Statistical Analysis

We consider a joint model of the three outcomes: the patient's time in coma, whether or not the patient develops neurosequelae, and the longitudinal CSF volume measurements. Specifically, we consider the following model:

$$\text{logit}(\Pr(\text{NSQ}_i = 1)) = \alpha_0 + \alpha_1 \times \text{U}_i$$

$$\log(\text{CSF}_{i,t}) \sim \text{Normal}\ (U_i + \beta_0 + (\beta_1 + \kappa \times U_i) \times t,\ \sigma_e^2)$$

$$\log(\text{T}_i) \sim \text{Normal}\ (\lambda_0 + \lambda_1 \times \text{U}_i,\ \sigma_c^2)$$

$$\text{U}_i \sim \text{Normal}\ (0, \sigma_u^2)$$

Note NSQ_i is the neurosequelae status at discharge of patient i; $\text{CSF}_{i,t}$ is the CSF volume measurement of patient i at time t; T_i is the time in coma of patient i; U_i is a latent factor associated with each patient which simultaneously can affect NSQ_i, $\text{CSF}_{i,t}$, and T_i. We take a Bayesian approach, put a very weakly informative prior on model parameters, and obtain the posterior distribution of each model parameter using the Markov Chain Monte Carlo (MCMC) method. We adjust for the case-control design of the study by weighting each observation with the reciprocal of the probability that it is included in the study. We leverage the model to predict the neurosequelae probability given a patient's history of CSF measurements and time in coma. A web application implementing the algorithm in real time is available via https://blantyre-malaria-1.shinyapps.io/web_app/.

Results

The posterior mean, standard deviation, and the 95% equal-tailed credibility interval for each parameter is summarized in Table 1.

	mean	Sd	2.5%	97.5%
α_0	0.02	0.22	-0.40	0.45
α_1	-1.35	0.93	-3.59	0.01
β_0	2.42	0.06	2.31	2.53
β_1	0.04	0.02	-0.01	0.09
κ	-0.02	0.03	-0.07	0.05
λ_0	3.72	0.12	3.48	3.96
λ_1	-0.10	0.36	-0.83	0.57

Table 1: Summary statistics of posterior distributions of parameters of interest

Larger U_i corresponds to higher CSF measurement at baseline in the model. Therefore, $\alpha_1 < 0$ implies lower baseline CSF predicts higher probability of developing the neurosequelae, $\lambda_1 < 0$ says lower baseline CSF is associated with longer time in coma, and $\kappa < 0$ says higher baseline CSF is correlated with slower rates of increase of CSF

over time.

We further leverage the model fitting result to make prognosis. Consider a patient still in coma at t = 55 hours with two CSF measurements, one at baseline (t = 0) with log(CSF) = 2 and the other at t = 24 hours with log(CSF) = 3. For this patient, we predict his/her probability of developing NSQ is 0.494 (posterior mean) with a 95% equal-tailed credibility interval being [0.264, 0.714]. See Figure 1(a). To draw a contrast, suppose a second patient is still in coma at t = 33 hours with two log(CSF) measurements equal to 2.5 and 1.5 at t = 0 and t = 24 respectively. The algorithm predicts his/her probability of developing NSQ is 0.596 (posterior mean) with a 95% equal-tailed credibility interval being [0.395, 0.853]. See Figure 1(b). In practice, a doctor may look at these two graphs and pay more attention and possibly allocate more resources towards the second patient. We may also plot the probability (posterior mean) of developing neurosequelae as a function of the log(CSF) measurement at t = 24 hours for a patient still in coma at time t = 48 hours and various log(CSF) measurement at baseline (t = 0). See Figure 2. See Figure 3 and 4 for similar plots for a patient who is still in coma at time t = 36 and 72 hours. Note for various baseline log(CSF) measurements, the probability of developing neurosequelae decreases as the log(CSF) measurement at t = 24 hours increases.

Figure 1: Posterior distribution of the probability of developing neurosequelae for two cases

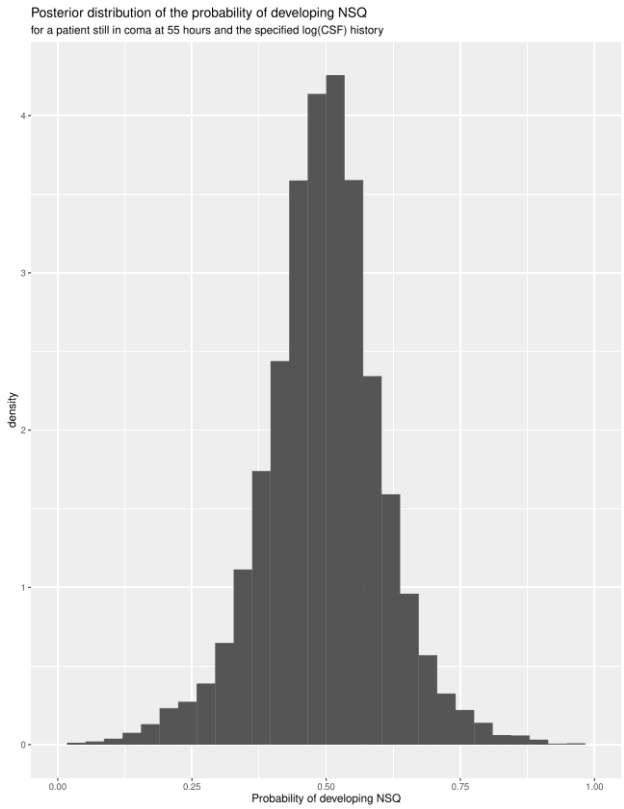

Figure 1(a): log(CSF) = 2 at baseline and 3 at 24 hours

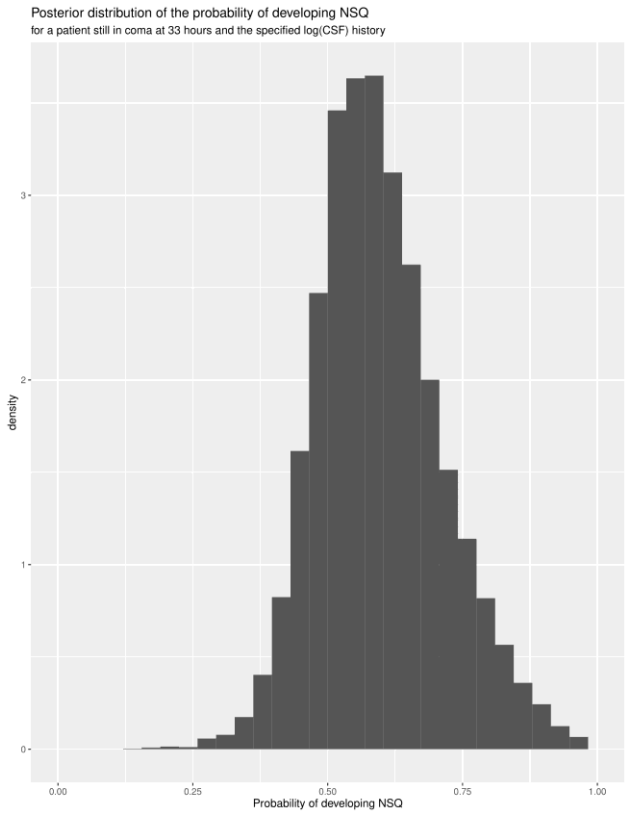

Figure 1(b): log(CSF) = 2.5 at baseline and 1.5 at 24 hours

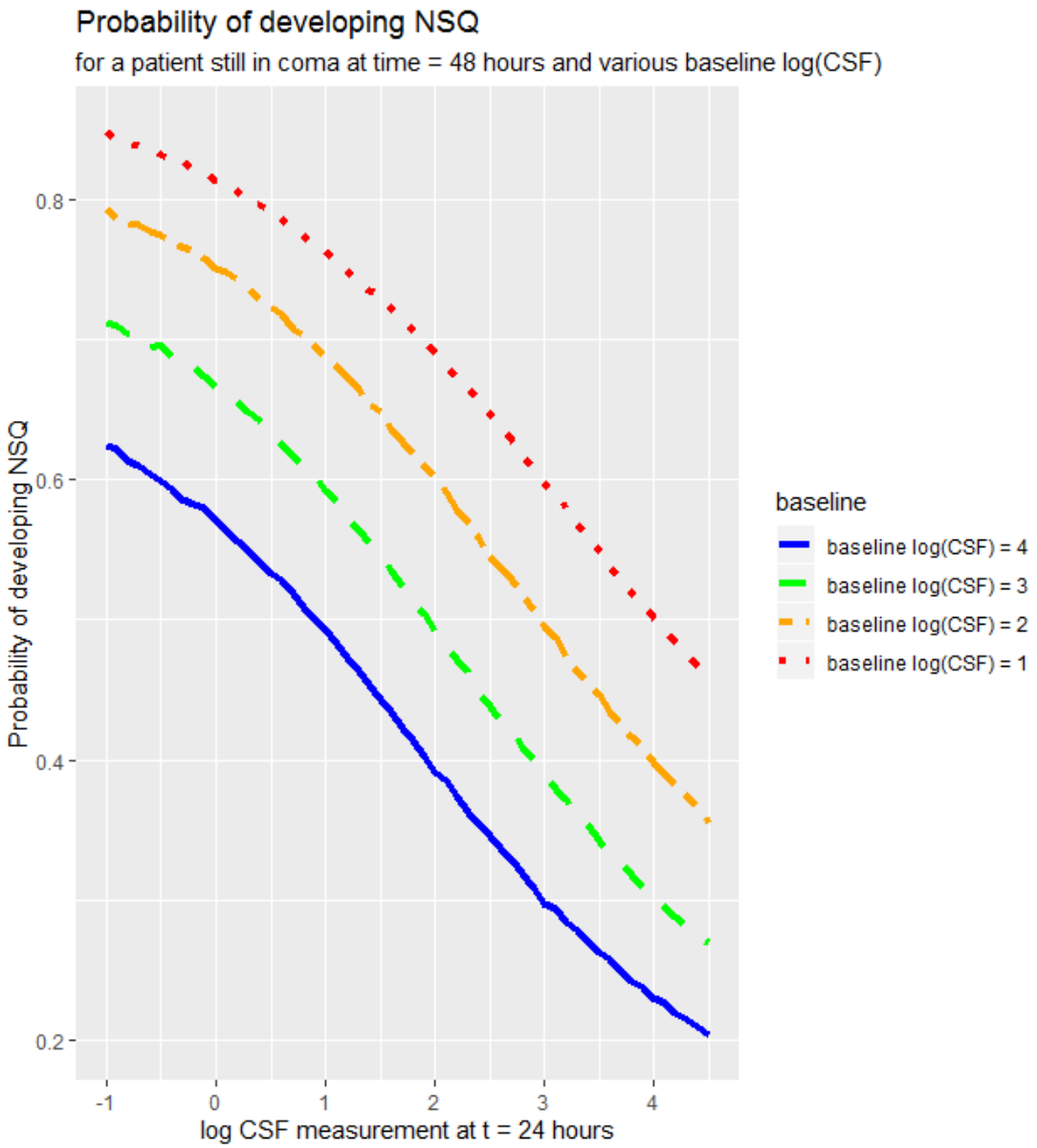

Fig 2. Probability of developing NSQ with coma of 48hrs.

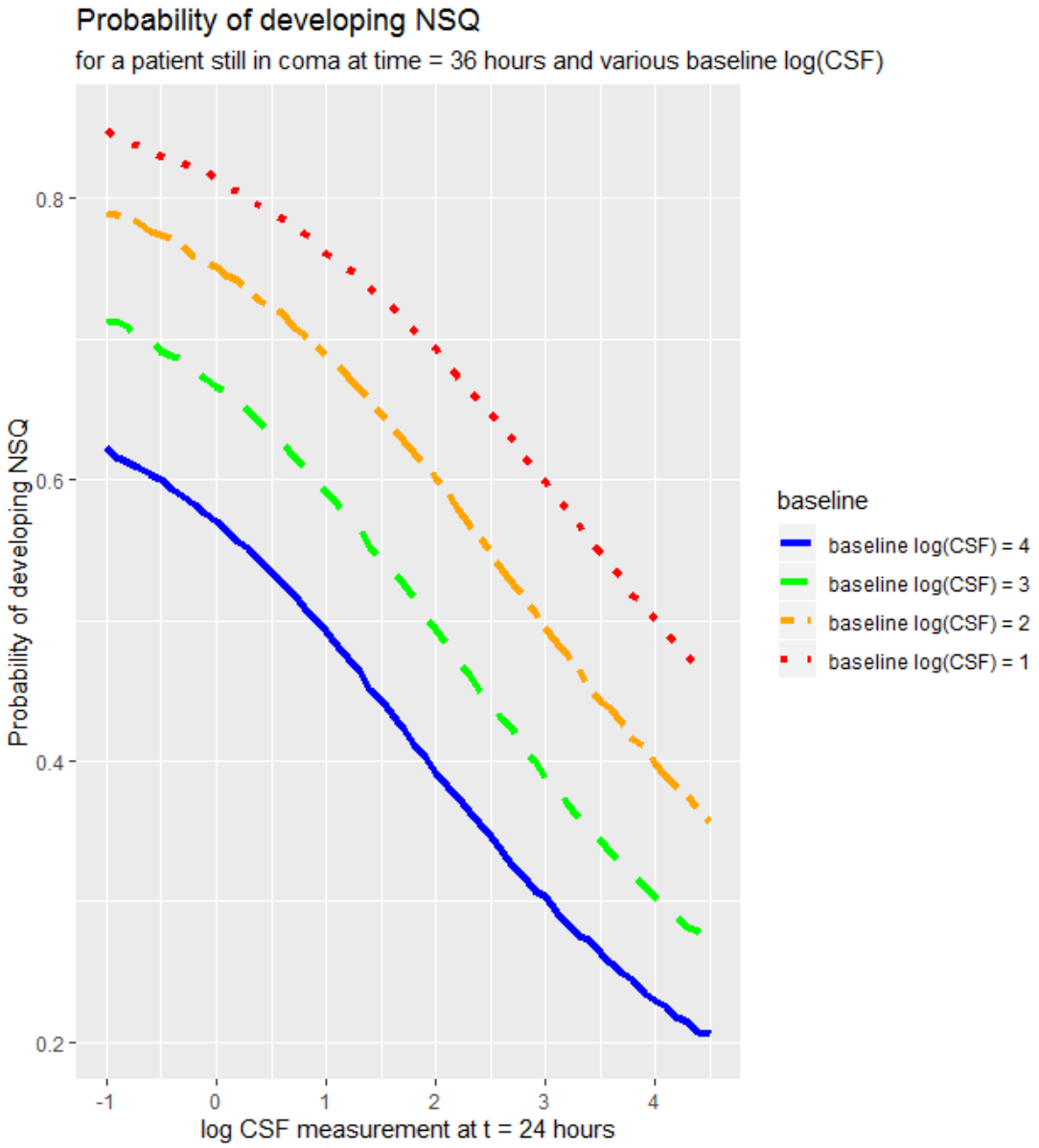

Fig 3. Probability of developing NSQ with coma of 36hrs.

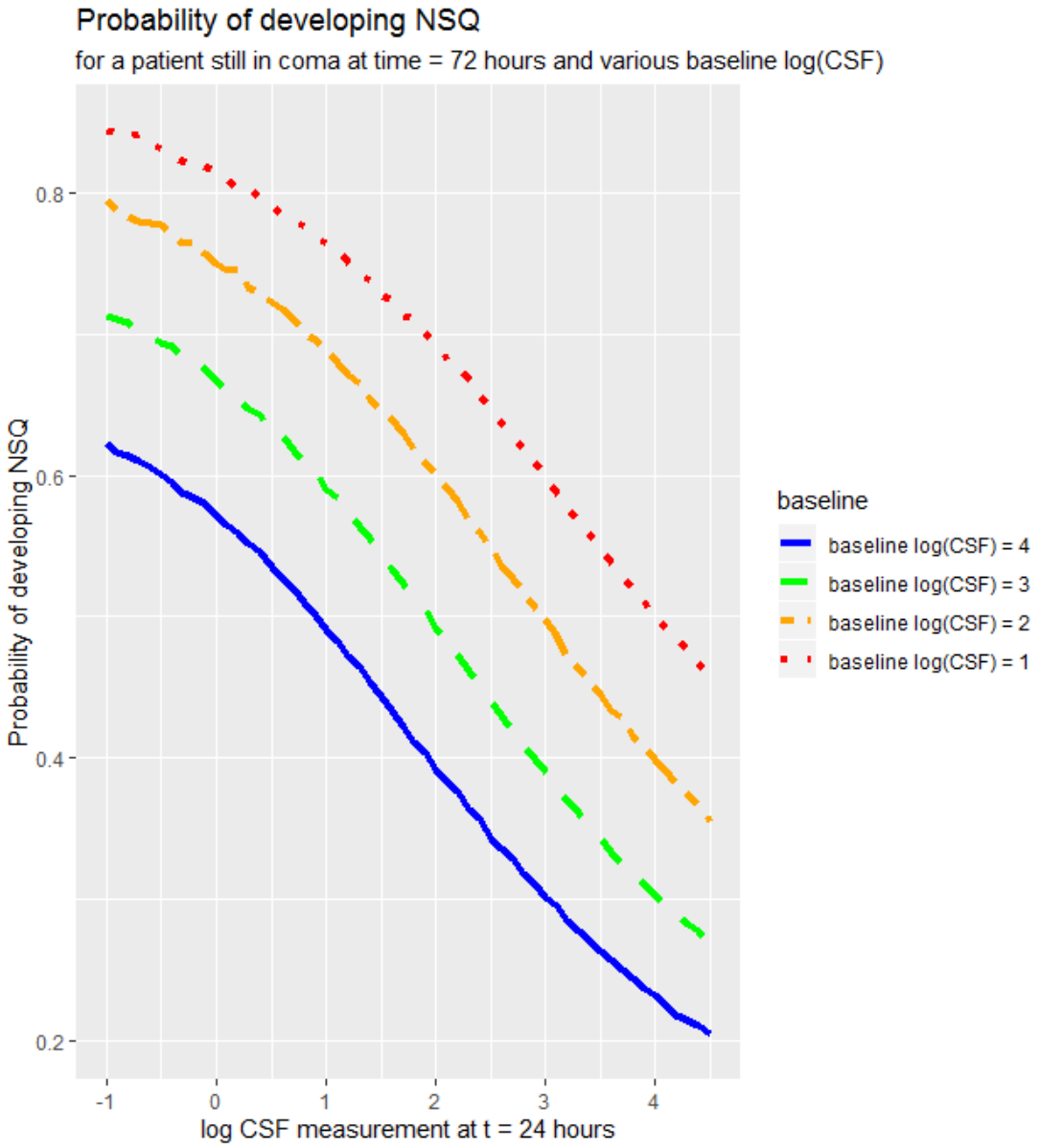

Fig 4. Probability of developing NSQ with coma of 72hrs