PI-82

Comparison of Censored Regression (CR) vs Standard Regression (SR) Analyses for Modeling Relationships Between Minimum Inhibitory Concentrations (MIC) and Patient- and Institution-Specific Variables

JP Hammel,[1] SM Bhavnani,[1,3] PG Ambrose,[1] RN Jones,[2] A Forrest,[3] MR Piedmonte[1]

[1]Cognigen Corporation, Buffalo, NY, [2]The JONES Group/JMI Laboratories, North Liberty, IA, and [3]SUNY at Buffalo, Buffalo, NY

For more information, please contact:
Jeffrey P. Hammel, M.S.
Cognigen Corporation
395 Youngs Road, Buffalo, NY, 14221
jeffrey.hammel@cognigencorp.com
716-633-3463, ext. 267

ABSTRACT

Background. A challenge in the treatment of resistant bacteria has been the difficulty in identifying patients likely to be infected with such pathogens. Novel methods may be applied to surveillance data to determine patient- and institution-specific factors predictive of increased MIC. The censored nature of some MIC values (e.g. MIC ≤ 0.5 or MIC > 8) is a difficulty for SR analyses. Simulations were performed to compare CR versus SR in which MICs of the form MIC ≤ 2^L or MIC > 2^R (left- or right-censored) were replaced with specific values or excluded.

Methods. Using a model relating MIC of piperacillin-tazobactam for *Enterobacter* species to categories of patient age and hospital bed size, 200 simulations of 500 isolates were performed. Various MIC censoring patterns were imposed using 26 (L, R) pairs. Data were fit with CR, and with SR using 3 procedures: (1) censored MIC excluded, (2) censored MIC replaced by 2^L or 2^R, and (3) censored MIC replaced by 2^{L-1} or 2^{R+1}.

Results. Censoring for the 26 pairs ranged from 7-86%. Using CR, average deviations from true parameter values were less than 0.10 $\log_2$ (mg/L) for all parameters and all (L,R) pairs, whereas for 7 of 8 parameters the average deviations were less than 0.10 $\log_2$ (mg/L) for less than 31% of (L,R) pairs. Coverage percentage of 2 standard error (SE) confidence intervals was as low as 0% for all SR methods, but not below 91.5% for CR.

Conclusions. When modeling censored outcomes such as MIC, CR is preferable to SR analyses to avoid biased parameter estimates.

INTRODUCTION

- A challenge in the treatment of resistant bacteria has been the difficulty in identifying patients likely to be infected with such pathogens. To address such questions, the Antimicrobial Resistance Rate Epidemiology Study Team (ARREST) was established and represents an integration of microbiological surveillance data and novel statistical and analytic techniques.
- Using data from the SENTRY Antimicrobial Resistance Program, multiple regression analyses were conducted to determine independent variables predictive of minimum inhibitory concentrations (MIC) in hospitalized patients with clinical isolates for several microorganism-antimicrobial agent pairs (Bhavnani SM, Hammel JP, et al., 40th IDSA Meeting, Chicago, IL, 2002; Bhavnani SM, Hammel JP, et al., Clin Infect Dis 2003, in press).
- For a given organism-agent pair, observed MICs were of the form 2^X for integer values of X, or of the form MIC ≤ 2^L or MIC > 2^R (left- or right-censored) for an integer-valued (L,R) censoring pair. For example, MICs with a censoring pair of (-1,3) had possible observed values of ≤ 0.5, 1, 2, 4, 8, and > 8 mg/L.
- Censoring was as frequent as 90% of individual samples, often with high imbalance between left and right censoring.
- Given the censored nature of MICs and the limited capability of standard regression (SR) methods to accommodate such data, a censored regression (CR) analysis capable of accounting for censored outcomes was used to model the above-described data.
- In order to examine the impact of using SR methods in comparison to CR on parameter estimating performance, simulations based upon a final model for piperacillin/tazobactam (Pip/Taz) MICs for *Enterobacter* species (ES) were carried out.

OBJECTIVE

The objective of this simulation study was to compare the parameter estimating performance of CR with SR methods where the censored MICs were either excluded or modified.

METHODS

Data Simulation

- The simulation model was an approximation of the final model obtained in the analysis of Pip/Taz MICs against ES, a model based on 356 blood isolates collected from 33 hospitals within the United States and Canada between 1997 and 2001 (Clin Infect Dis 2003, in press). As shown below, important independent variables demonstrating a relationship with MIC included categories of patient age and hospital bed size.
- A total of 200 datasets, each including 500 observed isolates, were simulated according to the following model:

$\log_2$(MIC) = intercept + age effect + hospital bed size effect + random error

intercept =	0.8	parameter 1
age effect =	0.8	parameter 2, if age ≤ 18
	1.2	parameter 3, if 41 ≤ age ≤ 60
	0.7	parameter 4, if 61 ≤ age ≤ 75
	0.6	parameter 5, if age > 75
hospital bed size effect =	-1.1	parameter 6, if 401 ≤ bed size ≤ 900
	-0.1	parameter 7, if 901 ≤ bed size ≤ 1350
	1.1	parameter 8, if bed size > 1350

Random errors were independent and normally distributed with mean 0 and standard deviation of 1.9 $\log_2$ (mg/L).

- $\log_2$(MIC) values were rounded to the nearest integer to create MIC data of the same discrete, yet quantitative, nature as collected MIC data.
- The frequencies of isolates within the age and bed size categories were randomly chosen and designed to approximate the frequencies observed in the analysis of Pip/Taz against ES.
- Twenty-six (L,R) censoring pairs were applied to MIC for each simulated dataset to provide a variety of percent total sample censored and different amounts of censoring balance between left- and right-censored MICs.

Regression Modeling

- Three SR methods and CR were used to estimate the model parameters for each of the simulated datasets and each (L,R) censoring pair.
- SR methods applied consisted of the following:
  1) **Exclude Observations**: least squares (LS) multiple regression with censored MICs excluded from the analyses
  2) **Ignore Inequality**: LS multiple regression with censored MICs of the form MIC ≤ 2^L or MIC > 2^R replaced by the censoring boundaries 2^L or 2^R
  3) **Adjust by 1**: LS multiple regression with censored MICs replaced by 2^{L-1} or 2^{R+1}
- The 3 SR methods were each designed to provide an outcome variable with numerical values suitable for LS multiple regression modeling.
- Of the SR methods, only adjusting by 1 attempted to account for the fact that the unknown true values of censored observations fell outside the censoring boundaries, on average, though the choice of an adjustment of +/- 1 was arbitrary.
- CR used maximum likelihood estimation, and incorporated censored observations into the estimation procedure using tail probabilities of the normal distribution.

Evaluation of Parameter Estimation Performance

- For each regression method and each parameter, the parameter estimate averages (PEAV) over the simulated datasets were computed for each (L,R) censoring pair. PEAV were plotted against the average percent of total sample censored and the average censoring balance (% left versus right).
- Performance of the methods was compared using the average absolute deviation between PEAV and the true parameter value, and using the percent of (L,R) pairs for which PEAV was within 0.10 $\log_2$ (mg/L) of the true value.
- Approximate 95% confidence intervals (CI) based on 2 standard error (2SE) differences from the parameter estimate were computed for each parameter. The percent of CIs, or coverage percentage, that contained the true parameter value was computed for each (L,R) pair.

RESULTS

- Averaged across the 200 simulated datasets, the percent of the total MIC sample censored ranged from 7-86% for the 26 (L,R) pairs, and MIC censoring balance ranged from 0.9-92% left-censored (Figure 1).

Figure 1: Simulated MIC Histogram with Censoring Conditions for the 26 (L,R) Censoring Pairs

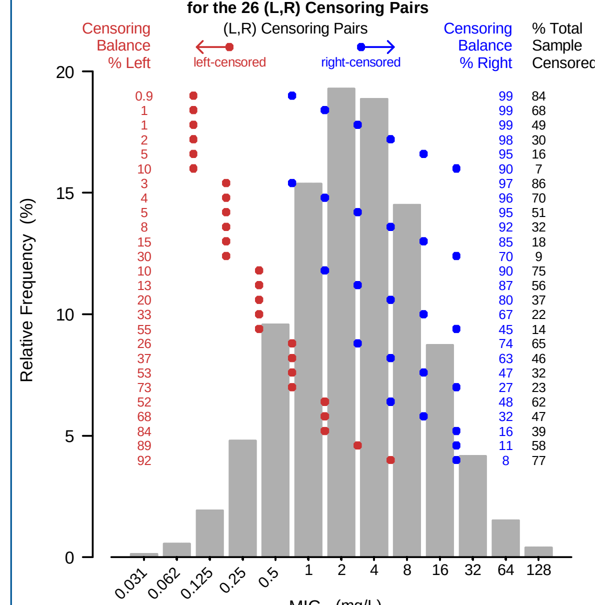
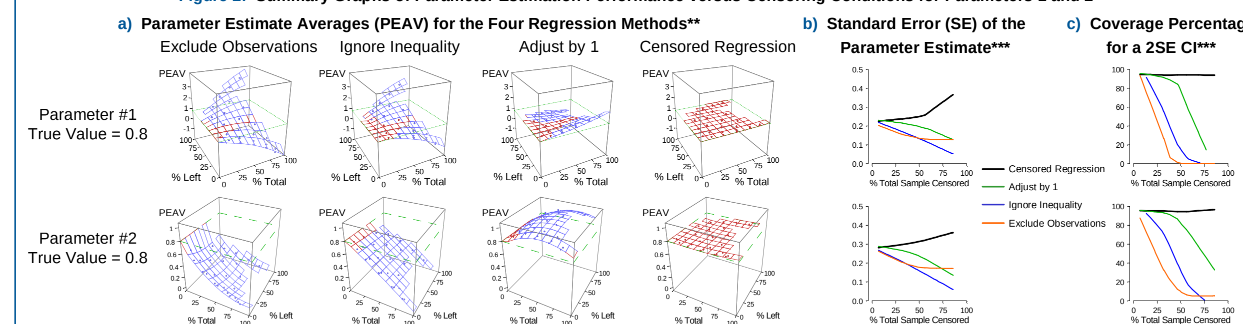


Figure 2: Summary Graphs of Parameter Estimation Performance versus Censoring Conditions for Parameters 1 and 2*



* Graphs for parameters 3-8 appeared similar to those of parameter 2, though in the opposite vertical direction for parameters 6 and 7 whose true values were negative.
** For display purposes, a surface was fit to the PEAV by a 2-order regression equation. Portions of the surface and PEAV within 0.10 $\log_2$ (mg/L) of the true value are displayed in red.
*** For display purposes, smoothed curves were fit to the SEs and coverage percentages.

Table 1: Summary Statistics of Parameter Estimate Averages (PEAV) and 2SE Confidence Intervals (CI) for All Parameters

Parameter		Exclude Observations		Ignore Inequality		Adjust by 1		Censored Regression		Range of Coverage Percentage for 2SE CIs***			
#	True Value	Average Deviation*	% within 0.10**	Average Deviation*	% within 0.10**	Average Deviation*	% within 0.10**	Average Deviation*	% within 0.10**	Exclude Observations	Ignore Inequality	Adjust by 1	Censored Regression
1	0.8	0.87	7.7	0.51	26.9	0.29	30.8	0.011	100	0-93.5	0-95.0	0-95.5	93.0-95.5
2	0.8	0.56	0	0.35	7.7	0.17	11.5	0.007	100	0-90.0	0-94.0	0-95.5	92.5-96.6
3	1.2	0.84	0	0.54	3.8	0.23	7.7	0.023	100	0-75.5	0-88.5	0-95.0	91.5-96.0
4	0.7	0.48	0	0.31	11.5	0.13	26.9	0.018	100	0-90.5	0-95.0	10.2-96.0	92.5-98.3
5	0.6	0.41	0	0.25	19.2	0.15	11.5	0.022	100	4-93.5	0-95.5	36.4-96.0	94.0-97.7
6	-1.1	0.75	0	0.46	7.7	0.26	3.8	0.017	100	0-84.5	0-93.5	0-95.0	94.0-97.5
7	-0.1	0.06	96.2	0.04	100	0.04	100	0.015	100	81.0-98.0	47.7-97.5	88.1-97.5	95.5-97.0
8	1.1	0.80	0	0.55	0	0.22	7.7	0.007	100	0-86.5	0-95.5	0-98.5	93.0-98.5

* Deviations (in absolute value) between the PEAV and the true value, averaged over the results for the 26 (L,R) pairs.
** Among the 26 (L,R) pairs, the percentage of PEAV that are within 0.10 $\log_2$ (mg/L) of the true value.
*** Among the 26 (L,R) pairs, the range in the percentage of 2SE (approx. 95%) CIs that included the true value.

- The model intercept parameter was estimated accurately using SR methods when the percent total MIC sample censored was near 0% or when the censoring was roughly evenly split between left- and right-censoring. CR provided an accurate estimate of the model intercept for all censoring results (Figure 2a).
- Using CR, PEAV was within 0.10 $\log_2$ (mg/L) of the true parameter value for all 8 parameters and all 26 (L,R) pairs. Using the SR methods, PEAV was within 0.10 $\log_2$ (mg/L) for less than 31% of the 26 (L,R) pairs for all parameters except #7 (Table 1, Figure 2a).
- For the 26 (L,R) pairs, the average absolute deviation between PEAV and the true parameter value was less than 0.025 $\log_2$ (mg/L) for all 8 parameters using CR. The SR methods yielded average absolute deviations ranging from 0.04-0.87 $\log_2$ (mg/L) (Table 1, Figure 2a).
- CR produced larger standard errors (SE) for the parameter estimates in comparison to SR methods, and CR was the only method for which SE increased as the percent of the total MIC sample censored increased (Figure 2b).
- For the 26 (L,R) pairs, the coverage percentage of the 2SE CIs ranged from 91.5-98.5% of the 200 simulated datasets. All SR methods yielded 2SE CIs with coverage percentage as low as 0% for some parameters and some (L,R) pairs (Table 1, Figure 2c).

CONCLUSIONS

- With respect to deviations from the true value and CI coverage, CR demonstrated the best estimating performance across the censoring conditions for all 8 parameters while the SR method of excluding censored MICs demonstrated the worst performance.
- SR methods could not consistently estimate the parameters accurately across all the censoring conditions. Performance was unacceptable for all parameters, though it improved for parameters with magnitudes closer to zero.
- CIs based on CR exhibited accurate coverage probabilities near 95%, but CIs based on SR methods displayed very poor coverage probability due to bias and underestimation of parameter SEs.
- The simulations demonstrated that CR was preferable to SR methods to avoid bias in parameter estimates and to ensure the proper coverage probability for CIs.
- The application of statistical techniques such as CR for censored outcomes such as MIC will allow for a more effective use of surveillance data in order to better understand factors predictive of antimicrobial resistance and to identify patient and institution profiles likely to be infected with pathogens with decreased susceptibility.