Bayesian Meta-analysis of Rare Events with Non-ignorable Missing Data

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Abstract

Meta-analysis is a powerful tool for drug safety assessment by synthesizing treatment-related toxicological findings from independent clinical trials. However, published clinical studies may or may not report all adverse events (AEs) if the observed number of AEs were fewer than a pre-specified study-dependent cutoff. Subsequently, with censored information ignored, the estimated incidence rate of AEs could be significantly biased. To address this non-ignorable missing data problem in meta-analysis, we propose a Bayesian multilevel regression model to accommodate the censored rare event data. The performance of the proposed Bayesian model of censored data compared to other existing methods is demonstrated through simulation studies under various censoring scenarios. Finally, the proposed approach is illustrated using data from a recent meta-analysis of 125 clinical trials involving PD-1/PD-L1 inhibitors with respect to their toxicity profiles.

Keywords: rare event; informative censoring; meta-analysis; Bayesian inference

1 Introduction

This work was motivated by a systematic review and meta-analysis of treatment-related adverse events of programmed cell death 1 (PD-1) and PD-1 ligand 1 (PD-L1) inhibitors for cancer immunotherapy [1]. The PD-1 pathway is negatively up-regulated in many tumors and in their microenvironment. Blockade of this pathway with antibodies to PD-1 or its ligands has led to remarkable clinical responses in various types of cancer [2], and is considered one of the most important breakthroughs in the treatment of cancer. These novel immune checkpoint inhibitors are clinically less toxic than traditional cancer treatments such as chemotherapy and radiation therapy, but can occasionally cause serious and sometimes life-threatening immune-related adverse events (AEs). Given the rarity of AEs, combining evidence from multiple studies is a powerful toll to examine the toxicological profile of the PD-1 and PD-L1 inhibitors.
Meta-analysis synthesizes findings from multiple independent clinical studies and provides a more powerful analysis than from a single study [3]. To quantify and understand the treatment-related AE incidence, one key challenge in meta-analysis is the incompleteness of the AE data. In the motivating anti-PD-1/PD-L1 example, approximately 60% of treatment-related AEs were not reported. Many AEs were missing due to the rarity of such events because their study-level observed frequency were lower than a pre-determined reporting cutoff (e.g. 3% or 5% of the study sample size). Subsequently, if the analysis was conducted only based on the likelihood of the reported data, the inferences on incidence rates would be significantly biased [4].

This type of censored data problem without individual level information has received little attention in the meta-analysis literature. Most of the research on missing data in meta-analysis focuses on the situations when the estimate from the whole study is missing, which may lead to publication bias [5]. At the individual participant level, some studies focused on the scenario where the count of patients with missing binary outcome is known [6, 7, 8, 9], while Yuan and Little investigated missing outcome data when the study attrition rates depend on the size of the underlying treatment effect [10]. None of those literature address the issue of non-ignorable censored data at the study level. Due to the lack of appropriate methods to deal with this problem, in current meta-analytic applications, most studies either totally ignored the AEs with low incidence, or completely discarded the studies with missing AE data [11], contributing to substantial publication selection bias or estimation error.

Another key challenge in the meta-analysis of treatment-related AEs is the rarity of such events [12]. Standard methods to model binary patient outcomes such as AEs rely on either approximation methods based on the normal distribution or exact methods based on the binomial distribution [13]. However, when the observed events are rare, approximation approaches may provide poor estimates of the true incidences and lead to significantly biased results [14, 15, 16, 17]. Some recent efforts have been made to overcome this limitation, including the Poisson random effects model to estimate relative risk between two treatment groups [18], asymptotically unbiased estimation for the treatment effect and heterogeneity parameter in the random-effect model [12], and the exact meta-analysis approach to combine inferences based on p-values from multiples studies in the rare event setting [19]. However, all the above methods were all developed for meta-analysis of rare events when there is no data missingness.

In this paper, we propose a one-stage Bayesian approach to model censored rare event data in the meta-analysis, with an aim to deliver the exact inference when the missing data are non-ignorable. The rest of the article is organized as follows. In Section 2 we present the general Bayesian modeling framework and implement the proposed approach in Just Another Gibbs Sampler (JAGS) with a tailored presentation for model assessment. In Section 3 we conduct numerical studies under different censoring scenarios by comparing the proposed Bayesian model of censored data with other existing methods. Real data meta-analysis results demonstrating the advantage of the proposed approach are presented in Section 4. Lastly, some concluding remarks and discussion are provided in Section 5 including the model generalizability to other types of missing data in meta-analysis.
2 Bayesian Modeling of Incomplete Data

2.1 General Framework

In order to handle informatively censored data, we proposed a Bayesian multilevel regression model. It incorporates cumulative probabilities into the likelihood function that allows the partial information contained in the censored data in the analysis, such that the proposed approach can yield proper parameter estimation and statistical inference. Compared with multiple imputation approach, Bayesian approach is efficient and recommended for modeling incomplete data especially without requiring the assumption of normality [20].

Let \( Y_j, j = 1, \ldots, J \), denote the primary response of interest of \( j \)th observation, which may not be fully observed. Denote \( \delta_j \) a binary variable to indicate whether \( Y_j = y_j \) is fully observed (\( \delta_j = 1 \)) or censored (\( \delta_j = 0 \)). Assume the random variable \( Y \) has the right continuous cumulative distribution function \( F_Y(y) = P[Y \leq y] \). For censored outcomes, the censoring mechanism can be defined by bounding variables \((A, B)\), with semi-closed boundaries \((A_j, B_j]\) for response variable \( Y_j \). Here, both bounding variables could be covariate-dependent. The joint density of a single censored observation is \([F_Y(b_j) - F_Y(a_j)]h_{A,B}(a, b)\), where \( h_{A,B}(a, b) \) is the joint density of \((A, B)\).

In a general setting, the likelihood function can be decomposed by the censoring status of the data. We first assume that the censoring mechanism is independent of the outcome model. This is also named noninformative censoring in survival analysis, which is a fundamental assumption behind most methodologies dealing with interval censoring [21]. Denote \( f_Y(y) \) the probability density/mass function of \( F_Y(y) \). Therefore, the likelihood function for both fully observed and censored observations can be written by:

\[
\mathcal{L} = \prod_{j=1}^{J} f_Y(y_j)^{\delta_j}[F_Y(b_j) - F_Y(a_j)]^{1-\delta_j},
\]

as the censoring mechanism does not contribute to the inference and model estimation.

The presentation of interval censoring [1] also contains right censoring and left censoring as special cases. If data is left-censored with cutoff \( B_j = c \), \( A_j \) can be non-random and specified such that \( F_Y(a_j) = 0 \) and \( F_Y(b_j) = F_Y(c) \). If data is right-censored with cutoff \( A_j = c \), then \( F_Y(a_j) = F_Y(c) \) and \( F_Y(b_j) = 1 \). Without loss of generality, hereafter we focus on one-sided censored cases.

2.2 Censored Adverse Events

In practice, the frequency of AEs may not always be reported. For example, left censoring occurs when some severe (grade 3 or higher) AEs are not observed due to low incidence. In this case, the cutoff boundaries are not random but fixed and study-specific, which automatically satisfies the noninformative censoring assumption. Denote the fixed cutoff by \( c_j \) for each study. The number of subjects having a specific AE in the \( j \)th study, \( Y_j \), follows a binomial distribution with study-level sample size \( n_j \) and AE incidence probability \( \theta_j \)

\[
Y_j \sim Bin(n_j, \theta_j).
\]
Therefore, we specify the general framework \( \mathcal{L} \) to

\[
\mathcal{L} = \prod_{o=1}^{O} f_Y(y_o) \prod_{l=1}^{L} [F_Y(b_l) - F_Y(a_l)] \prod_{r=1}^{R} [F_Y(b_r) - F_Y(a_r)]
\]

\[
= \prod_{o=1}^{O} f_Y(y_o) \prod_{l=1}^{L} [F_Y(c_l) - 0] \prod_{r=1}^{R} [F_Y(n_r) - F_Y(c_r)]
\]

\[
= \prod_{o=1}^{O} f_Y(y_o) \prod_{l=1}^{L} F_Y(c_l) \prod_{r=1}^{R} [1 - F_Y(c_r)]
\]

\[
= \prod_{o=1}^{O} f_Y(y_o) \prod_{l=1}^{L} \sum_{k_l=0}^{c_l} f_Y(k_l) \prod_{r=1}^{R} [1 - \sum_{k_r=0}^{c_r} f_Y(k_r)],
\]

where \( O \) is a set of fully-observed AE outcomes, \( L \) a set of left-censored outcomes, and \( R \) a set of right-censored outcomes. \( c_l \) and \( c_r \) are cutoff values for left-censored and right-censored data, respectively. If \( Y_j \) is left-censored, then \( Y_j \) lies in the semi-closed interval \( (A_l = 0^-, B_l = c_l] \), where \( c_l \) is corresponding cutoff value for left-censored data. If \( Y_j \) is right-censored, then \( Y_j \) lies in the semi-closed interval \( (A_r = c_r, B_r = n_r] \), where \( c_r \) is corresponding cutoff value for right-censored data and \( n_r \) is the total number of subjects in the \( r \)th study. This is specified to be consistent for the JAGS model implementation in \( 2^{3} \).

In the anti-PD-1/PD-L1 example, there are 125 studies with a total of 20,218 patients. To identify possible source of heterogeneity between studies, the following study-level information were also extracted: trial name, number of treated patients, selected immunotherapy drug, dosing schedule, cancer type, number of AEs within each category, and the pre-specified censoring criteria for AE reporting. To estimate the incidence probability of grade 3 or higher AE for different moderators and subgroups, we model the AE incidence \( \theta_j \) as follows,

\[
g(\theta) = \logit(\theta) = \alpha + \eta + \zeta = X_\beta,
\]

where \( g(\cdot) \) is an appropriate link function, either logit or probit link is a natural choice for binary/binomial outcome data. \( X_\beta \) is a known design matrix and \( \beta \) denotes a vector of random effects in the model. To specify the priors for random effects in the logit model, we assume normal distributions on main effects (such as study, drug-dose, and cancer type) as follows.

\[
\alpha \sim N(0, \sigma_\alpha^2), \quad \eta \sim N(0, \sigma_\eta^2), \quad \zeta \sim N(0, \sigma_\zeta^2)
\]

Following the recommendation of prior distributions for variance parameters in hierarchical models \( 22 \), we place weakly-informative half-Cauchy prior distributions to the standard deviation parameters as follows:

\[
\sigma_\alpha, \sigma_\eta, \sigma_\zeta \sim C^+(0, A),
\]

where the scale parameter, \( A \), is set to 25.
2.3 Model Implementation using JAGS

To derive inference from and perform assessment of the proposed Bayesian model above, we apply Just Another Gibbs Sampling (JAGS) to generate samples from the posterior distribution. JAGS makes Bayesian hierarchical models easy to implement using Markov Chain Monto Carlo (MCMC) simulation [23] in R and other computational software. In the presence of censored data in the response variable, an existing function, known as dinterval distribution, is commonly used to model censored data [24, 25]. However, such model specification for censored data in JAGS yields a mis-specified likelihood function [26], which also hinders the automatic calculation of the correct deviances of candidate models from JAGS for deviance-based model assessment and comparison.

Alternatively, we apply a simple but effective approach to censored data specification. To facilitate model implementation for censored observations (when $\delta_j = 0$) and avoid the miscalculated deviance via dinterval() function in JAGS. Here, we utilize the idea of data augmentation by first introducing ancillary indicator variables $W_j$. Each $W_j$ separates the left-censored from right-censored observations ($W_j = 1$ if left-censored, 0 if right-censored). By assuming $W_j$ following a Bernoulli distribution, we have the density function

$$f_{W_j}(w_j; p_j) = p_j^{w_j}(1 - p_j)^{1-w_j} = F_Y(c_l)^{w_j}[1 - F_Y(c_r)]^{1-w_j} = \left[\sum_{k_l=0}^{c_l} f_Y(k_l)\right]^{w_j} \left[1 - \sum_{k_r=0}^{c_r} f_Y(k_r)\right]^{1-w_j}$$

(6)

exactly matches the second and third terms for censored observations in (2), with the probability of left censoring $p_j$ defined from the cumulative binomial distribution of incidence probability of AE in the $j$th study, restricted by a pre-determined study-level cutoff value $c_j$. An extension to interval-censored data can be found in [27].

A JAGS model specification for the application is provided in Appendix 6 for illustrative purpose. Together with fully observed data that follow a binomial distribution, the full likelihood implemented in JAGS model is, in fact, identical to the exact likelihood of observed and censored cases in (2). This creates the right focus of model parameters and produces the proper posterior samples, as well as simultaneously computes the correct deviance for model selection. For example, by calling the deviance module in JAGS, a correct DIC [28] or penalized deviance [29] can be conveniently derived to assess candidate models for Bayesian model selection. It is important and beneficial to identify the best model, especially in the presence of complicated model features.

3 Simulation

In this section, we conduct a simulation study to assess the performance of the proposed Bayesian model in estimating the incidence rates and odds ratios (ORs) in the meta-analysis of rare adverse events (AEs) with censored information. We compare it with that of other popular methods applied with a standard setting [11].

3.1 Settings

To assess the performance of the proposed model that incorporates both observed and censored data, we consider four scenarios: (1) no censoring; (2) low percentage (40%) of censoring for all
drugs; (3) high percentage (80%) of censoring for all drugs; and (4) mixed percentage of censoring, which suggests no censoring for Drug 1, 40% for Drug 2, and 80% for Drug 3. In Scenario 1, the number of events for all studies are fully observed. In the other scenarios (Scenarios 2-4), which include censored observations, data with low incidence are censored to mimic real-world cases, where low and zero events are often censored. Therefore, in Scenario 2, we treat the 40% of AE data with low incidence as censored data and the 60% of AE data that have a relatively higher incidence as observed data. Similarly, in Scenario 3, in order to stress test the robustness of estimation in a more extreme case of censoring, 80% of AE data with low incidence are treated as censored and the remaining 20% are treated as observed. Lastly, in Scenario 4, which is more comprehensive, all studies corresponding to Drug 1, the top 60% of studies corresponding to Drug 2, and the top 20% of studies corresponding to Drug 3 are treated as observed data, and the remaining studies for each drug are treated as censored data. Such an unbalanced case of censoring for different drugs can illustrate the real performance of odds ratio (OR) estimation, when similar biased effects in incidence estimation can no longer be canceled out in OR estimation.

We compare the proposed model, Bayesian method of censored data (BMCD), with four other methods: the pooled estimation method after continuity correction (PEM) [30, 31], the normal approximation method (NAM) [32], the logistic regression method (LRM), and the normal approximation method with robust variance estimator (RVE) [33]. In BMCD, because of three levels, following the recommendation of weakly-informative prior distribution for logistic regression models [34], we assign a Cauchy prior distribution on drug effect, \( C(0, A) \), where the scale parameter, \( A \), is set to 10. In PEM [30], we pool observations by drug and add 0.5 correction to those studies with zero observations to avoid undefined OR of pairwise comparison. The 95% confidence intervals (CIs) for drug effects are calculated by the exact binomial test. We exponentiate the confidence limits of the logarithm of OR to obtain the 95% CIs of OR [31]. In NAM, as a standard method in practice [32], we use a normal likelihood procedure to estimate the incidence rate by taking the inverse logit of the observed logit incidence [13] of each drug weighted by its within-drug variance. In LRM, we estimate the drug effects by an exact method through fitting a generalized linear model with logit link. In addition, we compare the performance of NAM with and without robust variance estimators [33]. Therefore, in RVE, instead of Fisher information, we implement the sandwich estimator of variance into NAM to improve the robustness of the statistical inference on incidence rates and ORs.

The total number of studies for each drug is fixed at 10 to reflect the typical number of studies in a meta-analysis. The outcome of interest, the number of AEs for each study, is generated from a binomial distribution with number of patients \((n = 100)\) and probability of events \((d_1 = 0.025, d_2 = 0.025, \text{ and } d_3 = 0.013, \text{respectively})\). The probability of incidence is determined by the range of incidence rate for the main dose of the corresponding drug to mimic the real-world data example in the next section. Based on the selected incidence probabilities, the true OR between Drug 2 and Drug 1 is 1.0, and the true OR between Drug 3 and Drug 1 (or Drug 2) is 0.5. We assess the following metrics: coverage probability of 95% CIs, point estimations with associated standard errors, mean absolute deviations, and root mean squared errors of all six parameters of interest in the four scenarios.
3.2 Simulation Results

The results are based on 10,000 simulated data sets. For each method, we repeated the same data generation procedure in order to be able to compare results across methods. Figure 1 gives boxplots for point estimations with corresponding standard errors of incidence rates and odds ratios (ORs) by scenario and method. Coverage probabilities (CPs) of six parameters of interest by scenario and method are displayed in bar charts in Figure 2. In Table 1, performance in terms of both mean absolute deviations (MADs) and root mean square errors (RMSEs) of incidence rates and ORs based on the five methods are shown for the four scenarios.

![Figure 1: Point estimations (PEs) with standard errors (SEs) of drug effects (incidence rates of drugs; \(d\)) and odds ratios (ORs) for five methods, Bayesian method of censored data (BMCD), pooled estimation method after continuity correction (PEM), normal approximate method (NAM), logistic regression model (LRM), as well as normal approximate method with robust variance estimation (RVE) under four scenarios: (S1) 0% censoring; (S2) 40% censoring; (S3) 80% censoring; and (S4) mixed censoring.](image)

When there is no censoring (Scenario 1), the proposed method (BMCD) has CPs, MADs, and RMSEs on incidence rates and ORs that are almost identical to those of the PEM and LRM. Of the five methods compared, the PEM can be considered the gold standard/benchmark for both interval and point estimations. Our results indicate that the BMCD is not inferior to the PEM. They also indicate that the CP for each drug obtained from the NAM appeared to be unstable on...
estimating incidence rates of rare events compared with the other methods. The performance of the RVE is even worse compared with that of the NAM because the model was properly specified. The point estimations of incidence rates in both NAM and RVE are overestimated in Scenario 1. This finding is consistent with arguments mentioned in the normal approximation for rare events [15] and biased results of estimation for rare events using normal approximation [14].

When 40% of data are censored (Scenario 2), the proposed method (BMCD) performs better than the others in estimating incidence rates; its performance in Scenario 2 is as good as it is in Scenario 1. Because censored observations are ignored under other four methods (PEM, NAM, LRM, and RVE), it is unsurprising that the point estimations of incidence rates are overestimated and that the CPs in Scenario 2 are much lower than those in Scenario 1. In contrast, the performance of BMCD in Scenario 2 is almost identical to its performance in Scenario 1 for both interval and point estimations.

In a more extreme scenario where 80% of data are censored (Scenario 3), the proposed method (BMCD) performs well, with little information loss compared with Scenarios 1 and 2. However,
Table 1: Mean absolute deviations (MADs) and root mean square errors (RMSEs) of drug effects (d) and odds ratios (ORs) for five methods, Bayesian method of censored data (BMCD), pooled estimation method after continuity correction (PEM), normal approximate method (NAM), logistic regression model (LRM), as well as normal approximate method with robust variance estimation (RVE) under four scenarios: (S1) 0% censoring; (S2) 40% censoring; (S3) 80% censoring; and (S4) mixed censoring.

| Scenario | Parameter | True Value | % of Missing | Mean Absolute Deviation | Root-mean-squared Error |
|----------|-----------|------------|--------------|-------------------------|-------------------------|
|          |           |            |              | BMCD    | PEM    | LRM    | NAM/RVE | BMCD    | PEM    | LRM    | NAM/RVE |
| S1       | d₁        | 0.025      | 0%           | 0.004    | 0.004  | 0.004  | 0.009    | 0.005    | 0.005  | 0.005  | 0.010    |
|          | d₂        | 0.025      | 0%           | 0.004    | 0.004  | 0.004  | 0.009    | 0.005    | 0.005  | 0.005  | 0.010    |
|          | d₃        | 0.013      | 0%           | 0.003    | 0.003  | 0.003  | 0.008    | 0.004    | 0.004  | 0.003  | 0.009    |
|          | OR₂₁      | 1.000      |              | 0.245    | 0.242  | 0.235  | 0.190    | 0.326    | 0.322  | 0.313  | 0.246    |
|          | OR₃₁      | 0.500      |              | 0.152    | 0.151  | 0.150  | 0.170    | 0.201    | 0.200  | 0.200  | 0.221    |
|          | OR₃₂      | 0.500      |              | 0.148    | 0.147  | 0.146  | 0.169    | 0.194    | 0.194  | 0.193  | 0.219    |
| S2       | d₁        | 0.025      | 40%          | 0.004    | 0.009  | 0.008  | 0.015    | 0.005    | 0.011  | 0.010  | 0.016    |
|          | d₂        | 0.025      | 40%          | 0.004    | 0.009  | 0.008  | 0.015    | 0.005    | 0.011  | 0.010  | 0.016    |
|          | d₃        | 0.013      | 40%          | 0.003    | 0.007  | 0.006  | 0.013    | 0.004    | 0.008  | 0.007  | 0.014    |
|          | OR₂₁      | 1.000      |              | 0.248    | 0.220  | 0.218  | **0.196** | 0.329    | 0.289  | 0.287  | **0.253** |
|          | OR₃₁      | 0.500      |              | **0.155** | 0.156  | 0.156  | 0.174    | **0.207** | 0.210  | 0.210  | **0.228** |
|          | OR₃₂      | 0.500      |              | 0.151    | 0.154  | 0.154  | 0.174    | **0.200** | 0.206  | 0.206  | **0.226** |
| S3       | d₁        | 0.025      | 80%          | 0.005    | 0.021  | 0.019  | 0.026    | 0.006    | 0.023  | 0.021  | 0.028    |
|          | d₂        | 0.025      | 80%          | 0.005    | 0.021  | 0.019  | 0.026    | 0.006    | 0.023  | 0.021  | 0.028    |
|          | d₃        | 0.013      | 80%          | 0.003    | 0.016  | 0.015  | 0.021    | 0.004    | 0.017  | 0.016  | 0.022    |
|          | OR₂₁      | 1.000      |              | 0.290    | 0.237  | 0.239  | **0.229** | 0.391    | 0.316  | 0.319  | **0.302** |
|          | OR₃₁      | 0.500      |              | **0.177** | 0.197  | 0.196  | 0.206    | **0.241** | 0.266  | 0.266  | 0.273    |
|          | OR₃₂      | 0.500      |              | **0.176** | 0.199  | 0.197  | 0.208    | **0.239** | 0.266  | 0.266  | 0.274    |
| S4       | d₁        | 0.025      | 0%           | 0.004    | 0.004  | 0.004  | 0.009    | 0.005    | 0.005  | 0.005  | 0.010    |
|          | d₂        | 0.025      | 40%          | 0.004    | 0.009  | 0.008  | 0.015    | 0.005    | 0.011  | 0.010  | 0.016    |
|          | d₃        | 0.013      | 80%          | 0.003    | 0.016  | 0.015  | 0.021    | 0.004    | 0.017  | 0.016  | 0.022    |
|          | OR₂₁      | 1.000      |              | **0.248** | 0.465  | 0.448  | 0.288    | **0.330** | 0.601  | 0.582  | 0.377    |
|          | OR₃₁      | 0.500      |              | **0.160** | 0.772  | 0.691  | 0.530    | **0.214** | 0.880  | 0.801  | 0.608    |
|          | OR₃₂      | 0.500      |              | **0.158** | 0.425  | 0.381  | 0.365    | **0.208** | 0.511  | 0.468  | 0.438    |

all other estimators of drug effects led to inferior CP due to increased percentage of censoring. The point estimations obtained from PEM, LRM, NAM, and RVE in Scenario 3 are more biased than those obtained from these methods in Scenario 2. Based on the MAD and RMSE, there were larger deviations from true values of incidence rates compared with those in Scenario 2. Overall, the BMCD yields not only more stable and superior coverage, but also unbiased estimator of incidence rates and ORs in all three scenarios.

Keeping the censoring pattern fixed as in Scenario 2 (40% missing) and Scenario 3 (80% missing) across drugs results in the unbiased estimations on ORs even if the point estimations of incidence are overestimated. Therefore, other than fixed censoring in Scenarios 2 and 3, mixed censoring (0%/40%/80%; Scenario 4) is designed to show that the other four methods are all off-target in estimating CPs of ORs. When the censoring pattern is mixed, the bias in estimating incidence rates impacts both point and interval estimations of ORs for the other methods in Scenario 4.

Across all scenarios considered above, the BMCD is more powerful and robust than the other
four methods in dealing with rare and censored event data. The BMCD also outperforms the other four methods in estimating incidence rates as well as ORs when AEs have low incidence and when a high proportion of AEs are censored. Furthermore, the quality of an estimator can be measured by its efficiency, which is defined as the asymptotic variance of an estimator [35]. The larger the variance, the lower the efficiency of an estimator. Here, the asymptotic relative efficiency (RF) is given to examine the amount of information loss in comparing two scenarios. Information loss in informative censoring may lead to an inefficient estimator. According to the variance of the point estimator from BMCD, regarding the drug effects, the RFs of two estimators by comparing high percentage of censoring (Scenario 3) to no censoring (Scenario 1) are 0.73, 0.76 and 0.78, respectively. In other words, 80% of censoring only results in 27%, 24%, and 22% loss of efficiency in estimating incidence rates, respectively, compared with no censoring. Meanwhile, the relative efficiency of Scenario 3, with respect to Scenario 1, is approximately 0.70 on average for estimators corresponding to ORs, suggesting that only 30% of information is lost under 80% of informative censoring. In summary, the proposed method (BMCD) consistently achieves a reasonable performance in estimating the incidence rates and ORs.

4 Application

In this section, we apply the proposed Bayesian method of joint modeling to the real data meta-analysis of grade 3 or higher adverse events (AEs) with censored information [1]. The goal is to evaluate the incidence probabilities of pneumonitis (referring to inflammation of lung tissue) of two PD-1 and three PD-L1 inhibitors in a meta-analysis of 125 clinical studies. Such kind of inflammatory or immune-related AEs are of special interest for cancer immunotherapy.

The proposed model is implemented in the statistical software R and JAGS [23], which uses MCMC algorithms to generate samples from the posterior distribution of the parameters of interest. Along with listing the data and setting the initial values of model parameters, we defined the likelihood functions and priors of a Bayesian model before compilation in JAGS. We run three parallel chains for the model. For each MCMC chain, after discarding the burn-in period of 30,000 iterations, the 3 chains showed good mixing and successful convergence to the target distribution. We eventually obtain 10,000 posterior samples per chain by retaining one sample out of three. The 30,000 posterior samples of model parameters such as incidence probabilities of 20 drug-dose effects are saved for inference.

Figure 3 illustrates the estimated incidence probability for grade 3 or higher pneumonitis across 125 clinical trials. Figure 4 shows the incidence probabilities of grade 3 or higher pneumonitis and their 95% credible intervals by drug and dose in the forest plot. According to the subgroup analysis of incidence probability of AE by drug and dose, there were no significance differences in the incidence among different dosing schedules for PD-1/PD-L1 drugs. The vertical dashed line is the overall incidence probability of grade 3 or higher pneumonitis (0.54%; 95% CI, 0.34%-0.77%) across all studies. By contrast, if the censored outcomes were treated as missing at random, by ignoring them in the analysis, the estimated incidence rate would be biased and overestimated by 9.26%.
Figure 3: Incidence of grade 3 or higher AE (Pneumonitis) by study
Figure 4: Incidence of grade 3 or higher AE (Pneumonitis) by drug and dose
5 Conclusions and Discussion

In this paper, we proposed a novel Bayesian hierarchical model in the meta-analysis setting when the study-level event rates are rare and censored. Compared with multiple imputation methods, Bayesian approach is efficient without requiring the assumption of normality. Further, we demonstrated the superior performance of such method in simulations. Specifically, simulation results showed that the proposed Bayesian approach is capable of leading to limited information loss and unbiased estimations of drugs effects and odd ratios. Finally, we illustrated the implementation with a real data application. In this application, we found that using our proposed method significantly reduced the bias in estimated incidence rate.

Other than assessing the toxicity profile, the proposed method can be extended to meta-analysis of high-dimensional genomic data, in which large number of genes can be tested to estimate the mutation rate in the panels across studies. For such an extension, information on some mutations could be also censored due to low frequency, which should be considered in the model using pre-specified cutoff value determined by gene selection criteria.

The proposed Bayesian hierarchical model estimates the incidence probabilities using a one-stage approach. In contrast, meta-analysis of binary data is usually conducted using a two-stage approach [30, 37]. The summary statistics are first separately calculated for each trial and then combined by an appropriate meta-analysis model. However, the two-stage approach is likely to perform poorly in the first stage for each study due to the rarity of events [38]. Alternatively, a one-stage approach is preferred as it delivers more exact statistical inference [39]. This also applies to the scenario of rare events with missing data, as confirmed in the simulation studies.

The proposed general framework [1] applies to a wide range of models. A typical data structure in meta-analysis includes binary patient outcome with missing treatment response information, where the interval boundaries specified by the range from the number of observed responses to the number of potential responses (response + missing) for each treatment [6, 7, 8]. The proposed Bayesian model implementation strategy could also be generalized to analyze other censored data structures outside of meta-analysis including time-to-event data with right-censoring, count data and ranking data [40]. Further the proposed method can apply to many other fields such as behavior science [41], environmental science [42] and food science [43].

Incorporating individual patient-level data (IPD) in such meta-analysis of study-level / aggregated data (AD) can be a future direction of research. We can modify our current Bayesian model by using power priors [44] or commensurate priors [45] when combining AD with IPD in the meta-analysis. In this work we only focused on the case of grade 3 or higher AEs being left censored when they happened at a frequency lower than pre-specified cutoff values. We can also extend to joint modeling of the correlated all-grade and grade 3 or higher AEs. Specifically, in estimation of the all-grade AEs in meta-analysis, right censoring may also occur when some studies only report grade 2 or higher AEs instead of all-grade AEs [46], which can be simultaneously handled in our current framework.
6 Appendix

The JAGS model specification for the application is as follows. \( v1, v2, v3 \) represent three main covariates.

```r
model{

for (j in 1:J1){
    Y[j] ~ dbin(theta[j], N[j])
    logit(theta[j]) <- alpha[v1[j]] + eta[v2[j]] + zeta[v3[j]]
}

for (j in 1:J2){
    W[j] ~ dbern(p[j])
    p[j] <- pbin(cut[j], theta[j+J1], N[j+J1])
    logit(theta[j+J1]) <- alpha[v1[j+J1]] + eta[v2[j+J1]] + zeta[v3[j+J1]]
}

for (i1 in 1:n.v1){
    alpha[i1] <- mu.v1 + sigma.alpha*sn.v1[i1]
    sn.v1[i1] ~ dnorm(0,1)
}

mu.v1 ~ dnorm(0, .0001)
sigma.alpha ~ dt(0, a, 1)T(0,) # a=1/A^2 where A=25

for (i2 in 1:n.v2){
    eta[i2] <- mu.v2 + sigma.eta*sn.v2[i2]
    sn.v2[i2] ~ dnorm(0,1)
}

mu.v2 ~ dnorm(0, .0001)
sigma.eta ~ dt(0, a, 1)T(0,)

for (i3 in 1:n.v3){
    zeta[i3] <- mu.v3+sigma.zeta*sn.v3[i3]
    sn.v3[i3] ~ dnorm(0, 1)
}

mu.v3 ~ dnorm(0, .0001)
sigma.zeta ~ dt(0, a, 1)T(0,)
}
```
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