect previous event = $1 + (I \cdot e^{(T-TE) \cdot E_{SLOPE}})$	
I (-)	13.6 (23%)
E _{SLOPE} (hour ⁻¹)	-0.665 (21%)
Effect Morphine = $e^{M_{SLOPE} \cdot C_{MORPHINE}}$	
M _{SLOPE} (L/mcg)	-0.0391 (29%)
Interindividual variability (frailty)	
Variability on the base hazard (%CV)	24 % (49%)



- A strong increase in hazard for rescue morphine was observed for a short period after an event suggesting a lack of independence of consecutive rescue morphine events. (Table 1, Figure 1 and Figure 3)
- A log-linear relationship best characterized the relationship between morphine concentrations and the decrease in the hazard. (Table 1) Without the adjustment for the 'time since previous rescue morphine event', the morphine effect was under-estimated by 60.1%. (Data not shown)
- KbVHC shows that model predicts well the hazard for morphine rescue events. (Figure 2)

Conclusions

- The hazard for morphine rescue events after cardiac surgery in children receiving a loading dose of morphine at the end of surgery followed by intermittent paracetamol maintenance treatment by:
 - a decreasing Gompertz hazard with time after surgery,
 - an increased hazard after a morphine rescue event and
 - a decrease in hazard with increasing morphine concentrations.
- Accounting for the previous events, an unbiased morphine effect could be estimated.

References

1. de Hoogd et al. Pediatr Res. 2021;90(6):1201-1206.
2. Zeilmaker-Roest G et al., Critical Care. 2024;28(1):143.
3. Valkenburg AJ et al., Pediatric Critical Care Medicine. 2016;17(10):930-8.
4. Xiberras M et al., PAGE 32 2024 Abstr 11133