Approaches to Separation of Data in Assessment of Factors Associated with Spinal Subdural Hemorrhage in Children Evaluated for Abusive Head Trauma

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A Thesis

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Kenny Chen

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Dr. Kathryn Gray

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Abstract

Abusive head trauma (AHT) is the leading cause of traumatic brain injury in children under 2 years of age and a diagnosis requires careful consideration of the history of the child, physical examinations, and image findings. Spinal injuries have also been have also been observed in patients with abusive head trauma but have been less clearly characterized as they are often overlooked or not considered, particularly in nonfatal cases. The issue of identifying spine injuries is important as there are currently conflicting guidelines provided regarding the role of spine imaging in suspected AHT. This study aims to assess the relationships between spinal injuries, including spinal subdural hemorrhages (sSDH) and Abusive Head Trauma (AHT) as well as other clinical factors, using data obtained retrospectively through the Child Abuse and Protection Network (CAPNET) with information on children under the ages of 10 from 11 hospitals across the United States.

Generalized linear mixed effects model (GLMM) and generalized estimating equations models (GEE) were used to account for the hospital clustering effect; however, exploratory analysis of the data revealed issues of separation in the data which introduces issues of convergence and estimation in these models. To address this, we considered penalized versions of both types of models and evaluated the methods and effect it has on dealing with the separation of data. We considered two covariance structures for the GEE model and both resulted in comparable odds ratios and we observed a significant effect of intracranial subdural hemorrhage on the odds of having a spinal subdural hemorrhage after adjusting for other covariates. In the penalized

GLMM model, we also observed a significant effect of having an intracranial subdural hemorrhage on the odds of having a spinal subdural hemorrhage. Note that the interpretation of the GEE models is at the population level while the GLMM model is at the cluster-specific level. These results may assist clinicians in discerning when to perform spinal imaging when dealing with suspected abusive head trauma cases.

Chapter 1

Introduction

Until Every Child Is Well.

Abusive head trauma (AHT) is the leading cause of traumatic brain injury in children under 2 years of age with an estimated mortality of 15-25% (Arabinda K. Choudhary, Ishak, Zacharia, & Dias (2014)). There is no clear cause for abusive head trauma and so a diagnosis requires careful consideration of the history of the child, physical examinations, and image findings. Throughout several studies and the work of various clinicians, cranial injuries such as intracranial subdural hemorrhages, retinal hemorrhages, rib and classic metaphyseal fractures have been shown to be highly associated with abusive head trauma (Arabinda K. Choudhary et al. (2014), Rabbitt et al. (2020)). Spinal injuries have also been have also been observed in patients with abusive head trauma but have been less clearly characterized as they are often overlooked or not considered, particularly in nonfatal cases (Arabinda Kumar Choudhary, Bradford, Dias, Moore, & Boal (2012)). The lack of consideration might be due to the lack of a routine MRI procedure with respect to the spine in potential abusive head trauma cases which has prompted various conversations on the utility of MRI imaging as well as the utility of whole-spine vs cervical spine MRI imaging.

The issue of spine imaging is important as there are various guidelines regarding spine imaging in suspected AHT. The American College of Radiology (ACR) states the MRI of the cervical spine is "usually appropriate" in suspected AHT, while whole-spine MRI "may be appropriate" (Wootton-Gorges et al. (2017)). In contrast, guidelines in the United Kingdom ("The radiological investigation of suspected physical abuse in children | The Royal College of Radiologists — rcr.ac.uk") and a consensus statement published in Pediatric Radiology in 2018 recommend routine whole-spine MRI in suspected AHT cases (Arabinda Kumar Choudhary et al. (2018)).

Due to recent findings from a handful of small single-center retrospective studies in the last 15 years on spinal injuries in abusive head trauma, this has prompted discussion among experts in child abuse about the need for more multicenter, hypothesis-driven studies in order to better understand the mechanisms of spinal subdural hemorrhages (sSDH) in children evaluated for abusive head trauma (Arabinda Kumar Choudhary et al. (2012), Arabinda K. Choudhary et al. (2014), Rabbitt et al. (2020)).

In a single-center retrospective study of the incidence of spinal injury on MRI among children less than 5 years of age who underwent evaluation for AHT in the US, 29/47 (62%) of children who were diagnosed with AHT and had undergone spine MRI were found to have spinal abnormalities (Rabbitt et al. (2020)). Of the spinal injuries described in the study, sSDH was the only injury type associated with the combination of retinal hemorrhages, a diagnosis of AHT and a mechanism of injury consistent with acceleration/deceleration forces without impact, such as shaking (Rabbitt et al. (2020)).

Those who question the utility of whole-spine MRI in clinical practice contend that the identification of sSDH infrequently alters clinical management and may only represent the redistribution of intracranial subdural hemorrhages but sSDHs could lead to complications from spinal cord compression. They also argue that additional imaging is costly and prohibitive. In contrast, those in support of spine MRI point to the potential forensic implications of identifying sSDH if it provides incremental accuracy for a diagnosis of abuse and help us better highlight injury severity as well as elucidate the mechanism of abusive injury. For example, one study found an association of sSDH and the combination of non-contact head injury, retinal hemorrhage, and a diagnosis of AHT (Rabbitt et al. (2020)). As such, further investigation is needed to explore the clinical factors often looked at in children evaluated for abusive head trauma and assess their association with the presence of spinal subdural hemorrhages to better assist in providing care for this vulnerable population.

1.1 Study Objectives

The overarching objective of the study was to assess the relationships between spinal injuries, including spinal subdural hemorrhages and Abusive Head Trauma (AHT) as well as other clinical factors, using data obtained retrospectively through the Child Abuse and Protection Network (CAPNET) with information on children under the ages of 10 from 11 hospitals across the United States.

The specific aims of our study are as follows:

- Compare the rates of spinal imaging in all patients with intracranial injury by age, injury severity, level of concern for abuse, and concurrent injury types.

- Describe the incidence proportion of spinal injuries (including subdural hemorrhage (sSDH), epidural hemorrhage (sEDH), subarachnoid hemorrhage (sSAH), ligamentous or spinal Cord injury) according to the levels of AHT concerns.

- Examine the relationship of spinal subdural hemorrhage with other factors, including intracranial hemorrhage (presence vs absence), the severity of injury presentation (Glascow Coma Score, endotracheal intubation), clinical and non clinical markers of shaking (retinal hemorrhages, rib fractures, confession of shaking).

Chapter 2

Methods

2.1 Study Population

The study population included children <2 years old who underwent CT/MRI (including fMRI) of the brain and MRI spine as part of their evaluation for AHT. A majority of abusive head trauma presents in those less than 2 years old so we wanted to examine this group in particular. We further excluded any child that had no CT/MRI head imaging as we needed brain imaging in the diagnosis of abusive head trauma. We also excluded no intracranial injury for a similar reason and excluded those that had medical conditions that predisposed the child to injury since disorders such as glutaric acidemia could make interpretation of findings difficult and lastly, we excluded neuroimaging and spine imaging results that raised concern for possible spine injury as we wanted only definitive findings. The consort diagram below shows the participants composition with an analysis cohort of size $n = 887$.

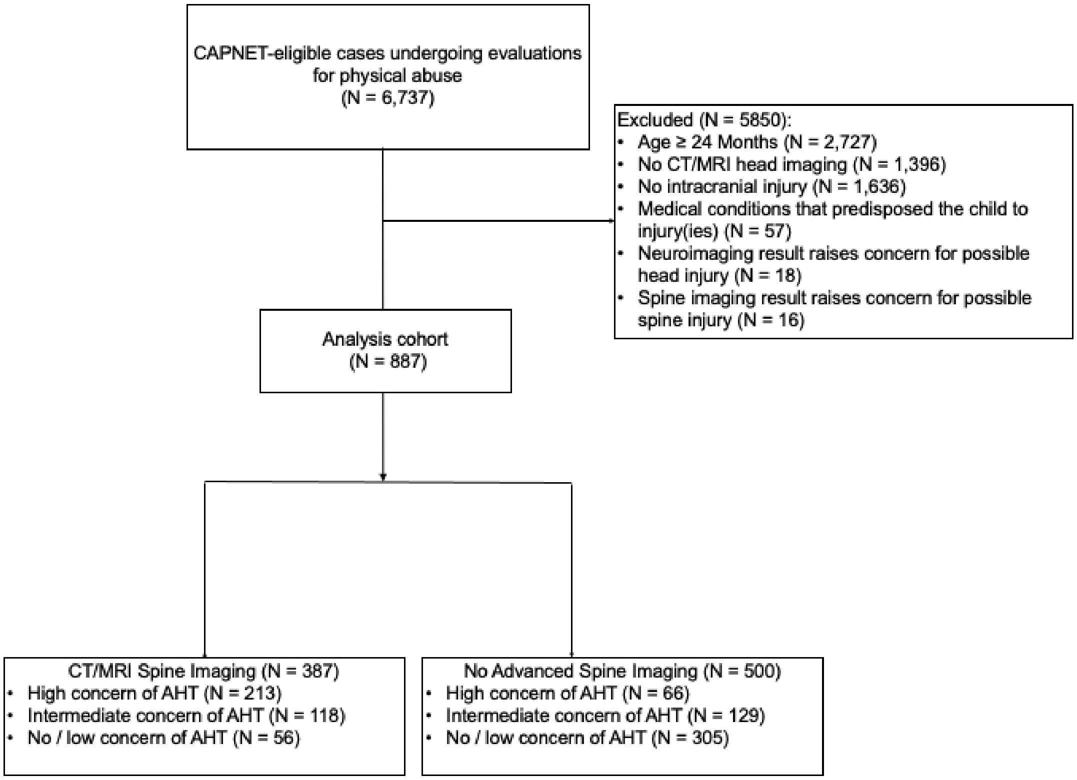

Figure 2.1. Consort diagram

2.2 Data

The data comes from the Child Abuse and Protection Network (CAPNET) and contains information on 6,737 children under the ages of 10 from 11 hospitals across the United States between February 2021 and September 2022 (Kratchman et al. (2022)).

CAPNET is a multi-center, federally-funded network dedicated to promoting child abuse research. CAPNET has been collecting data since February 1st, 2021 for children <10 years old who undergo sub-specialty evaluation by child abuse practitioners for physical abuse across 11 pediatric centers. At each site, completed child physical abuse consultations are reviewed for eligibility criteria by either participating clinicians or trained data collectors. The eligibility criteria states that a case is eligible for inclusion if: 1) age <10 years at the start of the encounter, 2) a clinical evaluation performed by a CAP during the enrollment period due to recent concerns (within 1 month) for suspected physical abuse, and 3) the patient was physically seen within a CAPNET hospital system, including those evaluated in outpatient clinics, emergency departments, and inpatient wards. A clinical evaluation is defined to have occurred when a child abuse specialist documents an assessment of abuse or and/or recommendations for the evaluation or reporting of abuse in the medical record. Data domains abstracted included reported mechanisms of trauma, presenting neurological signs and symptoms, presenting cardiorespiratory symptoms, imaging results for spine MRI and brain MRI/CT, intracranial injury types, as well as associated injuries such as rib fractures, classic metaphyseal lesions, and retinal hemorrhages (See Appendix A1).

2.3 Outcome of Interest

The outcomes of interest are the spinal injuries identified via MRI/CT which include spinal epidural hemorrhage (sEDH), spinal subdural hemorrhage (sSDH), spinal subarachnoid hemorrhage (sSAH), ligamentous injury and spinal cord injury. Each one is coded as a dichotomous outcome with Yes or No as the possible values. The primary outcome of interest is spinal subdural hemorrhage.

2.4 Statistical Methods

2.4.1 Exploratory Data Analysis

We first compare the rates of spinal imaging in all patients with intracranial injury by age, injury severity, level of concern for abuse (AHT status), and concurrent injury types. Fisher exact tests for categorical variables and Kruskal-Wallis tests for continuous variables will be used.

Among those patients with spine imaging data, the prevalence proportion of spinal injuries (including subdural hemorrhage (sSDH), epidural hemorrhage (sEDH), subarachnoid hemorrhage (sSAH), ligamentous or spinal Cord injury) according to the levels of AHT concerns were summarized. Similarly, fisher exact tests for categorical variables and Kruskal-Wallis tests for continuous variables will be used. Finally, we also describe the prevalence of spinal SDH with other factors, including intracranial hemorrhage (presence vs absence), the severity of injury presentation (GCS), clinical and non clinical markers of shaking (retinal hemorrhages, rib fractures, confession of shaking). Fisher exact tests for categorical variables and Kruskal-Wallis tests for continuous variables will be used. All tables will display (median (IQR)) for continuous variables due to the skewness of our variables and (%) for categorical variables. Two sided p-values were reported with a $p < 0.05$ considered statistically significant.

2.4.2 Logistic Regression

In order to examine the relationship between relevant clinical characteristics and spinal subdural hemorrhage (dichotomous outcome: one either experiences the spinal subdural hemorrhage or not), a logistic regression could be considered and such a model takes the following form:

$$\text{logit}(P(Y_i = 1|\mathbf{X})) = \log\left(\frac{P(Y_i = 1|\mathbf{X})}{1 - P(Y_i = 1|\mathbf{X})}\right) = \frac{e^{\mathbf{X}^T\boldsymbol{\beta}}}{1 + e^{X^T\boldsymbol{\beta}}}$$

where we have used the logit link function with Y_i as the outcome of interest, spinal subdural hemorrhage, with 0 indicating no presence and 1 indicating presence, $\mathbf{X}$ is the design matrix of size $n \times (p+1)$ for n observations and $\boldsymbol{\beta} \in \mathbb{R}^{p+1}$ is the vector of coefficients for the p covariates and intercept. After fitting, the resulting $\boldsymbol{\beta}$ coefficients are then interpreted as the log(Odds Ratios) of the event occurring in the exposed group versus unexposed group.

2.4.3 Adjusting for Clustered Data

Given the data were collected across multiple hospital sites or clustered data, we consider multilevel logistic mixed effects (also known as Generalized Linear Mixed Effects Models (GLMMS)) and Generalized Estimating Equations (GEEs) which each account for the clustering effect of hospital site. It is important to note that for nonlinear modeling as is in our case (status of spinal subdural hemorrhage is binary), the interpretations of the two will not be the same. For a mixed effects model, the interpretation will be at the clustering level while in a generalized estimation equations model, the interpretation is at the population averaged level. Although these two methods won't be exactly comparable, fitting both types of models gives us more options to choose from to explore the relationship between clinical factors and spinal subdural hemorrhages in a clustered setting.

2.4.4 Generalized Estimating Equations

We first consider implementation of Generalized Estimating Equations (GEE) introduced by Liang & Zeger (1986) that accounts for the correlation between patients. The GEE approach as its name suggests is motivated by "estimating equations". In this section, we use the following notation: Y_{ij} denotes the outcome (sSDH status) for the i^{th} hospital and j^{th} patient. Associated with each response Y_{ij} is a $p \times 1$ vector of covariates, X_{ij}. As GEE models are marginal models, they have the following three-part specification:

1. The conditional expectation of the response $E(Y_{ij}|X_{ij}) = \mu_{ij}$, depends on the covariates X_{ij} through a known link function

$$g(\mu_{ij}) = \eta_{ij} = X_{ij}^T \beta$$

2. The variance of each Y_{ij} given covariates, depends on the mean based on

$$V(Y_{ij}|X_{ij}) = \phi v(\mu_{ij})$$

where $v(\mu_{ij})$ is a known variance function and ϕ is a scale parameter.

3. The conditional within-subject association among vector of repeated responses, given covariates, is a function of a vector of association parameters, α (and also depends on the, μ_{ij})

And the model specification with binary response (primary outcome) looks like this:

1. Logistic regression:

$$\text{Logit}(\mu_{ij}) = X_{ij}^T\beta$$

2.

$$V(Y_{ij}|X_{ij}) = \mu_{ij}(1 - \mu_{ij})$$

3. $\text{OR}(Y_{ij},\, Y_{jk}) = \alpha_{jk}$ (unstructured odds ratios) where

$$\text{OR}(Y_{ij}, Y_{jk}) = \frac{Pr(Y_{ij} = 1, Y_{ik} = 1)Pr(Y_{ij} = 0, Y_{ik} = 0)}{Pr(Y_{ij} = 1, Y_{ik} = 0)Pr(Y_{ij} = 0, Y_{ik} = 1)}$$

GEEs can be thought of as arising from a minimization of the residuals $e_i = Y_i - \mu_i(\beta)$

$$\sum_{i}^{N}(Y_i - \mu_i(\beta))^T V_i^{-1}(Y_i - \mu_i(\beta))$$

with respect to β and V_i is treated as known and $\mu_i(\beta)$ is the vector of mean response with elements $\mu_{ij}(\beta) = g^{-1}(X_{ij}^T\beta)$. Then it can be shown that if a minimum of the above function exists, it solves the following:

$$U(\beta, \alpha) = \sum_{i=1}^{n} D_i' V_i^{-1}(y_i - \mu_i) = \mathbf{0}$$

where V_i is the "working" covariance matrix which serves as an approximation for the true covariance matrix, $D_i = \frac{\partial \mu_i}{\partial \beta}$ is the "derivative" matrix that transforms the original units of Y_{ki} to the units of $g(\mu_{ki})$. Then, this system of equations would then be solved in some iterative fashion if no closed-form solution exists. One advantage of Generalized Estimating Equations is that we can avoid distributional assumptions about Y_i and estimators of $\hat{\beta}$ are always consistent and asymptotically normal even if the covariance of Y_i has been misspecified.

2.4.5 Multilevel Logistic Mixed Effects

We also consider a two-level Logistic Mixed Effects model that accounts for patient clustering within hospitals by incorporating a random effect. We describe the model in the following way. Let Y_{ki} be the binary response taking on values 0 or 1 for diagnosis of spinal subdural hemorrhage of the i-th case (level 1 unit) in the k-th hospital (level 2 unit). With each response, we have a vector of p covariates, $\mathbf{X}_{ki}$. We can specify this model using a three part specification as laid out in Fitzmaurice, Laird, & Ware (2011):

1. We condition on the random effect b_i such that the Y_{ki} are independent with a Bernoulli distribution and $Var(Y_{ki}|b_i) = E(Y_{ki}|b_i)\{1 - E(Y_{ki}|b_i)\}$

2. We model the conditional mean of Y_{ki} with fixed and random effects via:

$$\log\left\{\frac{\mathbb{P}(Y_{ki}=1|b_i)}{\mathbb{P}(Y_{ki}=0|b_i)}\right\} = \mathbf{X}_{ki}\boldsymbol{\beta} + b_i$$

3. The random effect b_i is assumed to have a normal distribution with mean 0 and variance σ_b^2. Note here that the random effects can have any distribution but for computational convenience, we will assume a normal distribution with mean 0 and variance σ_b^2.

Estimation and inference can then be conducted using likelihood based approaches. One approach is to treat the random effects as unobserved latent variables and integrate them out but for binary outcomes, this integral has no closed-form solutions so numerical procedures are used. For instance, the package `lme4` by Bates, Mächler, Bolker, & Walker (2015) uses an adaptive Gauss-Hermite quadrature likelihood approximation.

2.4.6 Penalized Methods to Address Data Separation Issues

Initial exploratory analyses of the data revealed there to be multiple instances of complete or quasi-complete separation within the data which can cause issues with inference as likelihood approaches breakdown. Complete separation occurs when there exists some vector of coefficients $\boldsymbol{\beta}$ such that the response $y_i = 1$ whenever $\boldsymbol{\beta x_i}$ > 0 and $y_i = 0$ whenever $\boldsymbol{\beta x_i} \leq 0$ (Albert & Anderson (1984)). Take for example, a toy dataset $(x_1, y_1), (x_2, y_2), (x_3, y_3), (x_4, y_4) = (-4, 1), (-3, 1), (2, 0), (1, 0)$ such that we can draw a straight line between these four points to completely separate them. Quasi-complete separation is a related problem that occurs when there exists some vector of coefficients $\boldsymbol{\beta}$ such that $\boldsymbol{\beta x_i} \geq 0$ whenever the response $y_i = 1$ and $\boldsymbol{\beta x_i} \leq 0$ whenever $y_i = 0$ and equality holds for at least one case in each category of the dependent variable. In our dataset this looks something like the following 2x2 table where the status of having experienced a central nervous system injury limited to small focal injury directly beneath a skull fracture (CNS Injury) is the rows and the status of spinal subdural hemorrhage is on the columns. Observe that we have observations in each cell except in the case where an observation has both the central nervous system injury and has spinal subdural hemorrhage:

CNS Injury	**Spinal subdural hemorrhage(s)**	
	No (n=307)	Yes (n=33)
No (n=280)	280	33
Yes (n=27)	27	0

Table 2.2. Example of quasi-complete separation in CAPNET data

Having separation in our data is not a surprise as the variables we are working with are often rare events in a very specific population of children. The data separation results in convergence issues such that one or more estimated coefficients might tend towards infinity (positive or negative) meaning predicted probabilities are either 1 or 0 since the data with separation fits too well (Clark, Blanchard, Hui, Tian, & Woods (2023), Allison (2008)). Consider the following figure from Allison (2008) which shows the log-likelihood as a function of beta under complete separation. We want to maximize the log-likelihood which is at 0 but in order to get as close as possible, it requires beta to go towards infinity.

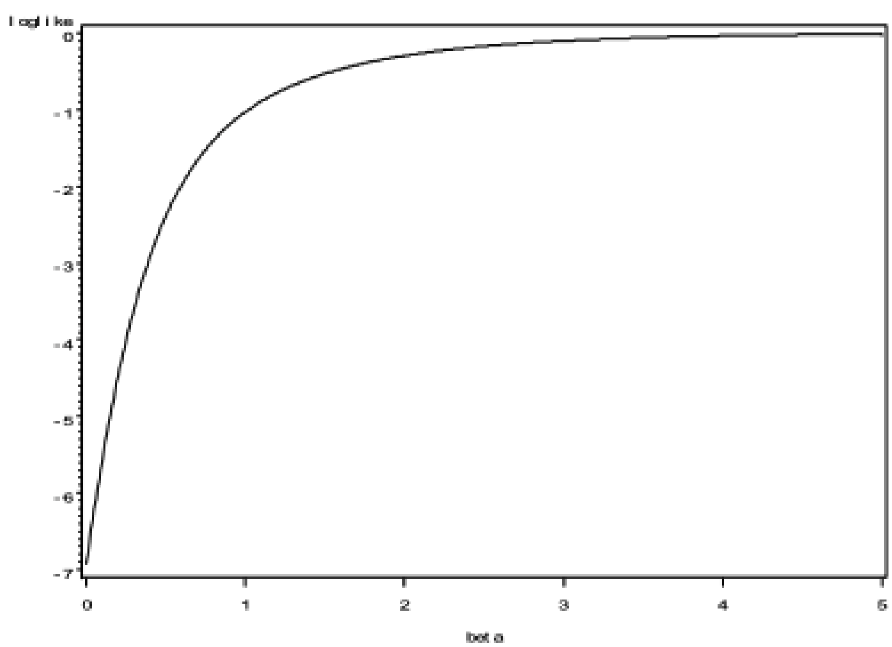

Figure 2.3. Log-likelihood as a function of the slope under complete separation

There are a variety of ways statisticians have approached this issue of separation.

One possible approach that Heinze & Schemper (2002) mentions is omitting the variables that cause the separation but they also raise concerns that omission of this "usually strong and therefore important risk factor" provides no information and does not allow adjusting effects of other risk factors for the effect of this variable. The approach we will consider is through penalization of the models we explored above.

2.4.7 Penalized Generalized Estimating Equations

A paper published recently proposed a penalized GEE by including a "Firth-type" penalty term to address bias and separation in small or sparse longitudinal binary data (Mondol & Rahman (2019)). Geroldinger, Blagus, Ogden, & Heinze (2022) demonstrated this penalized GEE substantially improved convergence compared to ordinary GEE, while showing a similar or even better performance in terms of accuracy of coefficient estimates and predictions. The Firth penalty was originally used in logistic regression models which implements a penalized maximum likelihood estimation, originally with the aim of reducing bias in logistic regression with small samples (Firth (1993)). It can be shown that this method by Firth always yields finite estimates under complete or quasi-complete separation (Heinze & Schemper (2002)).

Firth essentially proposes the following penalized likelihood given:

$$L(\beta)^* = L(\beta) \cdot |I(\beta)|^{\frac{1}{2}}$$

where $I(\beta)$ is the information matrix evaluated at β. Firth (1993) demonstrated the asymptotic consistency of this penalized likelihood and demonstrated that the $O(n^{-1})$ bias of the maximum likelihood estimates $\hat{\beta}$ is removed. Using this penalized likelihood, we can then derive the log-likelihood and obtain the following penalized score equations.

$$U(\beta_k)^* = U(\beta_k) + \frac{1}{2}\text{trace}[I(\beta)^{-1}\frac{\partial I(\beta)}{\partial \beta_k}]$$

where

$$U(\beta_k) = \frac{\partial \ell(\beta_k)}{\partial \beta_k} = 0$$

is the score equation for β_k. This approach ultimately has the effect of reducing bias as well as shrinking or "penalizing" coefficients such that the coefficient estimates and standard errors are usable and interpretable.

We chose to use this method in particular not only because its novelty will allow us to learn something new but there is an available R package that we can conveniently use (Mondol & Rahman (2019)). To briefly outline their methodology, they state that "the GEE is considered to be an extension of likelihood score equation for correlated response" and so they treat the GEE as if it were a likelihood score equation. Then, they add a Firth-type penalty to the following equation for the r-th regression coefficient:

$$U_r^*(\beta, \alpha) = U(\beta, \alpha) + A_r^*(\beta, \alpha) = \sum_{i=1}^{n} D_i' V_i^{-1}(y_i - \mu_i) + \frac{1}{2}\text{trace}[I(\beta, \alpha)^{-1}\frac{\partial I(\beta, \alpha)}{\partial \beta_k}] = \mathbf{0}$$

and this can be solved in the typical ways using iterative approaches. In this paper, they also consider a small-sample bias correction to the variance estimator using the proposed method by Morel, Bokossa, & Neerchal (2003) which not only reduces bias, but reduces type I error rate and also guarantees positive definiteness of the estimated variance covariance matrix. To run this penalized GEE, we will be using the `GEEfirth` R package (Mondol & Rahman (2019)).

We will also further assess the robustness of our results by using different covariance assumptions and comparing the sets of estimates. Due to limitations within the `GEEfirth` package, we will consider two different covariance assumptions: independence and exchangeable. These two characterize the correlation within the cluster in different ways. For the independence covariance matrix, the covariance matrix will have some homoskedastic variance σ^2 on the diagonal and 0s on the off-diagonals. For the exchangeable matrix, we have some homoskedastic variance σ^2 and the same correlation ρ on the off-diagonals. Note that the choice of covariance structure usually requires some thought on choosing the appropriate one. One might choose an independent covariance structure if they assume none of the responses are correlated or choose an exchangeable covariance when the responses from the same cluster are equally correlated, regardless of distance between the responses. One could also use the quasi-information criterion from Pan (2001) to select the best covariance, however, the package we are using has not implemented QIC measures so we show both structures to compare.

2.4.8 Penalized Multilevel Logistic Regression

We also consider penalized multilevel logistic regression to address issues of separation. We adopt the approach used by Clark et al. (2023) in which they consider a ridge penalty that penalizes based on the sum of the squared magnitudes of the coefficients as well as according to some tuning parameter (Hoerl & Kennard (1970)).

Ridge regression was first proposed by Hoerl & Kennard (1970) in their paper, "Ridge Regression: Biased Estimation for Nonorthogonal Problems". This method is similar to ordinary least squares, but a shrinkage penalty is added on when estimating the coefficients as defined below.

$$\text{Residual Sum of Squares} + \lambda \sum_{j=1}^{p} \beta_j^2 = \sum_{i=1}^{n} (y_i - \beta_0 - \sum_{j=1}^{p} \beta_i x_{ij})^2 + \lambda \sum_{j=1}^{p} \beta_j^2$$

where $\lambda \geq 0$ is called the *tuning parameter* that is not determined automatically.

From the above equation, we can see that we still want to make the residual sum of squares as small, similar to ordinary least squares, but now we also must consider the shrinkage penalty which has the effect of making $\hat{\beta}_1, \hat{\beta}_2, \ldots, \hat{\beta}_p$ shrink towards zero. This shrinkage penalty is based on the ℓ_2 norm of the coefficients ($||\beta||_2 = \sqrt{\sum \beta_j^2}$) which is the distance between the estimates from 0. The tuning parameter, λ, then tunes the relative influence of these two terms on the estimates. As $\lambda \to \infty$, the coefficients approach zero and when $\lambda = 0$, we are simply minimizing the residual sum of squares. This idea can then be extended to the logistic regression case, see Cessie & Houwelingen (1992).

We employ Clark et al. (2023)'s approach because currently there are no R packages that have implemented the Firth penalty in multi-level logistic regression. On the other hand, there is code to apply the ridge penalty in multilevel logistic regression since it can be viewed in the Bayesian sense (Clark et al. (2023)). It is equivalent to assuming a weakly informative prior on the fixed effects, where the choice of prior corresponds to a particular penalty function. For ridge penalty, it is equivalent to assuming independent normal prior distributions for the coefficients with variance set to the inverse of the tuning parameter as shown by Goldstein (1976).

There are several strategies for choosing the variance in the normal prior. Lemoine (2019) provides a guide to weakly informative priors where one way is to use domain expert knowledge by surveying the literature and experts to get a prior distribution. We consider the two-step approach used in Adenuga et al. (2018) in which they first apply Firth's penalized logistic regression without consideration of the clustered nature of the data to inform the priors to be used in the second step. In the second step, variance of the normal priors were chosen to be twice the variance of the largest parameter estimate. To test the sensitivity, we will in addition consider normal priors with mean 0 and 4 variances: 1, 4, 9, 16. The smaller the variance, the more we think the parameter estimates lie within a smaller range or in other words, a stronger degree of penalization. Note that these priors are acting on the log scale so for a parameter to have a normal distribution with variance 4, plus or minus 2 standard deviations away is (-4, 4) which is quite large on the logit scale which equals (exp(-4), exp(4)) = (0.018, 54.59) on the odds scale. By treating more extreme values as unlikely, a weakly informative prior helps with locating effect estimates in the model of interest and may help with convergence when (quasi)-complete separation occurs (Kimball, Shantz, Eager, & Roy (2018)). We can use the R package `blme` to fit this penalized multi-level logistic regression (Chung, Rabe-Hesketh, Dorie, Gelman, & Liu (2013)).

As a brief aside, Gelman, Jakulin, Pittau, & Su (2008) provides more insight into using other weakly informative priors in logistic regression such as t-distributions or Cauchy distributions. They recommend using a t-distribution with either 1 or 7 degrees of freedom and a scale parameter of 2.5 with the argument being the scale of 2.5 is large enough to allow the largest odds ratios likely to occur in most applications yet small enough to penalize large coefficient values, avoiding infinite parameter estimates. However, due to time constraints as well as simplicity, we will only explore using a Normal prior while keeping in mind that a Bayesian approach brings about a lot of flexibility and nuances in model creation.

Chapter 3

Results

3.1 Descriptive Statistics

3.1.1 Spinal imaging

	Overall (N=887)	No advanced spine imaging (N=500)	Spine CT/MRI (N=387)	P-value
Age, N (%)				0.4
< 6 months	604 (100%)	329 (54.5%)	275 (45.5%)	
6-12 months	193 (100%)	113 (58.5%)	80 (41.5%)	
> 12 months	61 (100%)	30 (49.2%)	31 (50.8%)	
History of trauma, N (%)				
Accidental	481 (100%)	303 (63%)	178 (37%)	<.001
Inflicted / Abusive	18 (100%)	7 (38.9%)	11 (61.1%)	0.2
None	389 (100%)	190 (48.8%)	199 (51.2%)	<.001
Level of concern for abuse, N (%)				<.001
High concern	279 (100%)	66 (23.7%)	213 (76.3%)	
Moderate concern	247 (100%)	129 (52.2%)	118 (47.8%)	
No / low concern	361 (100%)	305 (84.5%)	56 (15.5%)	
Intracranial Subdural Hemorrhage(s), N (%)	529 (100%)	229 (43.3%)	300 (56.7%)	<.001
Number of Retinal Hemorrhage(s) (Right Eye), N (%)				<.001
No exam performed	275 (100%)	230 (83.6%)	45 (16.4%)	
None	419 (100%)	228 (54.4%)	191 (45.6%)	
1-5	32 (100%)	8 (25%)	24 (75%)	
6-20	31 (100%)	5 (16.1%)	26 (83.9%)	
>20, too numerous to count	129 (100%)	28 (21.7%)	101 (78.3%)	
Number of Retinal Hemorrhage(s) (Left Eye), N (%)				<.001
No exam performed	275 (100%)	230 (83.6%)	45 (16.4%)	
None	417 (100%)	226 (54.2%)	191 (45.8%)	
1-5	29 (100%)	10 (34.5%)	19 (65.5%)	
6-20	33 (100%)	6 (18.2%)	27 (81.8%)	
>20, too numerous to count	131 (100%)	27 (20.6%)	104 (79.4%)	
Median Number of Rib Fracture(s) [IQR]	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	<.001
Classic Metaphyseal Lesion(s), N (%)	42 (100%)	11 (26.2%)	31 (73.8%)	<.001
Glascow Coma Score, N (%)				<.001
No GCS obtained	296 (100%)	193 (65.2%)	103 (34.8%)	
≤ 8 or Intubated	105 (100%)	30 (28.6%)	75 (71.4%)	
9-12	4 (100%)	0 (0%)	4 (100%)	
13-15	437 (100%)	263 (60.2%)	174 (39.8%)	
Endotrachial Intubation, N (%)	172 (100%)	51 (29.7%)	121 (70.3%)	<.001
Highest level of care, N (%)				<.001
Outpatient or Emergency Department Only	78 (100%)	71 (91%)	7 (9%)	
Inpatient Admission or Observation	388 (100%)	257 (66.2%)	131 (33.8%)	
ICU/PICU/NICU/Step down	421 (100%)	172 (40.9%)	249 (59.1%)	
Median Hospital Length of Stay (days) [IQR]	3.0 [6.0]	1.0 [2.0]	5.0 [10.0]	<.001
Median ICU Length of Stay (days) [IQR]	0.0 [2.0]	0.0 [1.0]	1.0 [6.0]	<.001

Table 3.1. Rates of Spinal Imaging by Clinical Characteristics.

In the total study population (n = 887), 387 (44%) received some form of spinal imaging with a median age of 4 months (age ranges from 0 to 24 months.) A majority of the study population was less than 6 months old (68%) and there is no indication of significant differences in spinal imaging status across age groups. In the high concern of abusive head trauma group (n = 279), the majority had imaging done (76.3%). In the moderate concern of abusive head trauma, it was more balanced with 52% having had no imaging and 48% having had imaging performed. In the no / low concern of abusive head trauma, we had 84.5% having no advanced spine imaging performed. In the >20 / too numerous to count groups for both eyes, we see a majority had spine imaging performed (roughly 80% each). The median number of rib fractures was 0 in both groups. 42 cases had atleast one classic metaphyseal lesion. 31 of those had imaging performed while 11 (26.2%) did not have spine imaging. Glascow Coma Scores were obtained for 591 cases with the majority being in the 13-15 range (n=437). For those with a GCS of 8 or lower or were intubated, 75 (71.4%) had spine imaging done. We had 172 cases that required endotrachial intubation and 121 (70.3%) had spine imaging done. All univariate analyses suggests significant differences in spine imaging status except for the History of Inflicted / Abusive Trauma. Overall, these results suggest different clinical characteristics for those who had spinal imaging performed versus those with advanced spine imaging with those that have done spine imaging having more severe clinical characteristics.

3.1.2 Summary of spinal injur(ies) based on spinal imaging data

	Spine Injury(ies): Epidural Hemorrhage (EDH) (N=10)	Spine Injury(ies): Subdural Hemorrhage (SDH) (N=43)	Spine Injury(ies): Subarachnoid Hemorrhage (SAH) (N=3)	Spine Injury(ies): Ligamentous Injury (N=32)	Spine Injury(ies): Spinal Cord Injury (N=5)
History of trauma, N(%)					
Accidental	5 (50%)	15 (34.9%)	1 (33.3%)	10 (31.2%)	3 (60%)
Inflicted / Abusive	0 (0%)	0 (0%)	0 (0%)	2 (6.2%)	0 (0%)
None	5 (50%)	28 (65.1%)	2 (66.7%)	20 (62.5%)	2 (40%)
Level of concern for abuse, N(%)					
High concern	**9 (90%)**	**34 (79.1%)**	3 (100%)	**29 (90.6%)**	5 (100%)
Moderate concern	**0 (0%)**	**7 (16.3%)**	0 (0%)	**3 (9.4%)**	0 (0%)
No / low concern	**1 (10%)**	**2 (4.7%)**	0 (0%)	**0 (0%)**	0 (0%)

Table 3.2. Spine Injuries by History of Trauma and Level of Concern for Abuse. Bolded values indicate significance.

In the accidental history of trauma, we see that 5 experienced a spinal epidural hemorrhage, 15 had a spinal subdural hemorrhage, 1 had a subarachnoid hemorrhage, 10 had a ligamentous injury, and 3 had a spinal cord injury. Only spinal subdural hemorrhage was significantly associated with an accidental history of trauma. In the inflicted / abusive group, only two had suffered ligamentous injuries. In the no history of trauma group, 5 experienced a spinal epidural hemorrhage, 28 had a spinal subdural hemorrhage, 2 had a subarachnoid hemorrhage, 20 had a ligamentous injury, and 2 had a spinal cord injury.

According to levels of concern of abusive head trauma, the high concern subset had 34 cases with spinal subdural hemorrhage and 29 cases of ligamentous injury. In the moderate concern group, 7 had spinal subdural hemorrhage and 3 had ligamentous injury with no other spinal injuries. In the no to low concern group, we see 1 had a spinal epidural hemorrhage and 2 suffered from a spinal subdural hemorrhage. It is important to note here that spine injuries would have been missed if spine imaging was not performed and that spine image findings can provide us additional evidence of trauma in instances when other diagnostic tools are insufficient such as nonspecific intracranial findings (Rabbitt et al. (2020)). Fisher exact tests also suggests an association between level of concern for abuse and each spinal injury type respectively.

3.1.3 Clinical characteristics associated with spine injury among children with spine MRI

	Overall (N = 387)	No Spinal Subdural Hemorrhage (N=344)	Spinal Subdural Hemorrhage (N=43)	P-value
Age, N(%)				1
< 6 months	275 (71.1%)	244 (70.9%)	31 (72.1%)	
6-12 months	80 (20.7%)	71 (20.6%)	9 (20.9%)	
> 12 months	31 (8%)	28 (8.1%)	3 (7%)	
Reported mechanism of inflicted trauma, N(%)				
Shaking	10 (2.6%)	8 (2.3%)	2 (4.7%)	0.3
Hit/kick/strike	5 (1.3%)	5 (1.5%)	0 (0%)	1
Choking/strangulation	0	0	0	
Reported mechanism of accidental trauma, N(%)				
Fall	168 (43.4%)	156 (45.3%)	12 (27.9%)	0.03
Hit with object	6 (1.6%)	6 (1.7%)	0 (0%)	1
Collision with an object	10 (2.6%)	8 (2.3%)	2 (4.7%)	0.3
Number of Retinal Hemorrhage(s) (Right Eye) , N(%)				<.001
No exam performed	45 (11.6%)	45 (13.1%)	0 (0%)	
None	191 (49.4%)	177 (51.5%)	14 (32.6%)	
1-5	24 (6.2%)	24 (7%)	0 (0%)	
6-20	26 (6.7%)	19 (5.5%)	7 (16.3%)	
>20, too numerous to count	101 (26.1%)	79 (23%)	22 (51.2%)	
Number of Retinal Hemorrhage(s) (Left Eye) , N(%)				<.001
No exam performed	45 (11.6%)	45 (13.1%)	0 (0%)	
None	191 (49.4%)	178 (51.7%)	13 (30.2%)	
1-5	19 (4.9%)	16 (4.7%)	3 (7%)	
6-20	27 (7%)	22 (6.4%)	5 (11.6%)	
>20, too numerous to count	104 (26.9%)	82 (23.8%)	22 (51.2%)	
Median Number of Rib Fracture(s) [IQR]	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	0.5
Classic Metaphyseal Lesion(s) , N(%)	31 (8%)	25 (7.3%)	6 (14%)	0.1
Spine ligamentous injury, N(%)	32 (8.3%)	24 (7%)	8 (18.6%)	0.02
Intracranial Subdural Hemorrhages, N(%)	300 (77.5%)	258 (75%)	42 (97.7%)	<.001
CNS Injury limited to small focal injury directly beneath a skull, N(%)	33 (8.5%)	33 (9.6%)	0 (0%)	0.04
Glascow Coma Score, N(%)				0.09
No GCS obtained	105 (27.1%)	99 (28.8%)	6 (14%)	
≤ 8 or Intubated	74 (19.1%)	61 (17.7%)	13 (30.2%)	
9-12	19 (4.9%)	17 (4.9%)	2 (4.7%)	
13-15	189 (48.8%)	167 (48.5%)	22 (51.2%)	
Endotrachial Intubation, N(%)	121 (31.3%)	95 (27.6%)	26 (60.5%)	<.001
Highest level of care, N(%)				0.006
Outpatient or Emergency Department Only	7 (1.8%)	7 (2%)	0 (0%)	
Inpatient Admission or Observation	131 (33.9%)	125 (36.3%)	6 (14%)	
ICU/PICU/NICU/Step down	249 (64.3%)	212 (61.6%)	37 (86%)	
Median Hospital Length of Stay (days) [IQR]	5.0 [10.0]	5.0 [8.2]	18.0 [24.0]	<.001
Median ICU Length of Stay (days) [IQR]	1.0 [6.0]	1.0 [5.0]	6.0 [10.5]	<.001
Perpetrator Confessions, N(%)				0.07
No	43 (11.1%)	41 (11.9%)	2 (4.7%)	
Yes	4 (1%)	4 (1.2%)	0 (0%)	
Unknown	6 (1.6%)	4 (1.2%)	2 (4.7%)	

Table 3.3. Clinical Characteristics According to Spinal Subdural Hemorrhage Status

From Table 3.3, we can see differences in the clinical characteristics for those with spinal subdural hemorrhage and those without. For children who have a spinal subdural hemorrhage, 42/43 (97.7%) had an intracranial subdural hemorrhage. In roughly

50% of cases also had greater than 20 retinal hemorrhages in either eye or were too numerous to count compared to approximately 23% in those without spinal subdural hemorrhages. The median length of stay was also different in the two groups, with 5 being the median for those without the outcome and 18 for those with the outcome. The number of right and left retinal hemorrhages were both respectively associated with spinal subdural hemorrhage status. As well as endotrachial intubation status and hospital and ICU length of stay (days). Overall, these results suggest patients who experience a spinal subdural hemorrhage tend to also display more severe clinical characteristics.

3.2 Model Results

The clinical factors or covariates that are considered relevant in assessing the relationship with spinal subdural hemorrhage are as follows:

- Intracranial subdural hemorrhages
- Classic Metaphyseal Lesions
- CNS Injury
- Glascow Coma Score
- Endotrachial Intubation
- Number of rib fractures
- Number of right retinal hemorrhages
- Spine ligamentous injury
- Age (months)
- History of accidental /inflicted / abusive trauma
- Reported mechanism of inflicted trauma: Shaking / Hit/kick/strike
- Reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object

- Highest level of care
- Hospital Length of Stay

Note: we dropped some variables from our modeling approach due to concerns of collinearity. For example, we have two variables for retinal hemorrhages in the right and left eye. Cross tabulations showed most observations lied on the diagonal which suggested that if a child had a certain number of retinal hemorrhages in one eye, they also had a similar severity in the other eye. So we decided to only incorporate the number of retinal hemorrhages in the right eye. Similarly, the correlation between hospital length of stay and ICU length of stay was quite high at 0.76 so we chose to only use hospital length of stay. A few variables, Perpetrator of confession and Choking / Strangulation, that are potentially relevant were excluded due to the incomplete or large amount of missing data.

3.2.1 Generalized Estimating Equations Results

We fitted three GEE models, one unpenalized and two using a Firth type penalization. We used the `geepack` package in R (Halekoh, Højsgaard, & Yan (2006)) to fit the unpenalized model with results being shown in Appendix A2. In the unpenalized model, we considered an exchangeable covariance structure and we obtained parameter estimates near the boundaries for odds (0 to $+\infty$), leading to uninterpretable results. On the other hand, with the penalized GEEs (exchangeable and independent covariance structure) displayed in Table 3.4 with Odds Ratios and 95% confidence intervals, we see the effect of the Firth penalization in attenuating the odds closer to 1 as well as providing sensible confidence intervals. The GEE model with an exchangeable covariance structure had identified having an intracranial subdural hemorrhage, having 6-20 right retinal hemorrhages, and hospital length of stay as significant variables. Patients with an intracranial subdural hemorrhage have 6.4 times the odds of spinal subdural hemorrhage versus a patient without an intracranial subdural hemorrhage after adjusting for other covariates. Patients with 6-20 right retinal hemorrhages have 2.8 times the odds of spinal subdural hemorrhage versus a patient with no right retinal hemorrhages and for each additional day spent in the hospital, the odds of a spinal subdural hemorrhage were 1.033 times higher.

The independent model had identified having an intracranial subdural hemorrhage and hospital length of stay as significant covariates. This model estimated that patients with an intracranial subdural hemorrhage have 6.9 times the odds of spinal subdural hemorrhage versus a patient without an intracranial subdural hemorrhage after adjusting for other covariates. For each additional day spent in the hospital, the odds of a spinal subdural hemorrhage were 1.036 times higher. The magnitude and direction of the odds ratios were comparable in both models. We omitted looking at an AR-1 covariance structure since our data is not longitudinal so it did not make sense to try to account for time in the covariance structure. It appears that the results are not extremely sensitive to choice of covariance structure as the coefficient estimates and 95% confidence intervals are roughly similar with the width of standard errors in the independent covariance structure being often wider. It would be useful to explore more structures if possible, but one good thing about GEEs is that inference is consistent even when we have misspecified the correlation structure.

	Penalized GEE (Exchangeable) OR (95% CI)	Penalized GEE (Independent) OR (95% CI)
Intracranial Subdural Hemorrhage vs no intracranial subdural hemorrhage (ref)	6.4 (1.9, 21.9) *	6.9 (2.1, 22.3) *
At least one classical metaphyseal lesion(s) vs no classical metaphyseal lesion(s) (ref)	2.1 (0.7, 7)	2.1 (0.6, 7.6)
CNS Injury limited to small focal injury directly beneath a skull vs no CNS Injury limited to small focal injury directly beneath a skull (ref)	0.3 (0, 8.2)	0.3 (0, 14.3)
Glascow Coma Score 9-12 vs Glascow Coma Score <= 8 or Intubated (ref)	0.7 (0.2, 2.4)	0.8 (0.2, 3.4)
Glascow Coma Score 13-15 vs Glascow Coma Score <= 8 or Intubated (ref)	2.2 (0.9, 5.2)	2.3 (0.8, 6.5)
No Glascow Coma Score obtained vs Glascow Coma Score <= 8 or Intubated (ref)	1.1 (0.4, 3.4)	1 (0.3, 2.9)
Endotrachial Intubation vs no endotrachial intubation (ref)	2.2 (0.9, 5.2)	2.2 (1, 5)
Number of rib fracture(s)	1 (0.9, 1.1)	1 (0.9, 1.1)
1-5 right retinal hemorrhages vs No right retinal hemorrhages (ref)	0.1 (0, 4.4)	0.1 (0, 6)
6-20 right retinal hemorrhages vs No right retinal hemorrhages (ref)	2.8 (1, 7.5) *	2.4 (0.7, 7.6)
>=20 or too numerous to count right retinal hemorrhages vs No right retinal hemorrhages (ref)	1.6 (0.9, 2.8)	1.6 (0.8, 3.1)
No exam performed vs No right retinal hemorrhages (ref)	0.4 (0, 5.1)	0.2 (0, 9.1)
Age (months)	1 (0.9, 1.1)	1 (0.9, 1.1)
History of Inflicted or Accidental trauma vs No history of Inflicted or Accidental trauma (ref)	0.7 (0.4, 1.3)	0.7 (0.4, 1.3)
Reported mechanism of inflicted trauma: Shaking or Hit/kick/strike vs No reported mechanism of inflicted trauma: Shaking or Hit/kick/strike (ref)	1.2 (0.3, 4.5)	1.1 (0.2, 5.1)
Reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object vs No reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object (ref)	1.1 (0.5, 2.4)	1.1 (0.5, 2.5)
Spine ligamentous injury vs no spine ligamentous injury (ref)	1.4 (0.5, 3.9)	1.4 (0.5, 4.4)
Highest level of care: Outpatient or Emergency Department Only vs ICU/PICU/NICU/Step down (ref)	2.4 (0.1, 95.5)	2.1 (0, 184.9)
Highest level of care: Inpatient Admission or Observation vs ICU/PICU/NICU/Step down (ref)	0.8 (0.4, 1.9)	0.8 (0.4, 1.6)
Hospital Length of Stay (days)	1 (1, 1.1) *	1 (1, 1.1) *

Table 3.4. Penalized GEE models assessing the relationship of sSDH status with clinical factors. * indicate statistical significance.

3.2.2 Multilevel Logistic Regression Results

We first started with the standard multilevel logistic model fitted using `glmer` from the `lme4` package (Bates et al. (2015)). Because there is generally no closed form to calculate the likelihood function of a mixed effects model, an optimizer is used to approximate the solution. When trying to fit the model, the default optimizer "bobyqa" failed to converge due to the separation exhibited in the data. While we were still able to get parameter estimates (see Appendix A3), these numbers should not be trusted due to the separation of our data and lack of convergence in our model. For example, the category level "1-5 right retinal hemorrhages" has an extremely large upper confidence interval that's written as `Inf` as R was unable to computationally handle that number. And as it so happens, this category exhibited separation (see Table 3.3). We then also considered alternative optimizers to see if it was potentially an optimizer issue so we considered L-BFGS-B and Nelder Mead, two other often used optimizers in these problems. They also failed to converge, indicating the potential issues that can arise when separation exists in the data.

We then used the two-step approach as outlined previously and placed Normal priors on the fixed effects with mean 0 and variance of 4.34, leading to a weakly informative prior. These results are displayed in Table 3.5. As we can see, the estimates for the Odds ratios and their 95% confidence intervals have been penalized by the prior we placed on the fixed effects. If we look at the category level "1-5 right retinal hemorrhages", its confidence interval ranges from 0.1 to 1.5. In this model, we had only one significant covariate which was intracranial subdural hemorrhage status. It is also important to remember that the interpretation of coefficients in a multilevel logistic model no longer have a marginal interpretation, but rather conditional with respect to the clustering. Fitzmaurice et al. (2011) explains "the fixed effects parameters in a two-level model for discrete data represent changes in the (transformed) mean response, for a single-unit change in the corresponding covariate, for any given level 2 unit" where in our case, the level 2 unit is the hospital site. So for example, those that experience an intracranial subdural hemorrhage have 4 times the odds of spinal SDH versus patients without after adjusting for other covariates and hospital effect. Lastly, we computed the intraclass correlation coefficient to be 0.11 which suggests the within-cluster variation is greater than the between-cluster variation.

Appendix A4 shows the results of considering other weakly informative priors with variances of 1,4, 9, 16 respectively. A variance of 1 is the most informative and 16 is the least informative. Here, we can see that the estimates are generally in agreement in magnitude and direction. The effect of the weakly informative prior also demonstrates itself in the width of the confidence intervals. In the model with variance 1, the confidence intervals are tighter since we placed our initial belief that the beta estimates following a tighter normal distribution. On the other hand, the one with variance 16 has larger widths, reflecting the belief that our parameters follow a normal with a larger standard deviation. The three models suggested intracranial subdural hemorrhage was significant while the first model had a confidence interval ranging from 0.8 to 5.1. These results suggest the choice of the weakly informative prior is not too sensitive as long as the prior is weakly informative. What weakly informative means is a highly debatable topic that can be its own thesis topic. We refer the interested read to Gelman et al. (2008) who provides general guidelines to choosing weakly informative priors. The results demonstrates that they are not entirely robust to changes in the tuning parameter so there needs to be careful consideration when it comes to fitting these types of models.

	GLMM (Var = 4.34) OR (95% CI))
Intracranial Subdural Hemorrhage vs no intracranial subdural hemorrhage (ref)	4.0 (1.0, 15.5) *
At least one classical metaphyseal lesion(s) vs no classical metaphyseal lesion(s) (ref)	1.9 (0.6, 6.1)
CNS Injury limited to small focal injury directly beneath a skull vs no CNS Injury limited to small focal injury directly beneath a skull (ref)	0.3 (0.0, 4.0)
Glascow Coma Score 9-12 vs Glascow Coma Score <= 8 or Intubated (ref)	0.6 (0.1, 3.1)
Glascow Coma Score 13-15 vs Glascow Coma Score <= 8 or Intubated (ref)	1.7 (0.6, 4.6)
No Glascow Coma Score obtained vs Glascow Coma Score <= 8 or Intubated (ref)	0.8 (0.2, 2.9)
Endotrachial Intubation vs no endotrachial intubation (ref)	1.8 (0.6, 5.3)
Number of rib fracture(s)	1.0 (0.9, 1.1)
1-5 right retinal hemorrhages vs No right retinal hemorrhages (ref)	0.1 (0.0, 1.5)
6-20 right retinal hemorrhages vs No right retinal hemorrhages (ref)	3.2 (0.9, 11.0)
>=20 or too numerous to count right retinal hemorrhages vs No right retinal hemorrhages (ref)	1.7 (0.8, 3.8)
No exam performed vs No right retinal hemorrhages (ref)	0.2 (0.0, 3.2)
Age (months)	1.0 (0.9, 1.1)
History of Inflicted or Accidental trauma vs No history of Inflicted or Accidental trauma (ref)	0.7 (0.3, 1.7)
Reported mechanism of inflicted trauma: Shaking or Hit/kick/strike vs No reported mechanism of inflicted trauma: Shaking or Hit/kick/strike (ref)	1.1 (0.2, 5.3)
Reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object vs No reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object (ref)	1.0 (0.4, 2.6)
Spine ligamentous injury vs no spine ligamentous injury (ref)	1.3 (0.5, 3.6)
Highest level of care: Outpatient or Emergency Department Only vs ICU/PICU/NICU/Step down (ref)	0.7 (0.0, 22.7)
Highest level of care: Inpatient Admission or Observation vs ICU/PICU/NICU/Step down (ref)	0.7 (0.2, 2.1)
Hospital Length of Stay (days)	1.0 (1.0, 1.1)

Table 3.5. Penalized GLMM assessing the relationship of sSDH status with clinical factors. * indicate statistical significance.

Conclusion

3.3 Discussion

Complications can arise when complete or quasi-complete separation occurs and leads to extremely large or small coefficient estimates, making it more difficult to perform statistical inference. In this thesis, we evaluated various approaches to handling separation in multilevel models and GEE models that accounted for clustering. We demonstrated how penalized approaches can be used to address this issue of complete or quasi-complete separation. There have also been several other approaches suggested to address this issue such as dropping the variables that cause the separation, collapsing predictor categories, or conducting exact inference using exact logistic regression as it is important to recognize that penalization is not the only way to tackle this issue (Allison (2008)).

Although the two models we considered accounted for clustering, they have different interpretations when it comes to the regression coefficients which is important to consider when trying to address our study objectives. For a multilevel logistic model, the interpretation is on the cluster level while in the GEE model, it is at the population level. Given that we are primarily interested in the regression coefficients themselves and not necessarily the individual effects, the use of the penalized GEE model seems to make reasonable sense. In addition, our penalized GEE model results show promising results in dealing with separation in clustered data that echo results of previous papers that implemented this method (Mondol & Rahman (2019), Geroldinger et al. (2022), Mussner (2022)). Due to the promising benefits of this, it would be beneficial to continue researching into this method. Moreover, the fact that in the penalized GLMM model, we had to choose a prior might be of concern if we fail to wisely and strategically choose our priors. As we saw, the choice of prior has the potential to alter our results.

Overall, the penalized GLMM and GEE models seemed to agree on the association between having an intracranial subdural hemorrhage and a spinal subdural hemorrhage. This supports the theory that spinal subdural hemorrhage is attributed to the tracking of intracranial blood (Rabbitt et al. (2020), Kemp, Cowley, & Maguire (2014), Arabinda K. Choudhary et al. (2014)), however this is still an ongoing debate. Another theory is based on injury to the vessels around the spinal cord and there has been no resounding evidence for a sole mechanism of spinal subdural hemorrhages (Rabbitt et al. (2020),Kim & Sim (2015)). However, since our results demonstrate an association between having an intracranial subdural hemorrhage and spinal subdural hemorrhage and previous literature have suggested intracranial subdural hemorrhages are associated with abusive head trauma (Arabinda Kumar Choudhary et al. (2012)), it can better assist clinicians in discerning when to perform spinal imaging when dealing with suspected abusive head trauma cases.

3.4 Limitations

There are some limitations to our data that prevent us from making more granular conclusions. In spine imaging, there is no distinction between whole-spine versus cervical spine MRI and the data are unable to determine the location of the spinal subdural hemorrhage. Moreover, the diagnosis of abusive head trauma is done after collection of the other variables meaning we could not include it in our models as a covariate and needed to use other variables such as intracranial subdural hemorrhage and retinal hemorrhages as proxy variables. And while multi-center research yields numerous benefits, variability exists between institutions and among providers at the same institution, particularly with regards to who is referred for a child abuse evaluation and what that child abuse evaluation entails. However, the CAPNet database is a relatively new endeavor at standardizing the way we collect data on child abuse, enabling clinicians and researchers alike to better study this unique and vulnerable population. Moreover, the number of clusters (hospital sites) is small at n = 11 which can lead to invalid estimates and inferences for GEE and multilevel models (Bell, Morgan, Kromrey, & Ferron (2010)).

3.5 Future Work

In this paper we only considered the ridge penalty for the mixed effects model but it would be interesting to consider a Lasso penalty which has been implemented in the `glmmLASSO` package (Groll & Tutz (2012)) which performs variable selection, but since the aim of the thesis was inference rather than prediction, variable selection was not a priority for us. We also only considered a weakly informative prior for the fixed effects but one could even take a further Bayesian approach by placing priors on the random effects and performing Bayesian inference (Chung et al. (2013), Kimball et al. (2018), Abrahantes & Aerts (2012)). There have also been several modifications to the GEE such as another penalized GEE that performs variable selection by Inan & Wang (2017) that would be interesting to explore. Simulation studies and a deeper dive into the impact of small-sample settings would also prove to be a worthwhile endeavor. There is no one size fits all / unified framework for dealing with (quasi)-complete separation in clustered data, but it is our hope that this thesis can shed light onto some ways we can tackle this issue.

Appendix A

In Chapter 2:

Variable	Description
Age	Age in months
Spine imaging	Child had either CT/MRI of spine performed
Spine Injuries	
Spine subdural hemorrhage(s)	Child has spine subdural hemorrhage(s) (Yes/No)
Spine epidural hemorrhage(s)	Child has intracranial subdural hemorrhage (Yes/No)
Spine subarachnoid hemorrhage(s)	Child has spine subarachnoid hemorrhage(s) (Yes/No)
Spine ligamentous injury	Child has spine ligamentous injury (Yes/No)
Spine cord injury	Child has spine cord injury (Yes/No)
Level of concern for abuse	1-7 Likert scale ranging from: 1. Definitely not abuse 2. No concern for abuse 3. Mildly concerning for abuse 4. Intermediately concerning for abuse 5. Very concerning for abuse 6. Substantial evidence of abuse 7. Definite abuse Grouped into: (1-2): No / low concern of abuse (3-5): Intermediate concern of abuse (6-7): High concern of abuse
History of accidental trauma	Child presented with a history of accidental trauma (Yes/No)
History of inflicted/abusive trauma	Child presented with a history of inflicted/abusive trauma (Yes/No)
No history of trauma	Child presented with no history of trauma (Yes/No)
Reported mechanism of inflicted trauma	
Shaking	Reported Mechanism(s) of Inflicted Trauma: Shaking (Yes/No)
Hit/kick/strike	Reported Mechanism(s) of Inflicted Trauma: Hit/Kick/Strike (Yes/No)
Choking/Strangulation	Reported Mechanism(s) of Inflicted Trauma: Choking/Strangulation (Yes/No)
Intracranial subdurahal hemorrhage(s)	Child has intracranial subdural hemorrhage (Yes/No)
Number of right retinal hemorrhage(s)	Number of retinal hemorrhages in right eye 1. 0 2. 1-5 3. 6-20 4. >20 / too numerous to count
Number of left retinal hemorrhage(s)	Number of retinal hemorrhages in left eye 1. 0 2. 1-5 3. 6-20 4. >20 / too numerous to count
Rib fractures	Number of rib fractures
Classical metaphyseal lesions(s)	Child has atleast one classical metaphyseal lesion in: Humerus, Radius, Ulna, Femur, Tibia, or Fibula.
Glascow Coma Score	Glascow Coma Score categorized as: 1. <8 or intubated 2. 9-12 3. 13-15
CNS injury limited to small focal injury directly beneath a skull fracture	Child experienced central nervous system injury limited to small focal injury directly beneath a skull fracture (Yes/No)
Endotrachial Intubation	Patient Experienced Event(s) as a Result of Suspected Abuse or Neglect: Endotracheal Intubation (Yes/No)
Highest level of care	Highest level of care required: 1. Outpatient or Emergency Department Only 2. Inpatient Admission or Observation 3. ICU/PICU/NICU/Step down
Hospital length of stay	Hospital length of stay (days)
ICU length of stay	ICU length of stay (days)
Perpetrator confession	Confession/Report of Harm By The Perpetrator (Yes/No)

A1. Data dictionary

In Chapter 3:

	GEE (Exchangeable) OR (95% CI)
Intracranial Subdural Hemorrhage vs no intracranial subdural hemorrhage (ref)	Inf (Inf, Inf)
At least one classical metaphyseal lesion(s) vs no classical metaphyseal lesion(s) (ref)	Inf (0, Inf)
CNS Injury limited to small focal injury directly beneath a skull vs no CNS Injury limited to small focal injury directly beneath a skull (ref)	0 (0, 0)
Glascow Coma Score 9-12 vs Glascow Coma Score <= 8 or Intubated (ref)	0 (0, Inf)
Glascow Coma Score 13-15 vs Glascow Coma Score <= 8 or Intubated (ref)	0 (0, Inf)
No Glascow Coma Score obtained vs Glascow Coma Score <= 8 or Intubated (ref)	0 (0, Inf)
Endotrachial Intubation vs no endotrachial intubation (ref)	0 (0, Inf)
Number of rib fracture(s)	0 (0, Inf)
1-5 right retinal hemorrhages vs No right retinal hemorrhages (ref)	0 (0, 0)
6-20 right retinal hemorrhages vs No right retinal hemorrhages (ref)	0 (0, Inf)
>=20 or too numerous to count right retinal hemorrhages vs No right retinal hemorrhages (ref)	Inf (0, Inf)
No exam performed vs No right retinal hemorrhages (ref)	0 (0, 0)
Age (months)	0 (0, Inf)
History of Inflicted or Accidental trauma vs No history of Inflicted or Accidental trauma (ref)	0 (0, Inf)
Reported mechanism of inflicted trauma: Shaking or Hit/kick/strike vs No reported mechanism of inflicted trauma: Shaking or Hit/kick/strike (ref)	Inf (0, Inf)
Reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object vs No reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object (ref)	Inf (0, Inf)
Spine ligamentous injury vs no spine ligamentous injury (ref)	Inf (0, Inf)
Highest level of care: Outpatient or Emergency Department Only vs ICU/PICU/NICU/Step down (ref)	Inf (0, Inf)
Highest level of care: Inpatient Admission or Observation vs ICU/PICU/NICU/Step down (ref)	0 (0, 0)
Hospital Length of Stay (days)	Inf (0, Inf)

A2. GEE with exchangeable covariance structure assessing the relationship of sSDH status with clinical factors. * indicate significance.

	GLMM OR (95% CI)
Intracranial Subdural Hemorrhage vs no intracranial subdural hemorrhage (ref)	9.6 (1.1, 83.9) *
At least one classical metaphyseal lesion(s) vs no classical metaphyseal lesion(s) (ref)	2.2 (0.6, 8.1)
CNS Injury limited to small focal injury directly beneath a skull vs no CNS Injury limited to small focal injury directly beneath a skull (ref)	0.0 (0.0, Inf)
Glascow Coma Score 9-12 vs Glascow Coma Score <= 8 or Intubated (ref)	0.7 (0.1, 4.3)
Glascow Coma Score 13-15 vs Glascow Coma Score <= 8 or Intubated (ref)	2.3 (0.7, 7.4)
No Glascow Coma Score obtained vs Glascow Coma Score <= 8 or Intubated (ref)	1.1 (0.3, 5.1)
Endotrachial Intubation vs no endotrachial intubation (ref)	2.4 (0.7, 8.0)
Number of rib fracture(s)	1.0 (0.9, 1.1)
1-5 right retinal hemorrhages vs No right retinal hemorrhages (ref)	0.0 (0.0, Inf)
6-20 right retinal hemorrhages vs No right retinal hemorrhages (ref)	3.6 (1.0, 12.2) *
>=20 or too numerous to count right retinal hemorrhages vs No right retinal hemorrhages (ref)	1.7 (0.7, 3.9)
No exam performed vs No right retinal hemorrhages (ref)	0.0 (0.0, Inf)
Age (months)	1.0 (0.9, 1.1)
History of Inflicted or Accidental trauma vs No history of Inflicted or Accidental trauma (ref)	0.7 (0.3, 1.9)
Reported mechanism of inflicted trauma: Shaking or Hit/kick/strike vs No reported mechanism of inflicted trauma: Shaking or Hit/kick/strike (ref)	1.3 (0.2, 7.6)
Reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object vs No reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object (ref)	1.1 (0.4, 3.2)
Spine ligamentous injury vs no spine ligamentous injury (ref)	1.3 (0.4, 3.9)
Highest level of care: Outpatient or Emergency Department Only vs ICU/PICU/NICU/Step down (ref)	0.0 (0.0, Inf)
Highest level of care: Inpatient Admission or Observation vs ICU/PICU/NICU/Step down (ref)	0.8 (0.2, 2.5)
Hospital Length of Stay (days)	1.0 (1.0, 1.1)

A3. Standard GLMM results assessing the relationship of sSDH status with clinical factors. * indicate significance.

	GLMM (Var = 1) OR (95% CI)	GLMM (Var = 4) OR (95% CI)	GLMM (Var = 9) OR (95% CI)	GLMM (Var = 16) OR (95% CI)
Intracranial Subdural Hemorrhage vs no intracranial subdural hemorrhage (ref)	2.0 (0.8, 5.1)	3.9 (1.0, 14.6) *	5.4 (1.1, 26.3) *	6.6 (1.2, 37.3) *
At least one classical metaphyseal lesion(s) vs no classical metaphyseal lesion(s) (ref)	1.5 (0.5, 4.0)	1.9 (0.6, 6.0)	2.0 (0.6, 6.9)	2.1 (0.6, 7.4)
CNS Injury limited to small focal injury directly beneath a skull vs no CNS Injury limited to small focal injury directly beneath a skull (ref)	0.5 (0.1, 2.2)	0.3 (0.0, 3.9)	0.2 (0.0, 6.6)	0.1 (0.0, 11.5)
Glascow Coma Score 9-12 vs Glascow Coma Score <= 8 or Intubated (ref)	0.6 (0.2, 2.1)	0.6 (0.1, 3.0)	0.6 (0.1, 3.5)	0.6 (0.1, 3.8)
Glascow Coma Score 13-15 vs Glascow Coma Score <= 8 or Intubated (ref)	1.2 (0.5, 2.6)	1.6 (0.6, 4.5)	1.9 (0.6, 5.6)	2.1 (0.7, 6.3)
No Glascow Coma Score obtained vs Glascow Coma Score <= 8 or Intubated (ref)	0.6 (0.2, 1.7)	0.8 (0.2, 2.8)	0.9 (0.2, 3.6)	1.0 (0.2, 4.1)
Endotrachial Intubation vs no endotrachial intubation (ref)	1.4 (0.6, 3.4)	1.8 (0.6, 5.2)	2.0 (0.6, 6.3)	2.1 (0.7, 6.9)
Number of rib fracture(s)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)
1-5 right retinal hemorrhages vs No right retinal hemorrhages (ref)	0.3 (0.1, 1.3)	0.1 (0.0, 1.5)	0.1 (0.0, 2.0)	0.1 (0.0, 3.0)
6-20 right retinal hemorrhages vs No right retinal hemorrhages (ref)	2.6 (0.9, 7.4)	3.2 (0.9, 10.9)	3.4 (1.0, 12.1)	3.5 (1.0, 12.7)
>=20 or too numerous to count right retinal hemorrhages vs No right retinal hemorrhages (ref)	1.7 (0.8, 3.4)	1.7 (0.8, 3.8)	1.7 (0.8, 3.9)	1.7 (0.7, 3.9)
No exam performed vs No right retinal hemorrhages (ref)	0.4 (0.1, 1.9)	0.2 (0.0, 3.0)	0.2 (0.0, 5.1)	0.1 (0.0, 8.6)
Age (months)	1.0 (0.9, 1.0)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)
History of Inflicted or Accidental trauma vs No history of Inflicted or Accidental trauma (ref)	0.7 (0.3, 1.5)	0.7 (0.3, 1.7)	0.7 (0.3, 1.8)	0.7 (0.3, 1.8)
Reported mechanism of inflicted trauma: Shaking or Hit/kick/strike vs No reported mechanism of inflicted trauma: Shaking or Hit/kick/strike (ref)	1.0 (0.3, 3.5)	1.1 (0.2, 5.2)	1.1 (0.2, 6.2)	1.2 (0.2, 6.7)
Reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object vs No reported mechanism of accidental trauma: Fall / Hit with object / Collision with an object (ref)	0.9 (0.4, 2.1)	1.0 (0.4, 2.6)	1.0 (0.4, 2.9)	1.1 (0.4, 3.0)
Spine ligamentous injury vs no spine ligamentous injury (ref)	1.2 (0.5, 3.0)	1.3 (0.5, 3.5)	1.3 (0.4, 3.7)	1.3 (0.4, 3.8)
Highest level of care: Outpatient or Emergency Department Only vs ICU/PICU/NICU/Step down (ref)	0.8 (0.1, 5.2)	0.7 (0.0, 20.5)	0.6 (0.0, 66.4)	0.5 (0.0, 190.2)
Highest level of care: Inpatient Admission or Observation vs ICU/PICU/NICU/Step down (ref)	0.6 (0.3, 1.6)	0.7 (0.2, 2.0)	0.7 (0.2, 2.2)	0.8 (0.2, 2.3)
Hospital Length of Stay (days)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)

A4. Penalized GLMMs results assessing the relationship of sSDH status with clinical factors. Penalized GLMMS had a ridge penalty that corresponded to a normal prior distribution with a mean of zero and standard deviation for all coefficients in the model.

References

Abrahantes, J. C., & Aerts, M. (2012). A solution to separation for clustered binary data. *Statistical Modelling*, *12*(1), 3–27. http://doi.org/10.1177/1471082x1001200102

Adenuga, A., Mateus, A., Ty, C., Borin, K., Holl, D., San, S., … Rudge, J. W. (2018). Seroprevalence and awareness of porcine cysticercosis across different pig production systems in south-central cambodia. *Parasite Epidemiology and Control*, *3*(1), 1–12. http://doi.org/10.1016/j.parepi.2017.10.003

Albert, A., & Anderson, J. A. (1984). On the existence of maximum likelihood estimates in logistic regression models. *Biometrika*, *71*(1), 1–10.

Allison, P. (2008). Convergence failures in logistic regression. *SAS Global Forum 2008*, *360*.

Angel, E. (2000). *Interactive computer graphics : A top-down approach with OpenGL*. Boston, MA: Addison Wesley Longman.

Angel, E. (2001a). *Batch-file computer graphics : A bottom-up approach with QuickTime*. Boston, MA: Wesley Addison Longman.

Angel, E. (2001b). *Test second book by angel*. Boston, MA: Wesley Addison Longman.

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1), 1–48. http://doi.org/10.18637/jss.v067.i01

Bell, B., Morgan, G., Kromrey, J., & Ferron, J. (2010). The impact of small cluster size on multilevel models: A monte carlo examination of two-level models with binary and continuous predictors. *JSM Proceedings, Section on Survey Research Methods*.

Cessie, S. L., & Houwelingen, J. C. V. (1992). Ridge estimators in logistic regression. *Applied Statistics*, *41*(1), 191. http://doi.org/10.2307/2347628

Choudhary, Arabinda Kumar, Bradford, R. K., Dias, M. S., Moore, G. J., & Boal, D. K. B. (2012). Spinal subdural hemorrhage in abusive head trauma: A retrospective study. *Radiology*, *262*(1), 216–223. http://doi.org/10.1148/radiol.11102390

Choudhary, Arabinda K., Ishak, R., Zacharia, T. T., & Dias, M. S. (2014). Imaging of spinal injury in abusive head trauma: A retrospective study. *Pediatric Radiology*, *44*(9), 1130–1140. http://doi.org/10.1007/s00247-014-2959-3

Choudhary, Arabinda Kumar, Servaes, S., Slovis, T. L., Palusci, V. J., Hedlund, G. L., Narang, S. K., ... Offiah, A. C. (2018). Consensus statement on abusive head trauma in infants and young children. *Pediatric Radiology*, *48*(8), 1048–1065. http://doi.org/10.1007/s00247-018-4149-1

Chung, Y., Rabe-Hesketh, S., Dorie, V., Gelman, A., & Liu, J. (2013). A nondegenerate penalized likelihood estimator for variance parameters in multilevel models. *Psychometrika*, *78*(4), 685–709. http://doi.org/10.1007/s11336-013-9328-2

Clark, R. G., Blanchard, W., Hui, F. K. C., Tian, R., & Woods, H. (2023). Dealing with complete separation and quasi-complete separation in logistic regression for linguistic data. *Research Methods in Applied Linguistics*, *2*(1), 100044. http://doi.org/`https://doi.org/10.1016/j.rmal.2023.100044`

Firth, D. (1993). Bias reduction of maximum likelihood estimates. *Biometrika*, *80*(1), 27–38. Retrieved from `http://www.jstor.org/stable/2336755`

Fitzmaurice, G. M., Laird, N. M., & Ware, J. H. (2011). *Applied longitudinal analysis*. Wiley. http://doi.org/10.1002/9781119513469

Gelman, A., Jakulin, A., Pittau, M. G., & Su, Y.-S. (2008). A weakly informative default prior distribution for logistic and other regression models. *The Annals of*

Applied Statistics, *2*(4). http://doi.org/10.1214/08-aoas191

Geroldinger, A., Blagus, R., Ogden, H., & Heinze, G. (2022). An investigation of penalization and data augmentation to improve convergence of generalized estimating equations for clustered binary outcomes. *BMC Medical Research Methodology*, *22*(1). http://doi.org/10.1186/s12874-022-01641-6

Goldstein, M. (1976). Bayesian analysis of regression problems. *Biometrika*, *63*(1), 51–58. http://doi.org/10.1093/biomet/63.1.51

Groll, A., & Tutz, G. (2012). Variable selection for generalized linear mixed models by l 1-penalized estimation. *Statistics and Computing*, *24*(2), 137–154. http://doi.org/10.1007/s11222-012-9359-z

Halekoh, U., Højsgaard, S., & Yan, J. (2006). The r package geepack for generalized estimating equations. *Journal of Statistical Software*, *15/2*, 1–11.

Heinze, G., & Schemper, M. (2002). A solution to the problem of separation in logistic regression. *Statistics in Medicine*, *21*(16), 2409–2419. http://doi.org/10.1002/sim.1047

Hoerl, A. E., & Kennard, R. W. (1970). Ridge regression: Biased estimation for nonorthogonal problems. *Technometrics*, *42*(1), 80–86. Retrieved from `http://www.jstor.org/stable/1271436`

Inan, G., & Wang, L. (2017). PGEE: An R Package for Analysis of Longitudinal Data with High-Dimensional Covariates. *The R Journal*, *9*(1), 393–402. http://doi.org/10.32614/RJ-2017-030

Kemp, A., Cowley, L., & Maguire, S. (2014). Spinal injuries in abusive head trauma: Patterns and recommendations. *Pediatric Radiology*, *44*(S4), 604–612. http://doi.org/10.1007/s00247-014-3066-1

Kim, M. S., & Sim, S. Y. (2015). Spinal subdural hematoma associated with intracranial subdural hematoma. *Journal of Korean Neurosurgical Society*, *58*(4), 397. http://doi.org/10.3340/jkns.2015.58.4.397

Kimball, A. E., Shantz, K., Eager, C., & Roy, J. (2018). Confronting quasi-separation in logistic mixed effects for linguistic data: A bayesian approach. *Journal of Quantitative Linguistics*, *26*(3), 231–255. http://doi.org/10.1080/09296174.2018.1499457

Kratchman, D. M., Vaughn, P., Silverman, L. B., Campbell, K. A., Lindberg, D. M., Anderst, J. D., … Wood, J. N. (2022). The CAPNET multi-center data set for child physical abuse: Rationale, methods and scope. *Child Abuse & Neglect*, *131*, 105653. http://doi.org/10.1016/j.chiabu.2022.105653

Lemoine, N. P. (2019). Moving beyond noninformative priors: Why and how to choose weakly informative priors in bayesian analyses. *Oikos*, *128*(7), 912–928. http://doi.org/10.1111/oik.05985

Liang, K.-Y., & Zeger, S. L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika*, *73*(1), 13–22. http://doi.org/10.1093/biomet/73.1.13

Mondol, M. H., & Rahman, M. S. (2019). Bias-reduced and separation-proof GEE with small or sparse longitudinal binary data. *Statistics in Medicine*, *38*(14), 2544–2560. http://doi.org/10.1002/sim.8126

Morel, J. G., Bokossa, M. C., & Neerchal, N. K. (2003). Small sample correction for the variance of GEE estimators. *Biom. J.*, *45*(4), 395–409.

Mussner, M. (2022). Simulation study on penalized generalized estimating equations after multiple imputation for repeated binary data with a rare event. Retrieved from `https://documentserver.uhasselt.be/handle/1942/38551`

Pan, W. (2001). Akaike's information criterion in generalized estimating equations. *Biometrics*, *57*(1), 120–125.

Rabbitt, A. L., Kelly, T. G., Yan, K., Zhang, J., Bretl, D. A., & Quijano, C. V. (2020). Characteristics associated with spine injury on magnetic resonance imaging in children evaluated for abusive head trauma. *Pediatric Radiology*, *50*(1), 83–97. http://doi.org/10.1007/s00247-019-04517-y

The radiological investigation of suspected physical abuse in children | The Royal College of Radiologists — rcr.ac.uk. `https://www.rcr.ac.uk/publication/radiological-investigation-suspected-physical-abuse-children`.

Wootton-Gorges, S. L., Soares, B. P., Alazraki, A. L., Anupindi, S. A., Blount, J. P., Booth, T. N., … Palasis, S. (2017). ACR appropriateness criteria ® suspected physical abuse—child. *Journal of the American College of Radiology*, *14*(5), S338–S349. http://doi.org/10.1016/j.jacr.2017.01.036