Using Joint Modeling to Assess the Impact of Calcineurin Inhibitors Variability on Long Term Survival Outcome for Kidney Transplantation Patients

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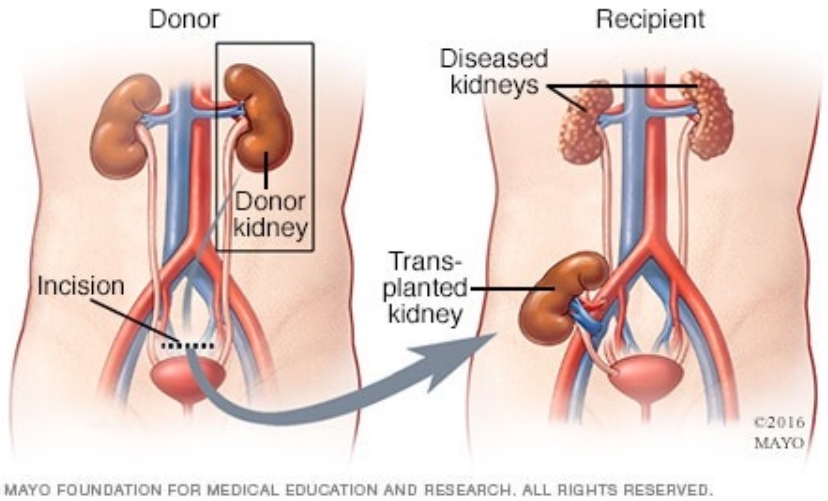
Background

Kidney transplantation



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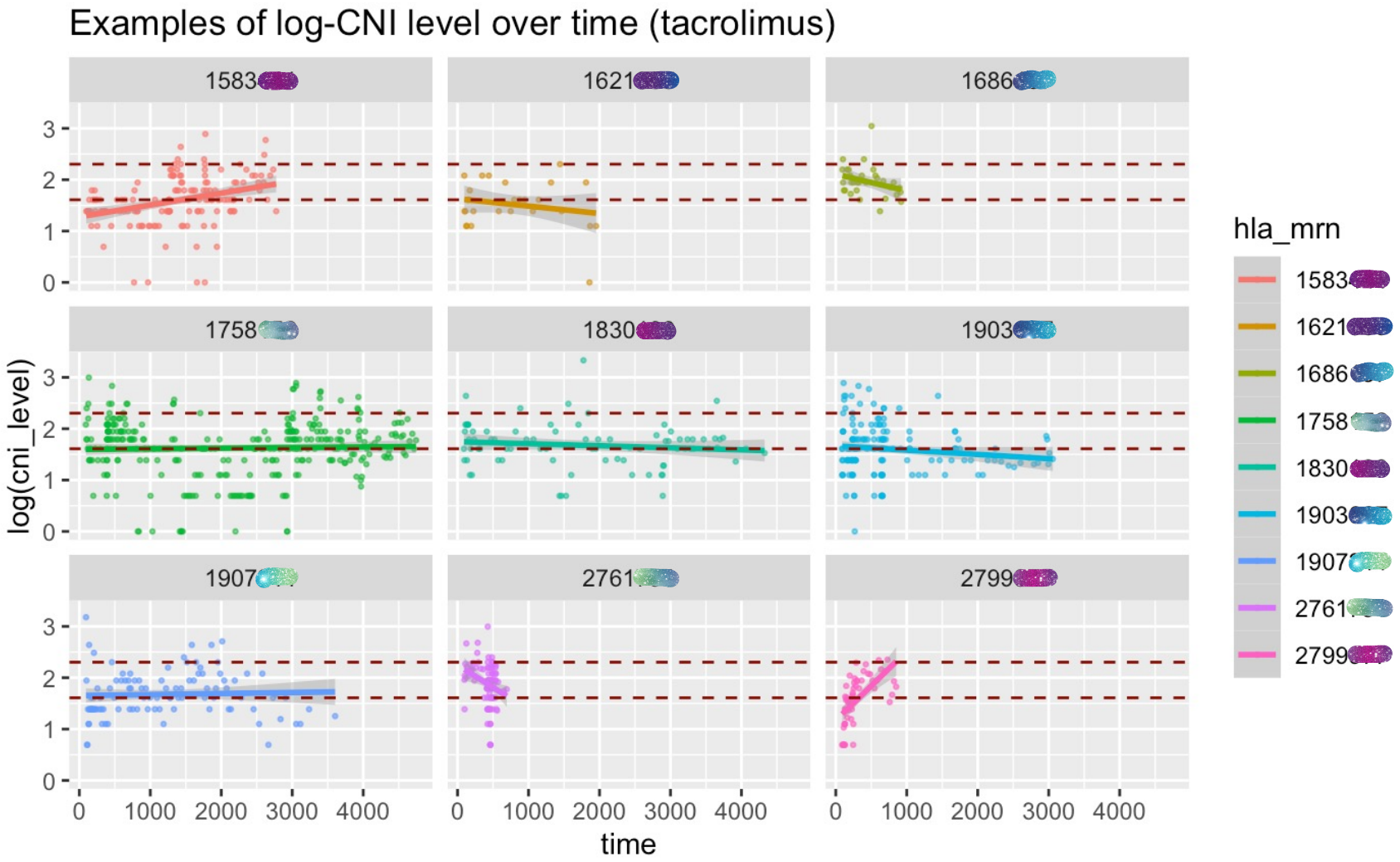
Immunosuppressive therapy

- Medication taken regularly.
- Commonly use calcineurin inhibitor (CNI): tacrolimus and cyclosporine.
- Therapeutic level: tacrolimus: 10-15ng/mL for first 6 weeks after transplantation, and 5-10 ng/ml thereafter.
- Is poor adherence associated with poor outcomes?

Longitudinal Data

Table: Summary of longitudinal data (2000–2016, tacrolimus)

	Mean (SD)	Median [Min, Max]
# of check-ups	58.6 (38.5)	51 [3, 310]
Follow-up time	1900 (1333) days	1666 [105, 6167] days
Patient-level mean	6.48 (1.38) ng/mL	6.46 [1.78, 12.62] ng/mL
Patient-level sd	2.66 (1.14) ng/mL	2.44 [0.49, 11.43] ng/mL

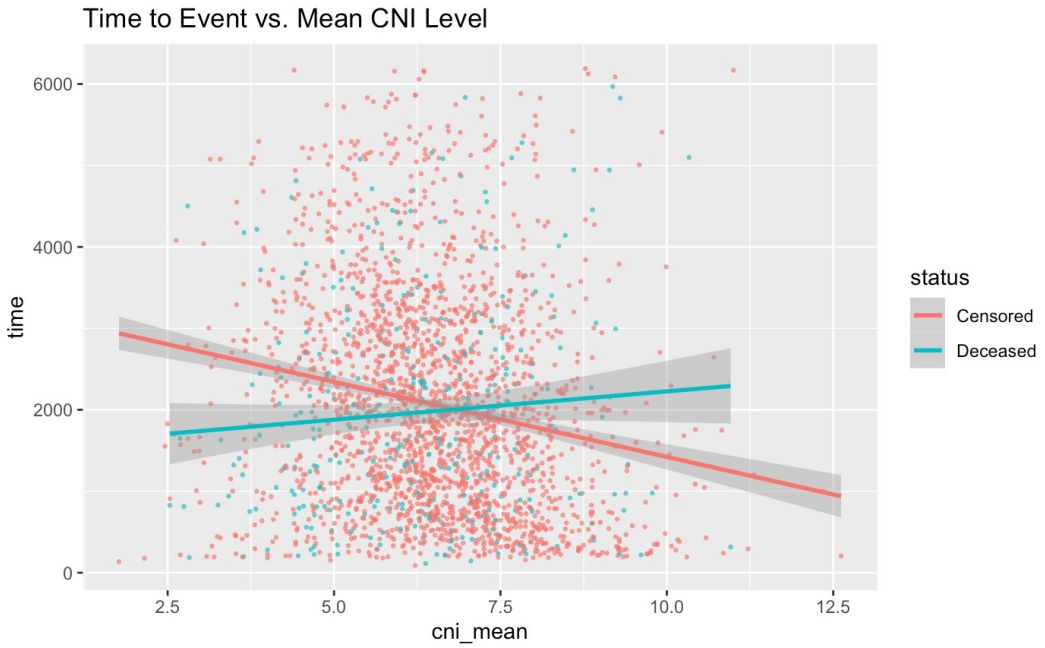


Survival Data

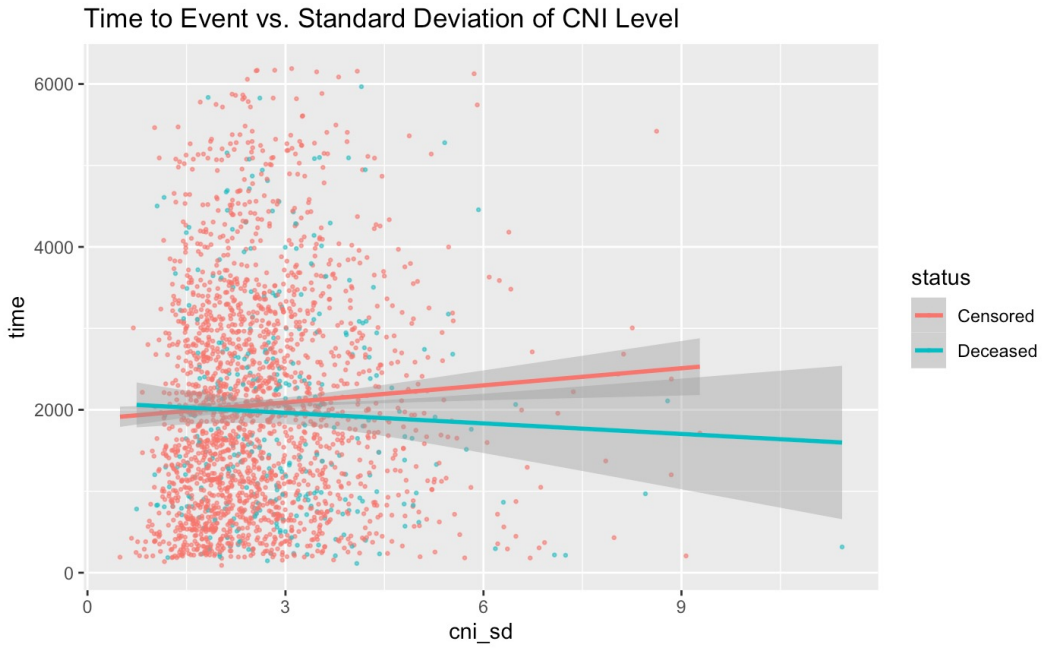
Table: Patient characteristics by outcome type (*partial table)

	Censored (N=2068)	Deceased (N=337)	Overall (N=2405)
pat_age_at_tx			
Mean (SD)	48.3 (14.7)	55.0 (10.9)	49.3 (14.4)
Median [Min, Max]	50.4 [1.50, 80.3]	56.3 [20.4, 80.1]	51.4 [1.50, 80.3]
sex			
M	1251 (60.5%)	216 (64.1%)	1467 (61.0%)
F	817 (39.5%)	121 (35.9%)	938 (39.0%)
race			
WHITE	1654 (80.0%)	279 (82.8%)	1933 (80.4%)
BLACK	237 (11.5%)	36 (10.7%)	273 (11.4%)
ASIAN	140 (6.8%)	12 (3.6%)	152 (6.3%)
OTHERS	37 (1.8%)	10 (3.0%)	47 (2.0%)
cause_of_esrd			
DN	438 (21.2%)	138 (40.9%)	576 (24.0%)
GN	547 (26.5%)	59 (17.5%)	606 (25.2%)
HTN	230 (11.1%)	32 (9.5%)	262 (10.9%)
PKD	302 (14.6%)	25 (7.4%)	327 (13.6%)
OTHERS	551 (26.6%)	83 (24.6%)	634 (26.4%)

Linking Longitudinal to Survival

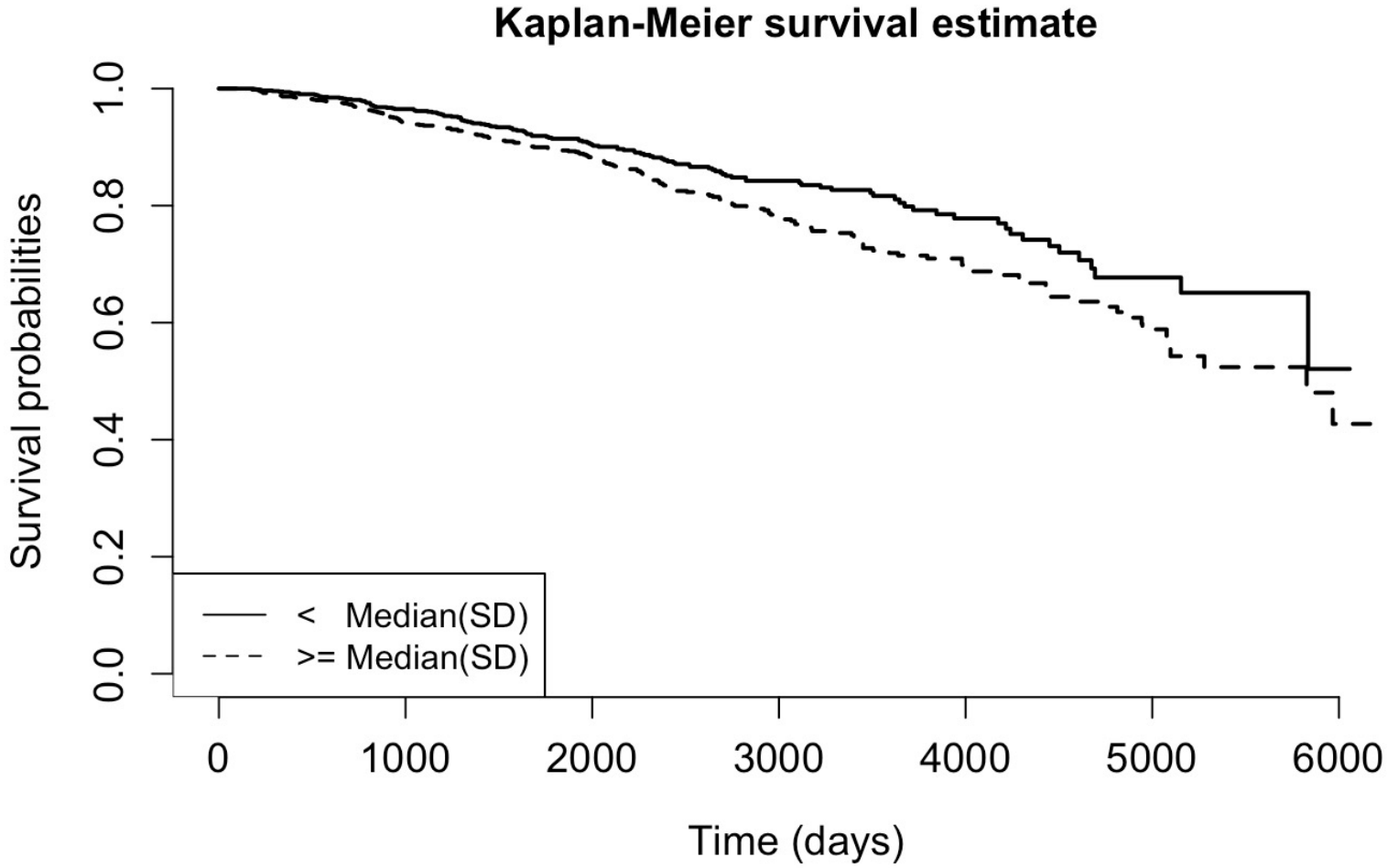


- Higher CNI, lower follow-up time.
- Higher CNI, better survival outcome.



- Higher SD, lower survival time.
- Not significant, however.

Linking Longitudinal to Survival



Joint Modeling

Joint modeling of longitudinal and survival data is of great interests in many clinical trials and observational studies:

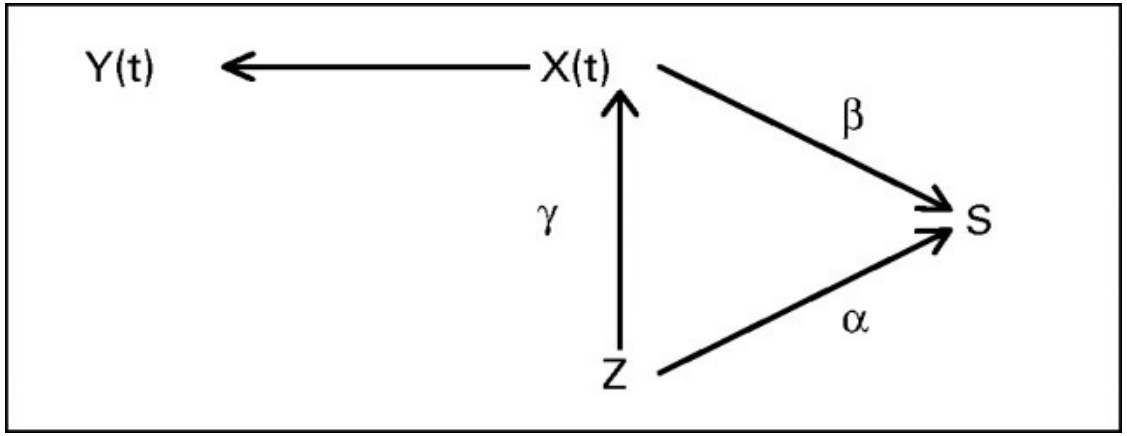
- circulating tumor cells → cancer progression
- CD4 cell count → death from AIDS
- CNI level → kidney failure

Measured Level True trajectory

$$Y_{ij} = X_{ij} + \varepsilon_{ij}$$

$$h(t) = h_0(t)\exp(\beta X_{ij} + \alpha Z_i)$$

Hazard function



Ibrahim, Chu, and Chen 2010

Joint Modeling Incorporating Variability

(Gao et al. 2011) proposed a joint-modeling approach to assess the impact of biomarker variability on the risk of developing clinical outcome. They studied the ocular hypertension → development of glaucoma.

$$\begin{aligned} Y_{ij} &= X_i(t)\beta + W_{1i} \\ &= X_i(t)\beta + I_i + S_i t_{ij} + e_{ij} \end{aligned}$$

$$e_{ij} \sim N(0, V_i)$$

$$\begin{aligned} h_i(t) &= h_0(t)\exp\{Z_i(t)\alpha + W_{2i}\} \\ &= h_0(t)\exp\{Z_i(t)\alpha + \gamma_1 I_i + \gamma_2 S_i + \gamma_3 \log V_i\} \end{aligned}$$

Our Approach

- Longitudinal sub-model: linear mixed model with heterogenous variance

$$Y_{ij} = (\beta_0 + I_i) + (\tau + S_i)t_{ij} + e_{ij}\,, \qquad e_{ij} \sim N\left(0, V_i^2\right)$$

$$I_i \sim N(0, \sigma_I^2)$$

$$S_i \sim N(0, \sigma_S^2)$$

$$\log V_i \sim N(\mu_V, \sigma_V^2)$$

V_i: subject-level standard deviation over the expected trajectory of log-CNI level (a proxy for variability)

- Survival sub-model: parametric (Weibull) Cox model

$$\lambda_i = \exp\left\{\alpha_0 + \sum_{k=1}^{p} \alpha_k x_{ik} + \gamma_1 I_i + \gamma_2 S_i + \gamma_3 V_i\right\}$$

x_{ik}: risk factors

$$h_i(t) = \rho\lambda_i t^{\rho-1} \Leftrightarrow T_i^{surv} \sim Weibull\left(\rho, \lambda_i^{-\frac{1}{\rho}}\right)$$

$\exp(\gamma_3)$ is the hazard ratio for 1 unit increase of the standard deviation of the log-CNI level.

$$T_i^{obs} = \min(T_i^{cens}, T_i^{surv})\,, \qquad T^{cens} \perp T^{surv}|X$$

Results

Outcome model (using STAN, 8-chain, 2500-iteration):

Table: Posterior summary for unadjusted model

	mean	sd	2.50%	97.50%	Rhat
rho	1.50	0.07	1.38	1.63	1.00
alpha_0	-5.62	0.25	-6.11	-5.16	1.00
gamma_1	-0.21	0.24	-0.68	0.27	1.00
gamma_2	-2.46	1.33	-5.21	-0.11	1.00
gamma_3	2.19	0.48	1.24	3.13	1.00
beta_0	1.79	0.01	1.78	1.80	1.01
tau	-0.02	0.00	-0.02	-0.01	1.01
sigma_I	0.26	0.00	0.26	0.27	1.00
sigma_S	0.08	0.00	0.07	0.08	1.01
mu_V	-1.00	0.01	-1.02	-0.99	1.00
sigma_V	0.32	0.01	0.31	0.33	1.01

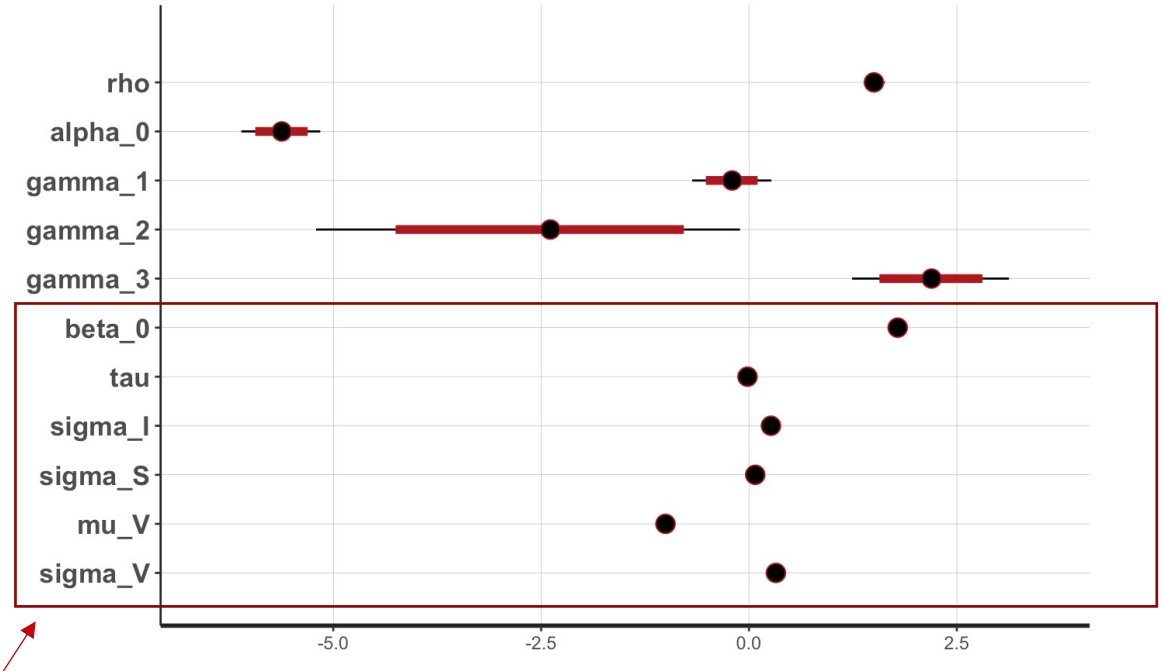


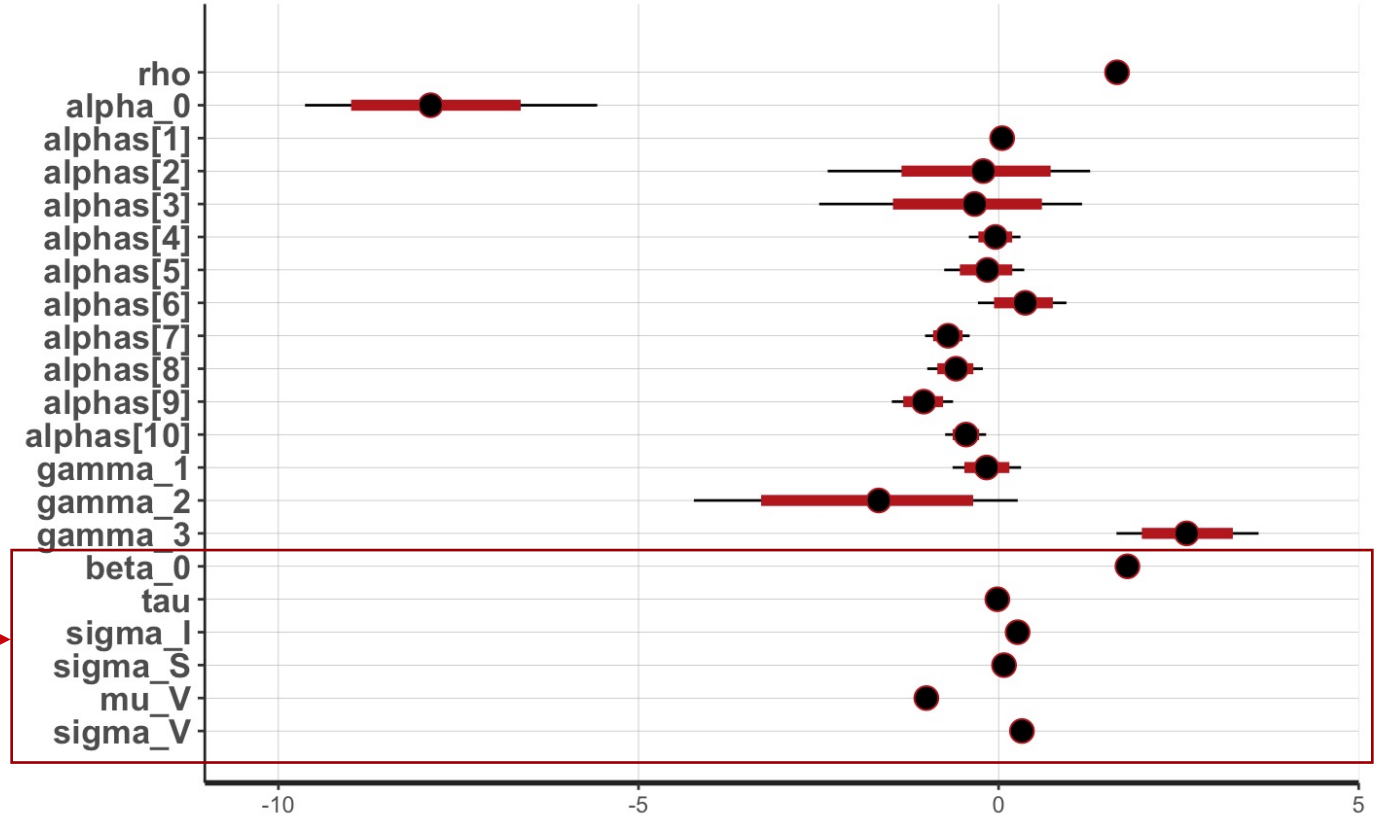
Figure: Posterior visualization for unadjusted model

CI level: 0.8, outer CI level 0.95

longitudinal estimates

Results

Risk factor adjusted model (age at transplantation, sex, race, cause of ESRD):



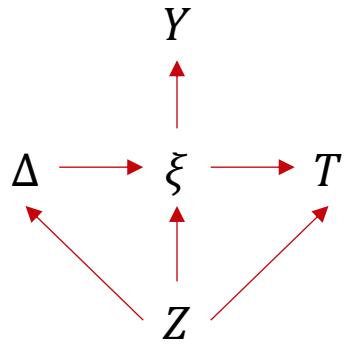
longitudinal estimates

Figure: Posterior visualization for adjusted model

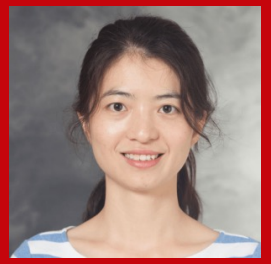
CI level: 0.8, outer CI level 0.95

Discussion

- Higher CNI variability is indeed <u>associated</u> with poorer survival outcome.
- What's next?
  - Find the variables that are highly associated with inferred variability. Can we make causal statement and propose intervention?
  - Different outcome types (graft failure, total graft loss, death-censored graft failure).
  - Cyclosporine group.
- Limitation
  - What's the estimand?



Thank you!
Q&A



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Appendix

Why STAN?

- See (Introduction to Stan by Cameron Bracken): [http://bechtel.colorado.edu/~bracken/tutorials/stan/stan-tutorial.pdf]
- Learn it by using it (check reference, do simulation projects).

How to handle censored data in STAN?

- $p(\theta|data) \propto p(data|\theta)p(\theta)$
- $p(T^{obs}, \delta) \propto f(T^{surv})^{\delta} S(T^{cens})^{1-\delta}$

How to speed up the posterior sampling?

- Priors
- Vectorization
- Non-centered parameterization
- See (Stan User's Guide, Ch. 22, Efficiency Tuning): [https://mc-stan.org/docs/2_24/stan-users-guide/optimization-chapter.html]