



Development of a Population Pharmacokinetic Model of Busulfan in Pediatric Patients

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Background

- Busulfan is a chemotherapeutic drug that is widely used for conditioning regimens before hematopoietic stem cell transplantation (HSCT) for patients with malignant disease (e.g., leukemia).
- However, the pharmacokinetic profile of busulfan varies significantly, especially for the pediatric population. Thus, therapeutic drug monitoring (TDM) is recommended to ensure efficacy and avoid toxicity (represented as area under the curve, AUC).
- This study aims to develop a new population pharmacokinetic model to use in daily TDM practice, especially in the pediatric population.

Method

Data:

- Retrospective dataset (Department of Pediatrics and Adolescent Medicine, Rigshospitalet, Denmark) from 2014 to 2024
- 69 patients (649 observations) including 68 children (Age (years) 0.6 – 18, median 7)
- Four consecutive days infusions. (Dose interval: 24h; Infusion time: 3h)

Clinical practice for past 10 years:

- TDM samples at around 0, 0.5, 1, 2, 4, 6 hours after infusion end on day 1
- $Dose = AUC_{target} \times CL_{predict}$
- First day $CL_{predict} = \frac{26.86 \times WT}{98.82 + WT}$
- First day TDM to check if $AUC_{target}/4$ is achieved.
- If not, $CL_{predict}(day2)$ was calculated by one or two compartment model fitted on previous day TDM observations.
- Turnaround time: 5–6 hours from sample receipt to report. If large variation from the 1st dose, repeat TDM on day 2 or 3.

Population model development:

- The M5 method for below limit of quantification data (BLOQ) (5.2% of the total number of observations)
- Forward selection ($p < 0.05$) and backward elimination ($p < 0.001$) for covariate model development (SCM)

Conclusion

- A time-varying clearance was found, where the clearance on days 2 and 3 was lower than that on day 1.
- New population model method showed a better prediction of the CL during first and second dose.
- Old method did not take the decrease in CL into account, which means around 10% higher predicted CL (10% higher in Dose) in second infusion
- With the new popPK model fewer blood samples can achieve similar prediction performance as the old method
- An open-source Shiny app for TDM is developed. (Available by reasonable request and will be on GitHub soon)

Results

A one compartment model was selected as final model:

Covariate model:

$$CL = \theta_{CL} \times \left(\frac{WT}{23.8}\right)^{\theta_{WT-CL}} \times \beta$$

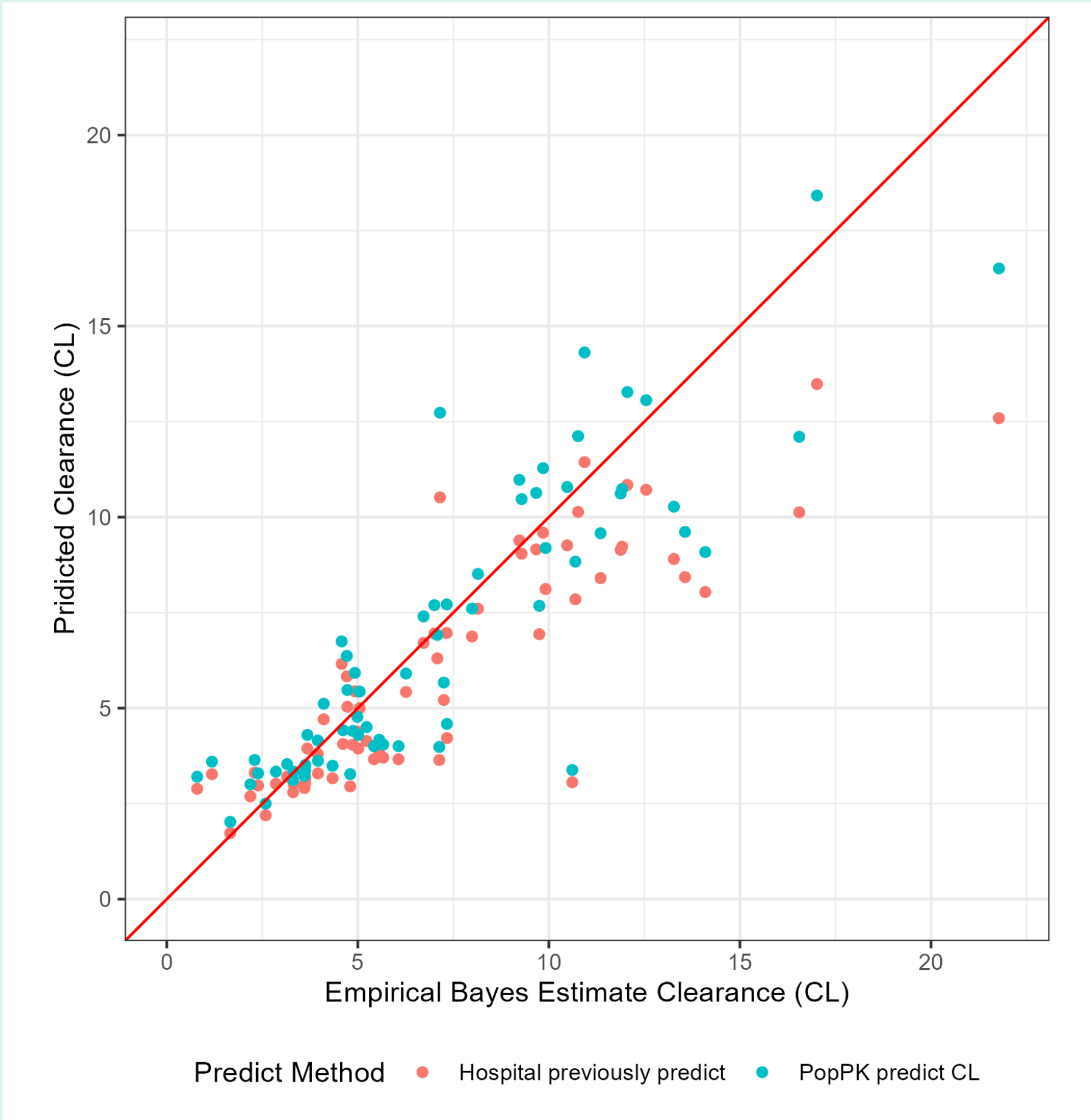
If 1st time infusion, $\beta = 1$;
If 2nd time infusion, $\beta = (1 + \theta_{infu2-CL})$;
If 3rd time infusion, $\beta = (1 + \theta_{infu3-CL})$;

$$V = \theta_V \times \left(\frac{WT}{23.8}\right)^{\theta_{WT-V}}$$

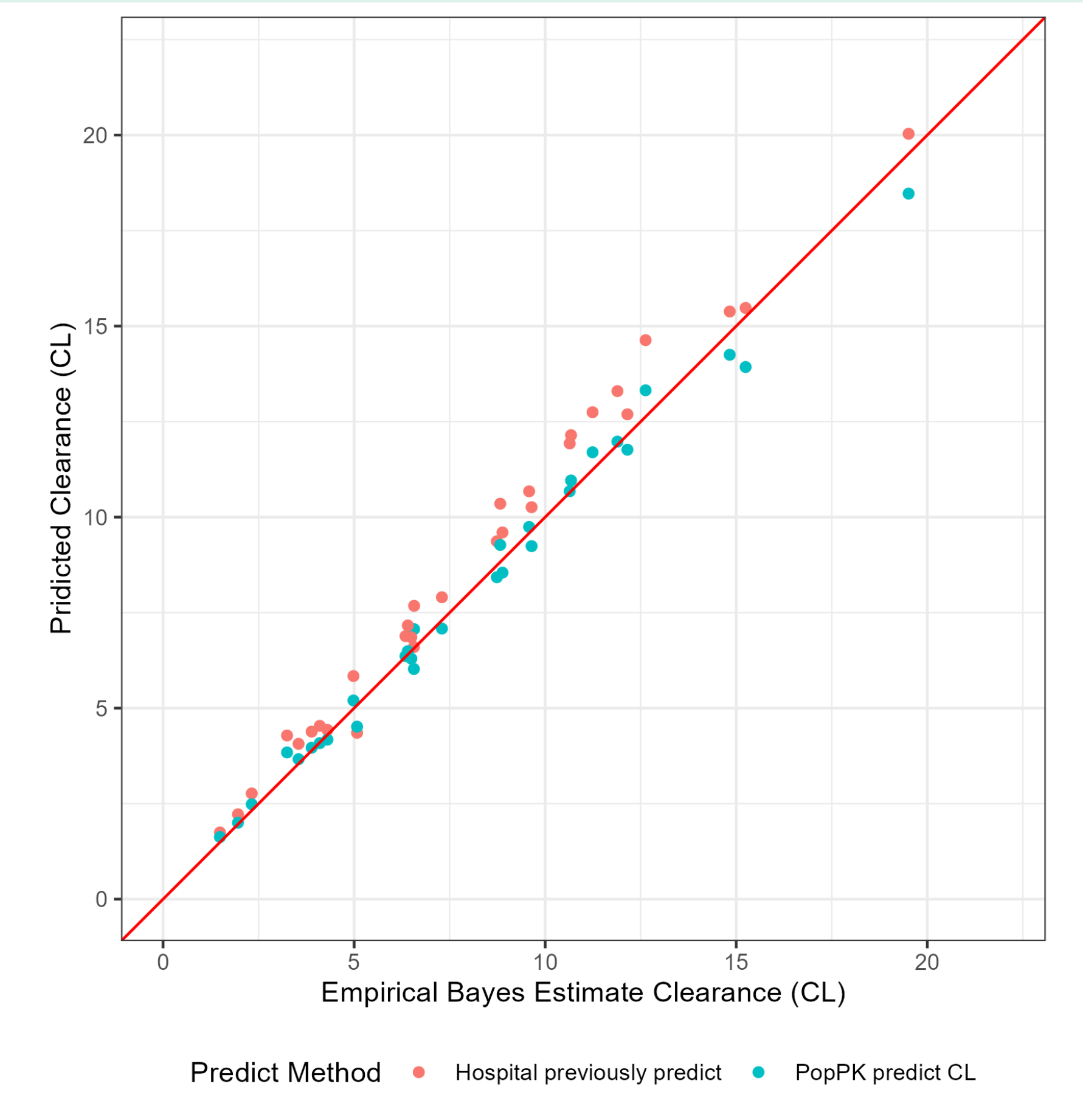
Final estimates:

Parameter	Estimate (RSE%)	Bootstrap 95% CI
θ_{CL} (L/h)	5.67 (4%)	[5.30, 6.12]
θ_V (L)	18.2 (4%)	[17.07, 19.47]
$\theta_{infu2-CL}$	-0.104 (16%)	[-0.13, -0.08]
$\theta_{infu3-CL}$	-0.132 (25%)	[-0.20, -0.03]
θ_{WT-CL}	0.823 (8%)	[0.71, 0.93]
θ_{WT-V}	0.902 (7%)	[0.80, 1.00]
ω_{CL}^2	0.117 (32%)	[0.06, 0.17]
ω_{CL-V}^2	0.0897	[0.03, 0.15]
ω_V^2	0.0937 (50%)	[0.03, 0.16]
σ_{prop}^2	0.00253 (24%)	[0.0014, 0.0034]
σ_{add}^2	3220 (12%)	[2647.57, 3902.1]

First Dose CL Prediction:



Second Dose CL Prediction:



	CL for First Dose			CL for Second Dose		
	RMSE	MDPE	F30	RMSE	MDPE	F10
HospPK Previously predict	2.47	-12.14%	73.13%	0.89	11.63%	40%
PopPK predict	2.05	-3.15%	77.61%	0.45	0.53%	93%

Prediction performance by less samples schedule:

Sample Schedule	RMSE	MDPE	MDAPE
2 samples: 0, 6 h	0.27	2.60%	2.60%
2 samples: 0, 4 h	0.17	0.81%	1.09%
4 samples: 0, 0.5, 2, 4 h	0.08	-0.37%	0.47%
4 samples: 0, 1, 2, 6 h	0.09	0.03%	0.54%

