

An Argument for Standardised Scaling: Comparison of Methods for Scaling Clearance in Children

Eva Germovsek^{*1}, Charlotte IS Barker^{1,2}, Joseph F Standing¹

¹Institute of Child Heath, University College London, London, UK; ² Institute for Infection and Immunity, St George’s, University of London, London, UK; *eva.germovsek.11@ucl.ac.uk



Background

Drug clearance (CL) changes with body size (represented by body weight) and due to maturation of organ functions, such as glomerular filtration, and drug metabolising enzymes [1]. Several methods have been used to parameterise CL for size and age. Debates on the best method are confounded by different datasets being used [2]. Standardising CL parameterisation will facilitate comparisons between studies.

Objectives

We aimed to compare different parameterisations of maturation and size fitted to the same dataset, hence providing a clear way to compare distinct methods.

Methods

A systematic literature review of PubMed was conducted (search updated in April 2015) for publications containing information about CL of intravenous gentamicin (mainly renally cleared) and midazolam (mainly hepatically cleared) in three different subpopulations (neonates/infants, children, adults). We also searched for models for size and maturation. The CL data were then fitted to the identified models. Visual comparison of the fit of the models was undertaken and the prediction errors (PE), mean prediction errors (MPE) and root mean square errors (RMSE) (equations 1) were compared.

$$PE = prediction - true\ value,$$
$$MPE = \frac{\sum_{i=1}^N PE_i}{N},$$
$$RMSE = \sqrt{\frac{\sum_{i=1}^N PE_i^2}{N}}.$$

(Eqs. 1)

Table 1: List of the compared models and results of the comparison

No.	Ref	Model equation	Gentamicin			Midazolam		
			AIC	MPE (L/h)	RMSE (L/h)	AIC	MPE (L/h)	RMSE (L/h)
1		$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{\theta_2}$	-83.5	0.51	1.68	159	-1.13	4.67
2		$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75}$	-23.0	-0.66	1.34	159	-2.08	5.03
3		$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.667}$	-9.4	-0.71	1.47	163	-2.48	5.46
4	[2]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^b$; b: 1.2 ≤ 3 mo; 1.0 > 3mo-2y; 0.9 > 2-5y; 0.75 > 5y	-109	0.23	0.88	134	0.01	4.51
5	[2]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^b$; b: 1.25 ≤ 9 kg; 0.76 > 9 kg	-92.6	0.50	1.21	138	0.53	4.54
6	[3]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^b$; b: $\theta_2 \leq 16.5$ kg; $\theta_3 > 16.5$ kg	-82.4	0.37	1.32	160	-1.26	4.60
7	[4]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^b$, b = $\theta_2 \cdot WT^{\theta_3}$	-109	-0.01	0.66	115	-0.70	4.25
8	[5]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^b$, b = $\theta_3 - \frac{\theta_5 \cdot WT^{\theta_2}}{\theta_4 \cdot \theta_2 + WT^{\theta_2}}$	-108	-0.05	0.56	91.3	-0.18	4.21
9	[6]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^b$, b = $\theta_3 - \frac{\theta_5 \cdot PNA^{\theta_2}}{\theta_4 \cdot \theta_2 + PNA^{\theta_2}}$	-118	0.01	0.61	91.8	-0.15	4.22
10	[7]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{\theta_2} \cdot (1 + \theta_3 \cdot PNA)$	-81.5	0.51	1.68	161	-1.13	4.67
11	[8]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{\theta_2} + \theta_3 \cdot PNA$	-81.5	0.52	1.71	161	-1.13	4.67
12	[9]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot (1 + \theta_2 \cdot (PMA - 40))$	-42.3	2.25	6.09	162	-2.00	5.00
13	[10]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot e^{\theta_2 \cdot (PMA - 40)}$	-27.4	-0.22	1.32	162	-2.00	5.00
14		$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{\theta_2} \cdot \frac{PMA^{\theta_3}}{\theta_4^{\theta_3} + PMA^{\theta_3}}$	-118	-0.02	0.61	93.9	-0.25	4.25
15	[9]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \frac{PMA^{\theta_2}}{\theta_3^{\theta_2} + PMA^{\theta_2}}$	-117	0.06	0.70	97.8	0.41	4.41
16	[11]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \left(1 - \theta_2 \cdot e^{-(PMA - 40) \cdot \frac{\ln 2}{\theta_3}}\right)$	-117	0.07	0.71	111	0.07	4.37
17	[12]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot (\theta_2 + (1 - \theta_2) \cdot (1 - e^{-PNA \cdot \theta_3}))$	-108	0.03	0.69	95.8	0.30	4.36
18	[13]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \left(\theta_4 + (1 - \theta_4) \cdot \frac{PNA^{\theta_2}}{\theta_3^{\theta_2} + PNA^{\theta_2}}\right)$	-106	0.02	0.69	94.2	0.36	4.37

AIC is the Akaike information criterion, θ_1 is the typical value of clearance for a 70kg adult, b is the allometric exponent, WT is body weight in kilograms, PNA is postnatal age in years, PMA is postmenstrual age in weeks, mo is months, y is years. All θ s represent estimated parameters.

Conclusions

- Most models that included size and age described the CL of both drugs well, and were able to capture the neonatal and adult CL.
- We suggest allometric weight scaling and a sigmoidal maturation function using PMA should be used, as exemplified here by gentamicin and midazolam, two drugs representing different elimination routes.
- Using the same parameterisation of clearance-related covariates for size and age would make comparison of CL estimates between studies of similar drugs easier, and thus more could be learned about clinical maturation and size-related CL changes.

Results

We identified 44 and 38 clearance reports for gentamicin and midazolam, respectively, and 18 distinct clearance covariate models. Visual examination showed that models with fixed allometric exponent and no function describing organ maturation overpredicted the neonatal CL for both drugs. Best fit according to the AIC and MPE (table 1) provided CL models where allometric weight scaling was combined with a sigmoidal maturation function or the allometric exponent changed with age in a sigmoidal fashion.

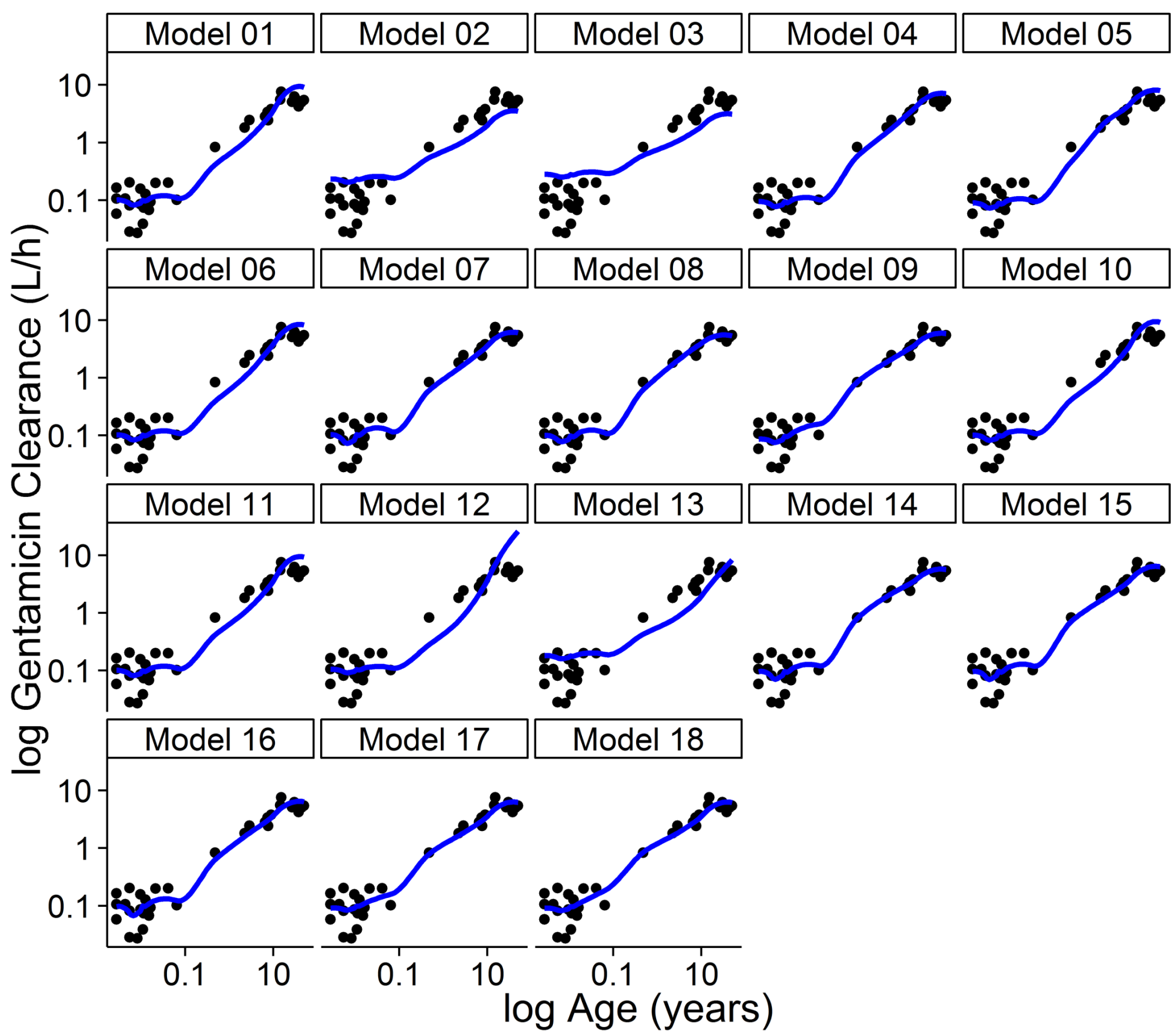


Figure 1: Loess line for predictions from models in table 1 superimposed on literature values for gentamicin clearance (black points) versus age.

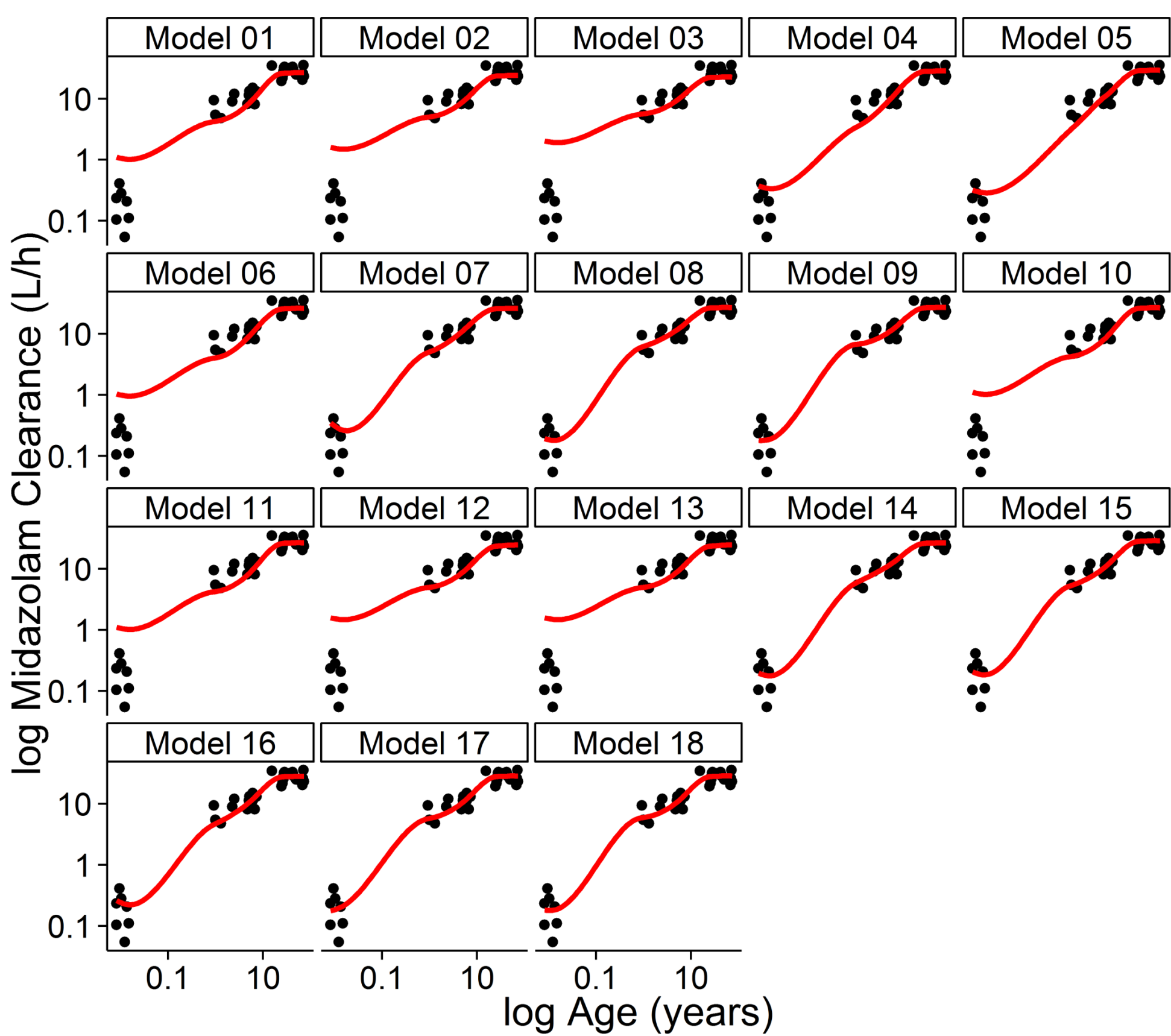


Figure 2: Loess line for predictions from models in table 1 superimposed on literature values for midazolam clearance (black points) versus age.

References

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