Supplementary Information

Time-varying clearance in milrinone pharmacokinetics from premature neonates to adolescents

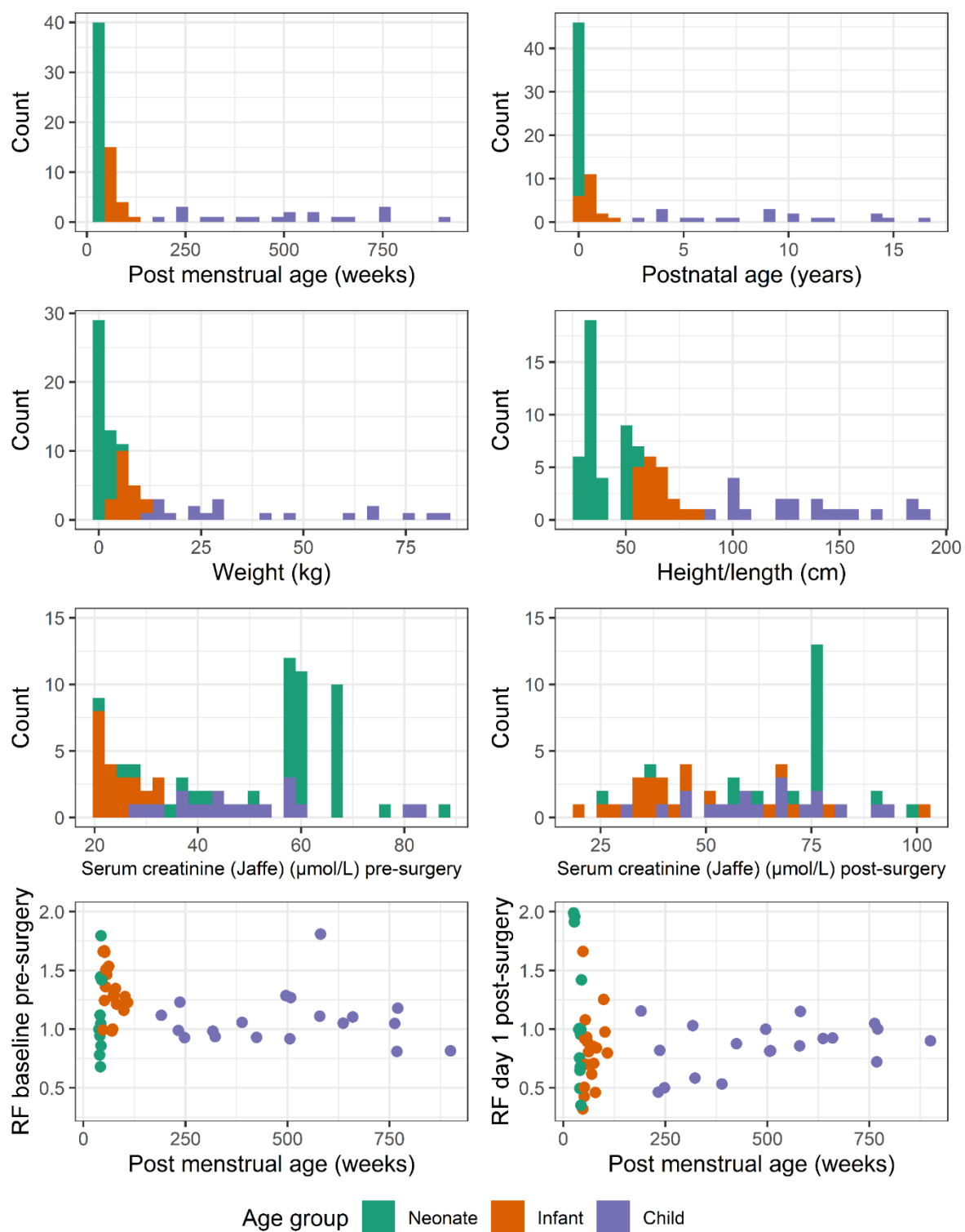Conor J O'Hanlon [1], Anita Sumpter[2], Brian J Anderson[2,3], Jacqueline A Hannam[1]

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Study demographics

Figure S1 – Histograms showing combined primary covariate distributions for the participants recruited into the Starship Hospital clinical study and data from Paradisis, Jiang [1] (first three rows). Bottom row shows the distribution of renal function values by age, calculated using O'Hanlon, Holford [2]. RF is assumed to be normal (RF=1) for neonates less than 2 postnatal days old. Neonates < 44 weeks PMA, infants < 2 years PNA, children < 16 years PNA.
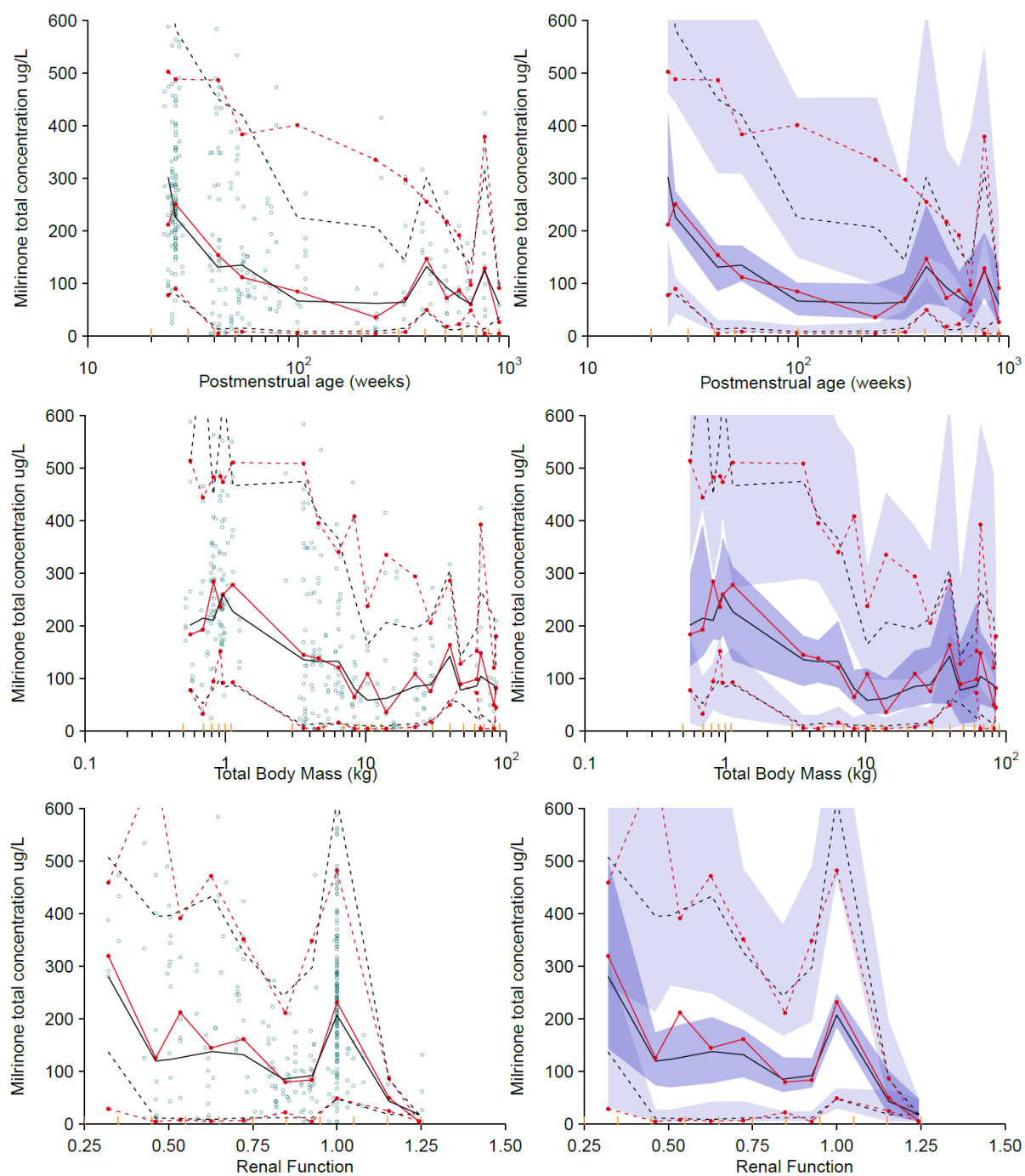
Visual predictive checks

Figure S2 – Visual predictive check for the milrinone pharmacokinetic model with PMA (top), TBM (middle) or RF (bottom) as the independent variable. The 5%, median and 95% percentiles of the distribution of the observations are red and predictions are black. The hollow circles in the left-side plot are the individual observations. The 95% confidence intervals for the prediction percentiles are shown by the purple shaded areas in the right-side plot. The yellow lines on the x-axis show the mid-point of data bins used in the construction of the VPC.
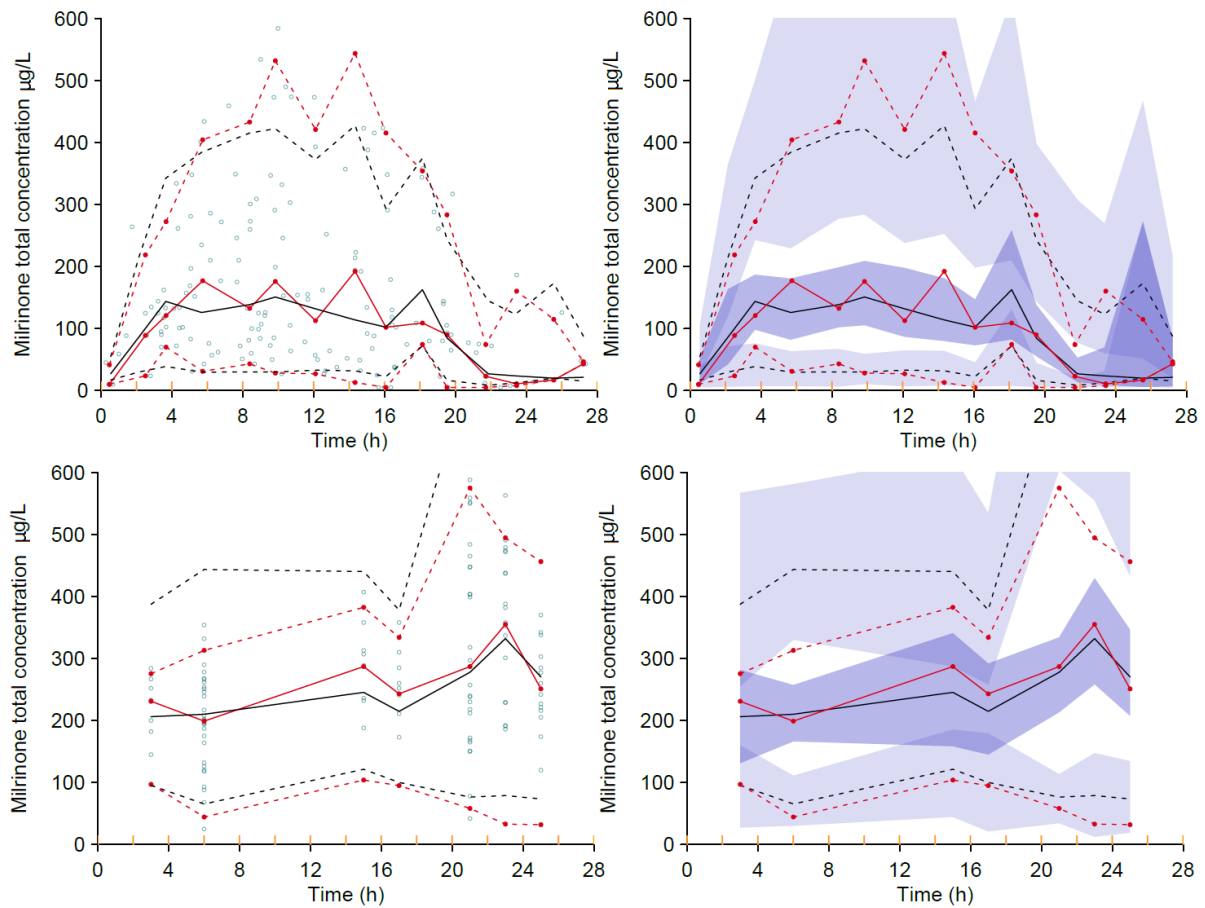
Figure S3 – Visual predictive check for the milrinone pharmacokinetic model separated by study - Starship Hospital clinical study (top) and Paradisis, Jiang [1] study (bottom). The 5%, median and 95% percentiles of the distribution of the observations are red and predictions are black. The hollow circles in the left-side plot are the individual observations. The 95% confidence intervals for the prediction percentiles are shown by the purple shaded areas in the right-side plot. The yellow lines on the x-axis show the mid-point of data bins used in the construction of the VPC.

Simulations

Table S1 – Proposed milrinone dosing regimen by indication and postnatal age, from Vogt [3].

| Age group	LCOS prophylaxis		LCOS treatment	
	Loading dose (µg/kg over 1 h)	Maintenance dose rate (µg/kg/min)	Loading dose (µg/kg over 1 h)	Maintenance dose rate (µg/kg/min)
0 PNA days	75	0.4	75	0.25
>0 days to <1 month	75	0.5	75	0.375
1 month to <6 months	82.5	0.625	82.5	0.5
6 months to <1 year	82.5	0.75	82.5	0.625
1 year to <9 years	100	1.0	100	0.75
9 years to <15 years	82.5	0.75	82.5	0.625
>15 years	82.5	0.7	75	0.375

LCOS low cardiac output syndrome, *PNA* postnatal age.
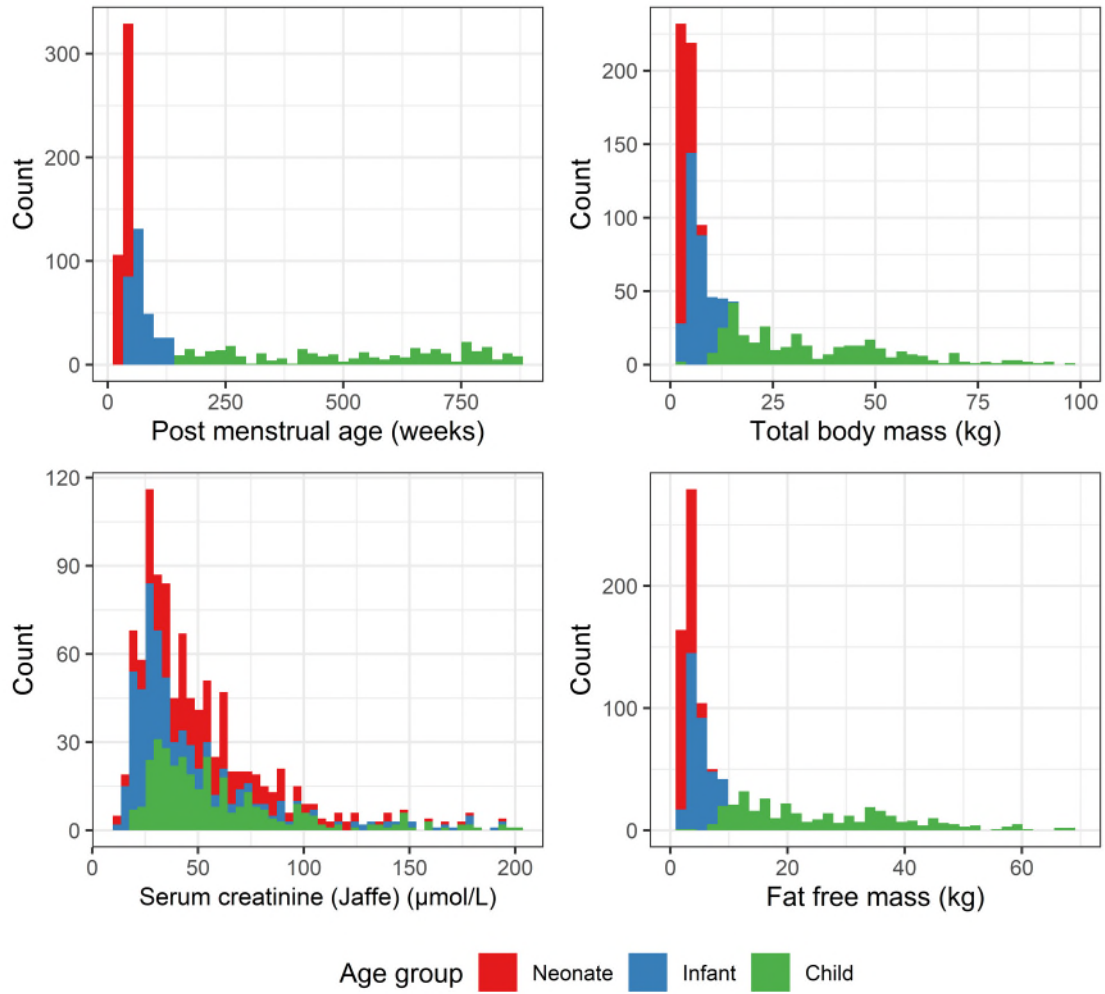
Figure S4 – Histograms showing covariate distributions for 1000 subjects sampled from Holford [4], used in the milrinone simulations. Neonates < 44 weeks PMA, infants < 2 years PNA, children < 16 years PNA.
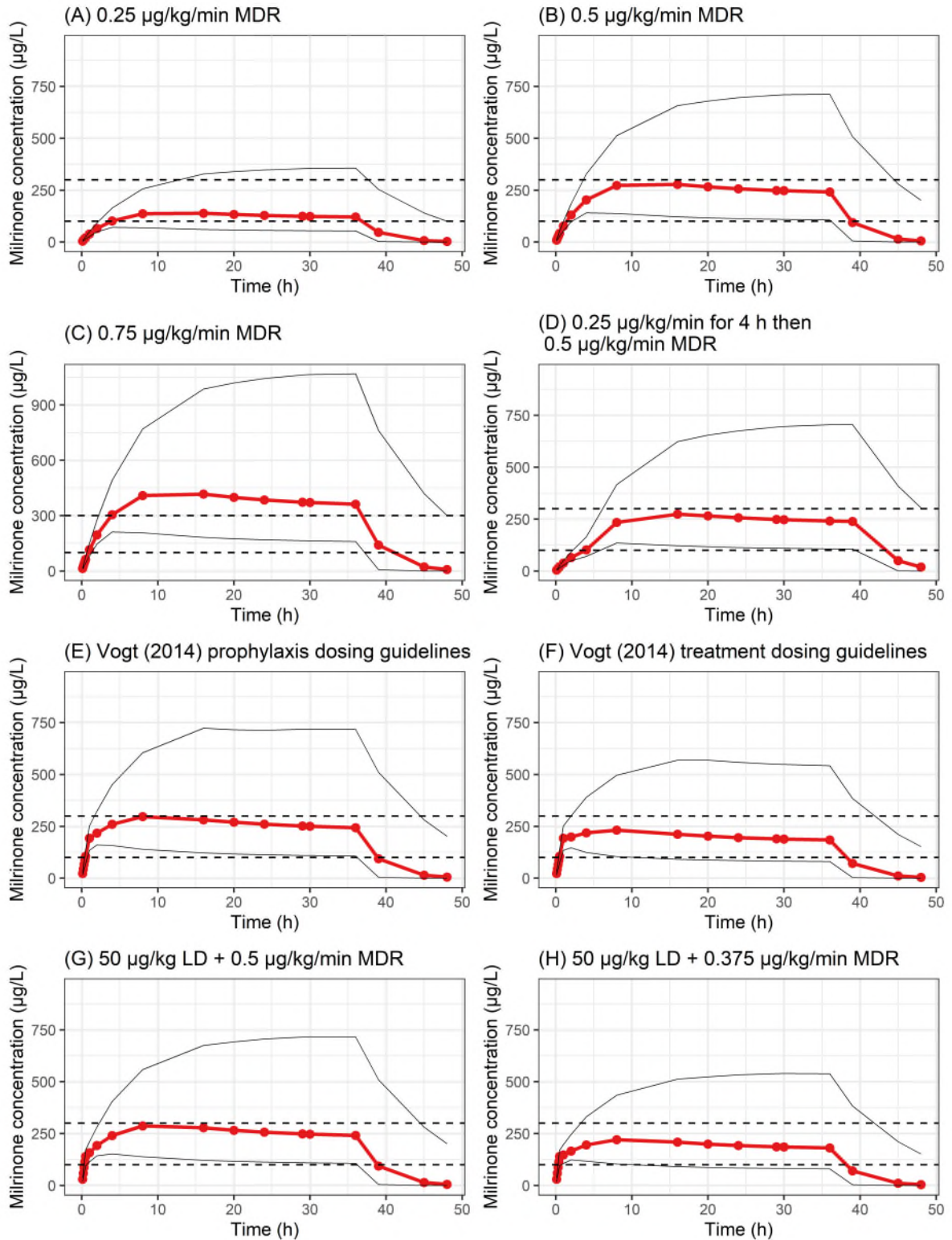
*Figure S5 – Simulation studies for **neonates** only (from Figure 3) using the final PK models described in this work and dosing regimens presented in Supplementary Table S1. Subject covariate distributions presented in Supplementary Figure S4. The red lines are the median predictions, the coloured dots are the simulated time points and the outer thin black lines form the 95th prediction percentiles. The dashed lines indicate the acceptable concentration range (100 – 300 µg/L). MDR – maintenance dose rate, LD – loading dose.*
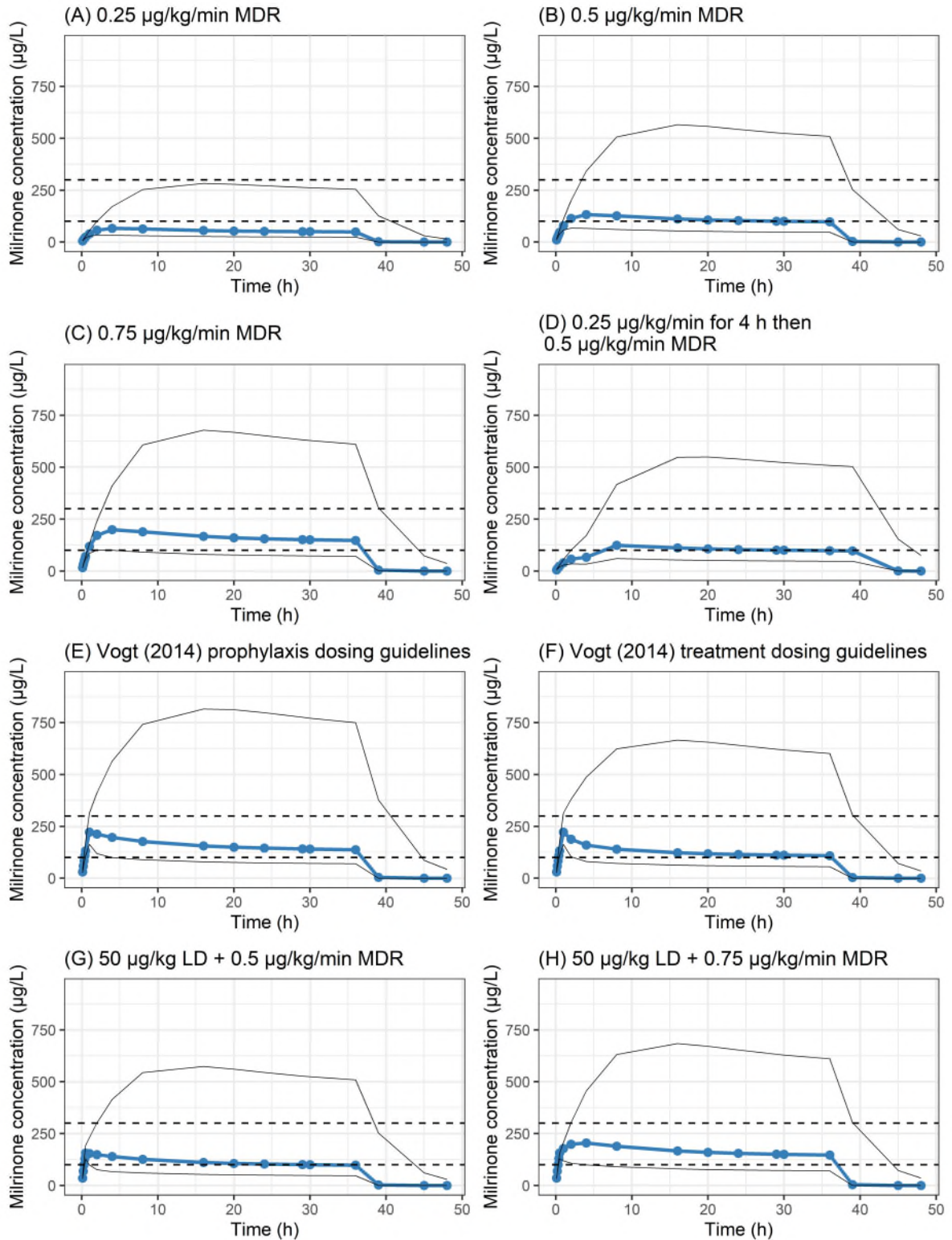
*Figure S6 – Simulation studies for **infants** only (from Figure 3) using the final PK models described in this work and dosing regimens presented in Supplementary Table S1. Subject covariate distributions presented in Supplementary Figure S4. The blue lines are the median predictions, the coloured dots are the simulated time points and the outer thin black lines form the 95th prediction percentiles. The dashed lines indicate the acceptable concentration range (100 – 300 µg/L). MDR – maintenance dose rate, LD – loading dose.*
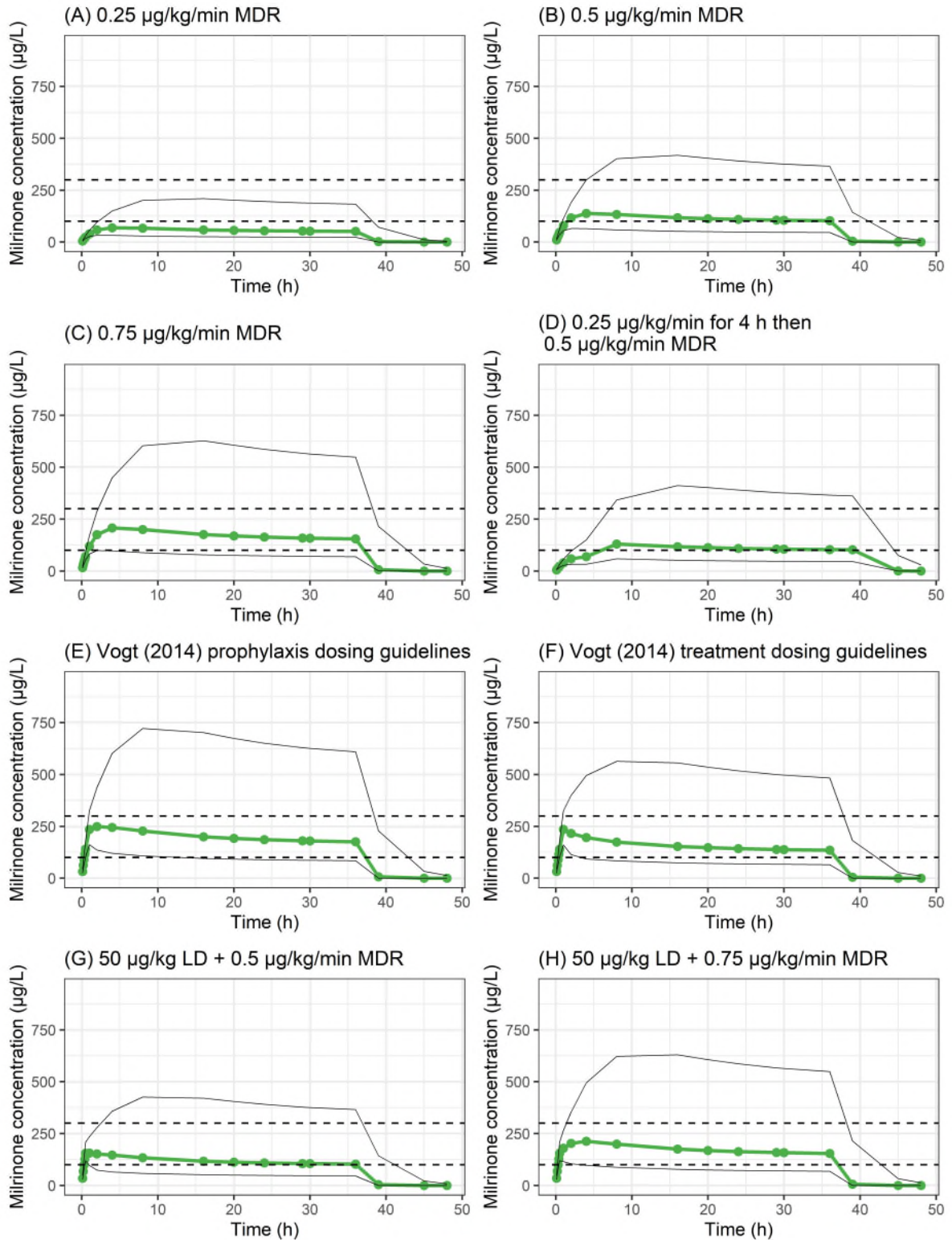
*Figure S7 – Simulation studies for **children** only (from Figure 3) using the final PK models described in this work and dosing regimens presented in Supplementary Table S1. Subject covariate distributions presented in Supplementary Figure S4. The green lines are the median predictions, the coloured dots are the simulated time points and the outer thin black lines form the 95th prediction percentiles. The dashed lines indicate the acceptable concentration range (100 – 300 µg/L). MDR – maintenance dose rate, LD – loading dose.*

Table S2 – Summary of model selection. Delta parameters and delta OFV is the difference between the model and the reference model. The p-value for the difference between the model and reference model is calculated using the chi-square test, and presented in parentheses.

Model	Description	OFV	Reference model	Δ parameters	Δ OFV (p-value)
1	One-compartment, maturation parameter estimated	3105.194	.	.	.
2	Two-compartment, maturation parameters estimated	3096.537	1	+4	-8.657 (p > 0.05)
3	Three-compartment, maturation parameters estimated	3098.208	1	+8	-6.986 (p > 0.05)
4	Include RF as a covariate, *Ffat* parameters estimated	3068.013	1	+2	-37.181 (p < 0.0001)
5	Include RF as a covariate, single set of maturation parameters, *Ffat* parameters fixed to 0 (equivalent to scaling size by FFM)	3064.796	1	0	-40.398 (p < 0.0001)
6	Include RF as a covariate, single set of maturation parameters, *Ffat* parameters fixed to 1 (equivalent to scaling size by TBM)	3075.748	1	0	-29.446 (p < 0.0001)
7	Covariance between CL and V	3055.129	5	+1	-9.667 (p < 0.01)
8	Time varying CL	3032.307	7	+2	-22.822 (p < 0.0001)
9	PMA maturation of V	3041.32	7	+2	-13.809 (p < 0.001)
10	PNA maturation of V	3031.589	7	+2	-23.540 (p < 0.001)
11	Time varying CL and PMA maturation of V	3026.312	7	+4	-28.817 (p < 0.0001)
12	Time varying CL and PNA maturation of V	3010.603	7	+4	-44.526 (p < 0.0001)
13	Time varying CL and PNA + PMA maturation of V	3018.838	7	+6	-36.291 (p <0.0001)

CL clearance, *FFM* fat free mass, *OFV* objective function value, *PMA* postmenstrual age, *PNA* postnatal age, *RF* renal function, *TBM* total body mass, *V* volume of distribution.
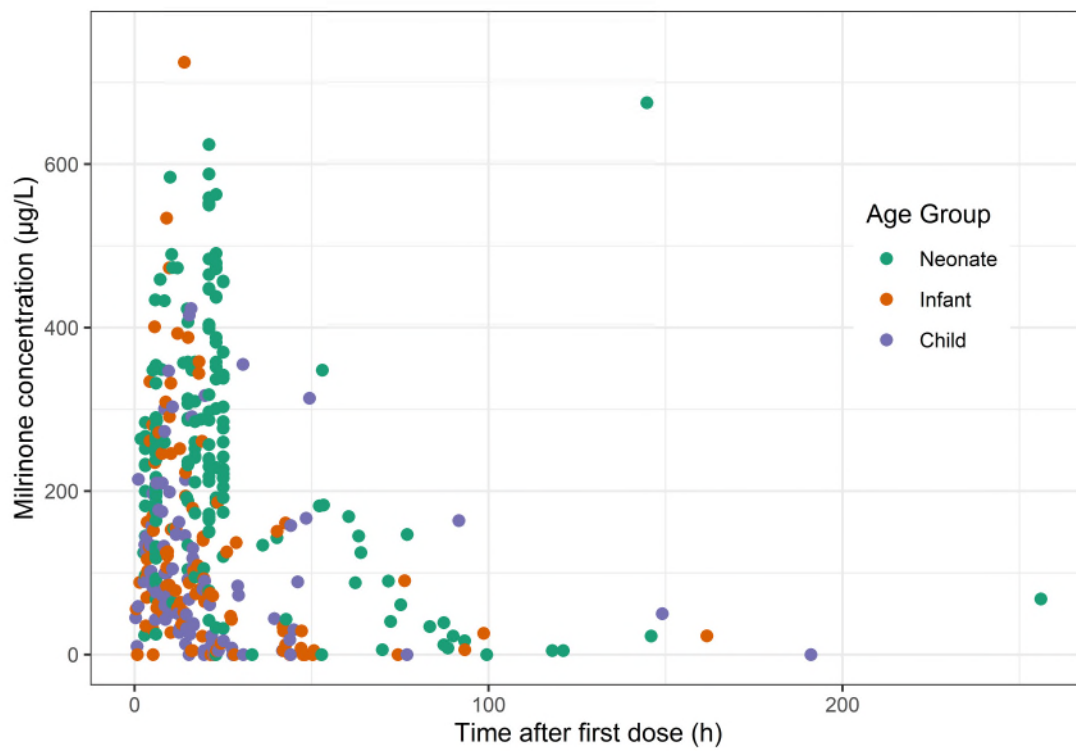
Milrinone observations

Figure S8 – Milrinone concentration observations stratified by age-group.
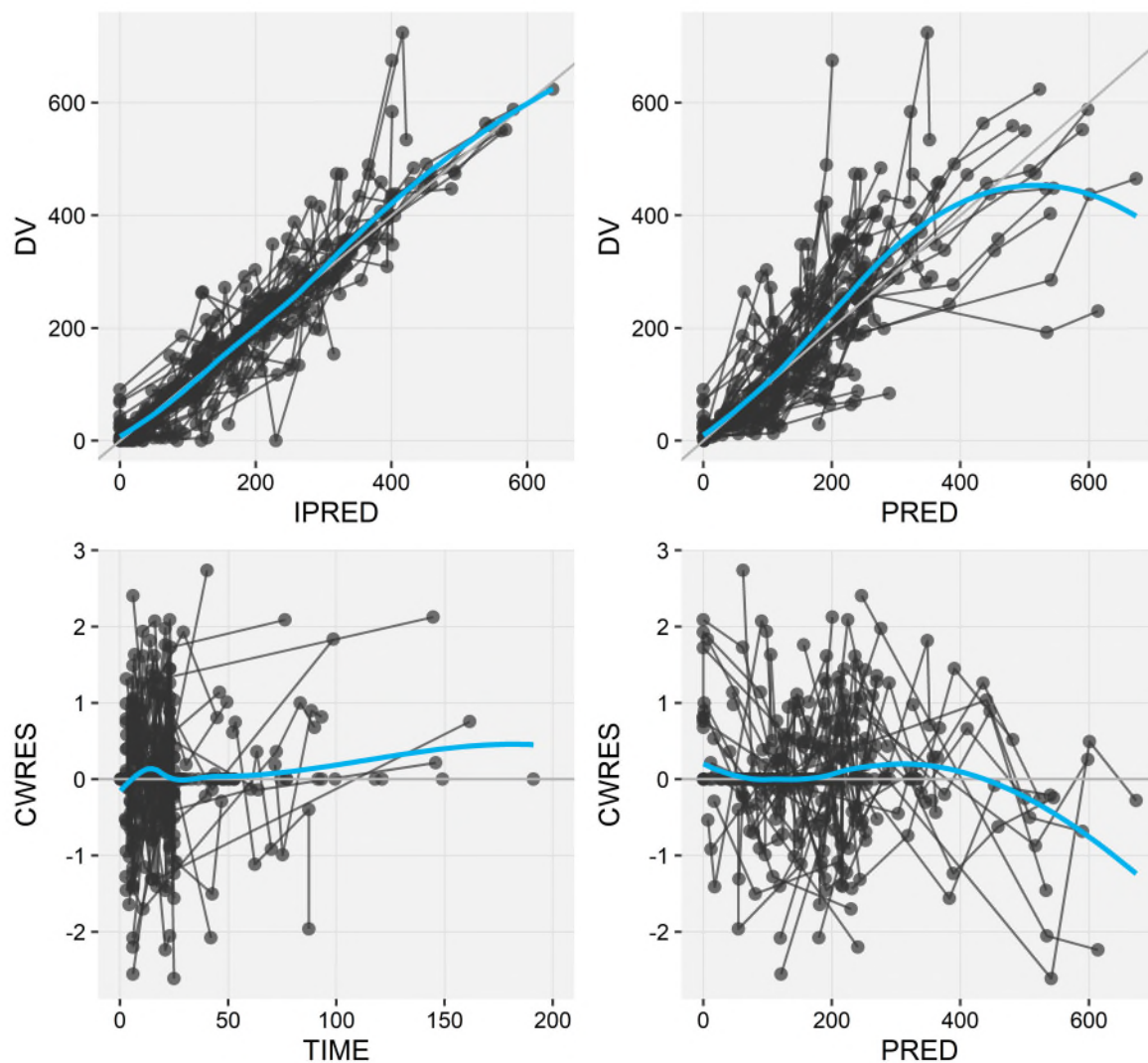
Goodness of fit plots

Figure S9 – Goodness of fit plot for the final model.

References

1. Paradisis M, Jiang X, McLachlan AJ, Evans N, Kluckow M, Osborn D. Population pharmacokinetics and dosing regimen design of milrinone in preterm infants. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2007;92(3):F204-F9.
2. O'Hanlon CJ, Holford N, Sumpter A, Al-Sallami HS. Consistent Methods for Fat Free Mass, Creatinine Clearance and Glomerular Filtration Rate to describe Renal Function from Neonates to Adults. CPT: Pharmacometrics and Systems Pharmacology. 2023;12(3):401-12.
3. Vogt W. Evaluation and optimisation of current milrinone prescribing for the treatment and prevention of low cardiac output syndrome in paediatric patients after open heart surgery using a physiology-based pharmacokinetic drug–disease model. Clinical pharmacokinetics. 2014;53(1):51-72.
4. Holford NH, editor Systems Pharmacology – Learning from GAVamycin. PAGANZ; 2017 8 February; Adelaide [https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin/].