Joint analysis of the relationships between drug exposure and liver enzyme elevations for assessing drug-induced liver injury

Weihan Zhao[1], Ling Cheng[1], Xiu Huang[1], and Wei Liu[2]

[1]Data and Statistical Sciences, AbbVie Inc., North Chicago, IL; [2]Clinical Pharmacology and Pharmacometrics, AbbVie Inc., North Chicago, IL

2020 ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop, September 22 – 25, 2020

Abstract

Drug-induced liver injuries (DILI) caused by therapeutic drugs are serious and sometimes even fatal in some patients and have resulted in disapproval of new drugs and removal of approved drugs from the market. To evaluate DILI, both the widely accepted Hy's law and the FDA's evaluation of drug-induced serious hepatotoxicity (eDISH) program focus on two key liver chemistry tests, namely alanine aminotransferase (ALT) and total bilirubin (TBL). An association of elevated ALT and TBL with drug exposure would indicate a high DILI risk to subjects exposed, especially to those with high exposures. Despite the fact that ALT and TBL elevations are generally correlated and may be associated with different risk factors, in practice exposure-response analyses are usually performed individually for these two measures with the same set of covariates considered in each analysis.

In this work, simulated continuous and categorical (binary and ordinal) data are used to compare statistical methods for correlated bivariate data for assessing the relationship between drug exposure and ALT/TBL elevations. Model recommendations are provided for different data assumptions, although it was found that the appropriate method to use is largely dependent on the objective and available data. These statistical models for correlated continuous and categorical data are applied in the exposure-safety analyses of an AbbVie dataset to predict the safety impact under scenarios of increased exposures. The results are compared with those from the univariate models to demonstrate the advantages of the joint analysis.

Introduction

Acute liver failure (ALF) refers to the rapid loss of liver function and can cause serious complications. According to Lee (2013), it is estimated that annually in the U.S. there are approximately 2000 people experiencing ALF, among which about 60% are drug-induced liver injury (DILI), i.e. ALF caused by approved drugs.

DILI is also a major reason for NDA rejection and removal of drug from the market. Over the past 25 years there have been numerous regulatory actions due to DILI, including the withdrawals of bromfenac and troglitazone, and warnings to acetaminophen. It is worth noting that in many cases the drug is not particularly dangerous, but a small number of patients may be especially susceptible to the hepatotoxic effect.

The Hy's Law (Temple 2001; Reuben 2004), which was based on the observation that hepatocellular injury causing hyperbilirubinemia is an ominous indicator of DILI, has the following components: 1. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x upper limit of normal (ULN); 2. total bilirubin (TBL) > 2x ULN; and 3. not primarily cholestatic; not caused by disease but by drug. Based on the Hy's Law, the FDA's developed evaluation of Drug-Induced Serious Hepatotoxicity (eDISH), which is an analytical tool focusing on ALT/AST and TBL elevations to find identify rare subjects of special interest from large controlled clinical studies.

Exposure-response analyses are critical in determining safety and effectiveness levels and dosages of drugs. Such analyses usually complement primary efficacy and safety analysis and are used to support new target population, dose regimen, formulation, etc.

Bivariate Logistic and Ordinal Regression Models

Models for continuous outcomes with normal (or other) error structures may not be a good fit for DILI assessment with ordinal clinical outcomes. Traditionally, univariate binary logistic models have been used to individually assess ALT and TBL elevations (e.g. ≥ Grade 2). However, these models do not account for the correlation between these two events. Moreover, with these models one cannot predict events of simultaneous ALT and TBL elevations, which is the key question to be addressed in DILI assessment. To this end, it would make perfect sense to use bivariate binary and ordinal models for analyzing ALT and TBL data in DILI assessment.

According to Palmgren (1989), the stochastic component of the bivariate logistic regression model can be written as:

$$Y_{11} \sim Bernoulli(\pi_{11})$$
$$Y_{10} \sim Bernoulli(\pi_{10})$$
$$Y_{01} \sim Bernoulli(\pi_{01})$$

where $\pi_{rs} = \Pr(Y_1 = r, Y_2 = s)$, and $\pi_{00} = 1 - \pi_{11} - \pi_{10} - \pi_{01}$.
The marginal probabilities and the odds ratio can be modeled by:

$$\pi_j = \frac{1}{1+exp(-x_j\beta_j)}, \text{for } j = 1,2$$
$$\varphi = \pi_{00}\pi_{11}/\pi_{01}\pi_{10} = exp(-x_3\beta_3)$$

Solving for π_{11} using

$$\begin{cases} \pi_{10} = \pi_1 - \pi_{11} \\ \pi_{01} = \pi_2 - \pi_{11} \\ \pi_{00} = 1 - \pi_{11} - \pi_{10} - \pi_{01} \end{cases} \qquad \varphi = \pi_{00}\pi_{11}/\pi_{01}\pi_{10}$$

gives $\pi_{11} = \frac{-b+\sqrt{b^2-4ac}}{2a}$, where $a = 1-\varphi; b = 1-(1-\varphi)(\pi_1+\pi_2); c = -\varphi\pi_1\pi_2$.

Cumulative links can be used for modeling ordinal responses. We assume observed category Y_i come from an underlying latent variable $\tilde{Y}_i$ with $\tilde{Y}_i = \beta_0 + \boldsymbol{x}_i^T\boldsymbol{\beta} + \epsilon_i$, where ϵ_i is the error with zero mean and distribution function F, and $Y_i = r$ iff $\theta_{r-1} < \tilde{Y}_i \le \theta_r$, $r \in \{1, \dots, K\}$, where $-\infty \equiv \theta_0 < \theta_1 < \cdots < \theta_{K-1} < \theta_K \equiv \infty$. Let π_{ir} be the probability that observation i falls in category r, then the cumulative link model (McCullagh 1980) is $P(Y_i \le r) = P(\beta_0 + \boldsymbol{x}_i^T\boldsymbol{\beta} + \epsilon_i \le \theta_r) = F(\theta_r - \beta_0 - \boldsymbol{x}_i^T\boldsymbol{\beta}) = \pi_{ir} + \cdots + \pi_{ir}$. Typical choices for F are normal and logistic distributions.

To create a bivariate ordinal regression model, two ordinal outcomes, each following a univariate cumulative link model marginally, were linked with a joint error distribution, i.e.

$$Y_{ij} = r_j \text{ iff } \theta_{j,r_j-1} < \tilde{Y}_{ij} \le \theta_{j,r_j}, r_j \in \{1, \dots, K_j\},$$

where

$$-\infty \equiv \theta_{j,0} < \theta_{j,1} < \cdots < \theta_{j,K_j-1} < \theta_{j,K_j} \equiv \infty$$
$$\tilde{Y}_{ij} = \beta_{j0} + \boldsymbol{x}_{ij}^T\boldsymbol{\beta}_j + \epsilon_{ij}$$

The link function can be customized based on distribution assumptions, with typical choices between multivariate probit (i.e. multivariate normal error) and multivariate logit involving errors with t copula (O'Brien and Dunson 2004).

Varin, Reid, and Firth (2011) provided model estimation using pseudo-likelihood by aggregating likelihoods from marginal distributions. An R package 'mvord' is available for implementing composite likelihood in estimating probit and logit models for multivariate ordinal outcomes.

Simulation Studies

Simulation Setup:

- **Explanatory variables**: $LAUC \sim N(8.55,1)$; $BSALT \sim Gamma(3.5,0.05)$; $BSBIL \sim Gamma(20,2)$
- **ALT Elevation**: $\tilde{Y}_{i1} = \beta_{10} + \boldsymbol{x}_{i1}^T\boldsymbol{\beta_1} + \epsilon_{i1}$, $Y_{i1} = \text{G0} \le ULN < \text{G1} \le 3 \times ULN < \text{G2} \le 5 \times ULN < \text{G3} \le 20 \times ULN < \text{G4}$ $(ULN = 43\ U/L)$
- **TBL Elevation**: $\tilde{Y}_{i2} = \beta_{20} + \boldsymbol{x}_{i2}^T\boldsymbol{\beta_2} + \epsilon_{i2}$, $Y_{i2} = \text{G0} \le ULN < \text{G1} \le 1.5 \times ULN < \text{G2} \le 3 \times ULN < \text{G3} \le 10 \times ULN < \text{G4}$ $(ULN = 20.52\ \mu mol/L)$
- **Variance and Correlation**: $\sigma_1 = 10, \sigma_2 = 20, \rho = 0.3$
- **Binary Model**: $\pi_1 = \frac{1}{1+exp(7-\omega_1)}$, $\pi_2 = \frac{1}{1+exp(13-\omega_2)}$, $\varphi = 1.2,\ 3,\ 10$
- Sample Size: $n = 1000$; Number of Iteration: $m = 1000$

Simulation Result (Binary Outcomes):

	φ	*m* /*uni*	LAUC1 (0.4)	BSALT1 (0.005)	LAUC2 (0.8)	BSBIL2 (0.17)	LAUC	BSALT	BSBIL
Mean (Sd)	1.2	1000 /657	0.4011 (0.1639)	0.0045 (0.0040)	0.8052 (0.2740)	0.1674 (0.1116)	**1.9466 (5.7156)**	**-0.0052 (0.1636)**	**0.3593 (2.8183)**
	3	1000 /912	0.4033 (0.1662)	0.0045 (0.0042)	0.8155 (0.2676)	0.1673 (0.1008)	**2.1577 (7.3569)**	**-0.0156 (0.1755)**	**0.1396 (2.0627)**
	10	1000 /994	0.4027 (0.1689)	0.0046 (0.0040)	0.8320 (0.2748)	0.1663 (0.1074)	**1.2140 (2.4118)**	**-0.0014 (0.0304)**	**0.1052 (0.5528)**

	φ	AUC	π_1	π_2	π_{00}	π_{10}	π_{01}	π_{11}	π_{11} Univariate
Pred (Obs)	1.2	1x	0.0415 (0.0416)	0.0168 (0.0167)	0.9428 (0.9428)	0.0404 (0.0405)	0.0157 (0.0156)	0.0011 (0.0011)	0.0016 (0.0011)
		5x	0.0771 (0.0758)	0.0580 (0.0557)	0.8711 (0.8749)	0.0709 (0.0694)	0.0518 (0.0493)	**0.0062 (0.0063)**	**0.0166 (0.0063)**
	3	1x	0.0423 (0.0422)	0.0170 (0.0170)	0.9431 (0.9432)	0.0399 (0.0398)	0.0146 (0.0146)	0.0024 (0.0024)	0.0026 (0.0024)
		5x	0.0788 (0.0769)	0.0598 (0.0568)	0.8738 (0.8784)	0.0664 (0.0648)	0.0474 (0.0447)	**0.0124 (0.0121)**	**0.0211 (0.0121)**
	10	1x	0.0410 (0.0410)	0.0165 (0.0163)	0.9477 (0.9477)	0.0359 (0.0360)	0.0113 (0.0112)	0.0052 (0.0051)	0.0052 (0.0051)
		5x	0.0766 (0.0748)	0.0590 (0.0546)	0.8866 (0.8920)	0.0543 (0.0534)	0.0368 (0.0331)	**0.0222 (0.0214)**	**0.0289 (0.0214)**

Compared to a univariate logistic model for the joint outcome (ALT & TBL ≥ G2), a bivariate logistic model not only is more likely to converge and capture the important predictors, but also provides less biased and more efficient (i.e. smaller RMSEs, data not shown) model predictions.

Simulation Result (Ordinal Outcomes with Proportional Odds):

Observed		TBL Elevation <G2	TBL Elevation ≥G2	TBL Elevation Total
ALT Elevation	<G2	0.504	0.408	0.913
	≥G2	0.038	0.049	0.087
	Total	0.543	0.457	1.000

Ordinal Error Mean		TBL Elevation <G2	TBL Elevation ≥G2
ALT Elevation	<G2	-0.00013	0.00021
	≥G2	0.00013	-0.00022

Binary Error Mean		TBL Elevation <G2	TBL Elevation ≥G2
ALT Elevation	<G2	-0.00018	0.00029
	≥G2	0.00017	-0.00028

Observed		TBL Elevation <G3	TBL Elevation ≥G3	TBL Elevation Total
ALT Elevation	<G3	0.918	0.061	0.979
	≥G3	0.020	0.001	0.021
	Total	0.938	0.062	1.000

Ordinal Error Mean		TBL Elevation <G3	TBL Elevation ≥G3
ALT Elevation	<G3	0.00000	-0.00007
	≥G3	-0.00002	0.00008

Binary Error Mean		TBL Elevation <G3	TBL Elevation ≥G3
ALT Elevation	<G3	NA	NA
	≥G3	NA	NA

Simulation Result (Ordinal Outcomes with Non-Proportional Odds):

Observed		TBL Elevation <G2	TBL Elevation ≥G2	TBL Elevation Total
ALT Elevation	<G2	0.682	0.258	0.940
	≥G2	0.041	0.019	0.060
	Total	0.723	0.277	1.000

Ordinal Error Mean		TBL Elevation <G2	TBL Elevation ≥G2
ALT Elevation	<G2	0.00130	-0.00118
	≥G2	-0.00032	0.00020

Binary Error Mean		TBL Elevation <G2	TBL Elevation ≥G2
ALT Elevation	<G2	0.00011	-0.00014
	≥G2	0.00002	0.00002

Observed		TBL Elevation <G3	TBL Elevation ≥G3	TBL Elevation Total
ALT Elevation	<G3	0.959	0.025	0.984
	≥G3	0.015	0.000	0.016
	Total	0.975	0.026	1.000

Ordinal Error Mean		TBL Elevation <G3	TBL Elevation ≥G3
ALT Elevation	<G3	-0.00045	0.00044
	≥G3	0.00003	-0.00002

Binary Error Mean		TBL Elevation <G3	TBL Elevation ≥G3
ALT Elevation	<G3	NA	NA
	≥G3	NA	NA

When the proportional odds assumption is reasonable, a bivariate ordinal model not only is more likely to converge (especially in cases where the binary events are rare), but also provides less biased model predictions.

Application to A Real Case Exposure-Safety Analysis

Observed ALT and TBL elevations in Product A global studies

Laboratory Abnormalities	Treatment	CTCAE Grade, N (%) Grade 1	Grade 2	Grade 3	Grade 4	Total
Post-nadir ALT elevation	Active (N = 2560)	109 (4.3%)	9 (0.4%)	3 (0.1%)	0 (0%)	121 (4.7%)
	Placebo (N = 100)	13 (13%)	9 (9%)	3 (3%)	0 (0%)	25 (25%)
Post-baseline total bilirubin elevation	Active (N = 2560)	172 (6.7%)	52 (2.0%)	9 (0.4%)	0 (0%)	233 (9.1%)
	Placebo (N = 100)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	4 (4%)

2 subjects had ALT & TBL ≥ G2

Exposure-safety analyses were originally performed using univariate logistic regression models individually on ALT or TBL ≥ G2 against Product A exposure. Predictions were then made for ALT and TBL rates under 2- and 5-fold Product A exposures.

	----- Ordinal Model ----- ALT≥G2 %	TBL≥G2 %	ALT≥G2 & TBL≥G2 %	----- Binary Model ----- ALT≥G2 %	TBL≥G2 %	ALT≥G2 & TBL≥G2 %
1x Product A AUC	0.453	2.46	0.0376	0.469	2.39	0.0677
2x Product A AUC	0.614	3.83	0.0707	0.607	3.73	0.124
5x Product A AUC	0.904	6.67	0.155	1.10	10.1	0.446

Bivariate ordinal and binary models were used to fit the same data and predict ALT and TBL ≥ G2 under different Product A exposure assumptions. Predictions for individual outcomes from the bivariate models were in-line with those from the univariate binary model. But the bivariate models were able to provide predictions of simultaneous ≥ G2 ALT and TBL elevations. In addition, where events are rare (e.g. joint outcome rate < 1 % as seen in the simulation studies) , the ordinal model was able to converge and provide predictions (assuming proportional-odds is reasonable), while the binary model would not converge.

Conclusion

Bivariate logistic and ordinal regression models not only account for the correlation between the two clinical outcomes of interest, namely ALT and TBL elevations, but also provide unbiased and efficient predictions of the joint outcome of simultaneous ALT and TBL elevation, which is one of the key criteria in DILI assessments.

Disclosures
This poster was sponsored by AbbVie. AbbVie contributed to the design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are employees of AbbVie Inc. and may own AbbVie stock.

Reference

1. Lee, W. (2013) Drug-induced acute liver failure. *Clin Liver Dis*. 17(4):1–15.
2. Reuben, A. (2004) Hy's Law, *Hepatology*, 39(2):574-8.
3. Temple, R. (2001) Hepatotoxicity Through the Years: Impact on the FDA, presented 2/12/2001.
4. Palmgren, J. (1989) Regression Models for Bivariate Binary Responses. UW Biostatistics Working Paper Series.
5. McCullagh P (1980). "Regression Models for Ordinal Data." *Journal of the Royal Statistical Society. Series B (Methodological)*, pp. 109–142.
6. O'Brien SM, Dunson DB (2004). "Bayesian Multivariate Logistic Regression." *Biometrics*, **60**(3), 739–746.
7. Varin C, Reid N, Firth D (2011). "An Overview of Composite Likelihood Methods." *Statistica Sinica*, 21(1), 5–42.