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STATISTICAL METHODS FOR DETERMINING RISK FACTORS OF CHRONIC OTITIS MEDIA WITH EFFUSION

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SUMMARY

We use logistic regression with paired Bernouilli outcomes to analyse data on subjects who have either one or two organs (e.g. ears) each of which may develop disease. In this model, subject-specific covariates are related to the probability of developing disease. The proposed method is applied to determine risk factors for chronic otitis media with effusion.

1. INTRODUCTION

Approximately 70 per cent of all children have at least one otitis media episode before their fifth birthday.[1-3] Of these children, 10 to 20 per cent experience chronic otitis media with effusion (chronic OME), i.e. middle ear effusion persisting for at least 8 continuous weeks.[1-3] Recurrence and chronicity of OME appear to have an adverse effect on speech, language and cognitive development during early childhood, presumably caused by fluctuating hearing loss.[4-7] Moreover intractable pathology, such as granulation tissue and cholesteatoma, develops in the middle ear space as sequelae of chronic OME.[8-9] Factors that predict chronic OME could be used by clinicians to distinguish between high-risk children with OME who might benefit from early, aggressive intervention to prevent sequelae, and children whose OME would be likely to resolve without treatment.

Many studies have been conducted to examine factors associated with chronic OME.[2,10-14] However, the results of these studies are difficult to interpret because many lacked defined criteria for cases or for diagnosis of chronic OME, and others enrolled only a small number of subjects. Our investigation was undertaken to identify predictors for chronic OME among children with a significant history of otitis media using standard diagnostic criteria and trained observers. This paper presents proper statistical methods for analysis of these data, taking into account the dependence between the responses of the two ears of the same patient.

2. STUDY DESIGN

Between January 1982 and September 1984 a controlled clinical trial was conducted at the Pediatric Clinics of the Park Nicollet Medical Center (St. Louis Park, Minnesota) to compare three medical intervention strategies for chronic OME. This paper is concerned with the pre-randomization phase of the study in which 386 children, aged 10 months to 8 years, were enrolled. These subjects met the following eligibility criteria: presence of OME for two to four weeks before

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enrolment, three or more episodes of physician-documented otitis media during the preceding 18 months, and absence of tympanostomy tubes. Children with OME were enrolled if they had an appropriately treated episode of acute otitis media (AOM), or an episode of OME documented during the 4 weeks before enrolment. Exclusion criteria included: presence of significant health problems; allergy to penicillin, sulphonamides or non-steroidal anti-inflammatory drugs; and delayed childhood immunizations. On average these children had more severe ear infection problems than would be seen in a typical general practice.

Children meeting the study criteria, and for whom consent to the study was obtained, were examined for middle ear effusion at enrolment and at 3 and 6 weeks after enrolment using the Cantekin[15] algorithm, which combines pneumatic otoscopy and impedance audiometry findings. Additional data were gathered by interview and medical record review on a number of demographic and otitis-media-related factors at the time of enrolment. These factors included age, sex, race, age at first symptomatic otitis media episode, number of prior physician-documented otitis media episodes, duration of effusion before enrolment (between 2 and 4 weeks), type of otitis media episode before enrolment (acute or asymptomatic), birth weight, neonatal respiratory disease, physician-diagnosed respiratory allergy, day care attendance, parent-reported hearing difficulty, parent-reported language disability, family history of frequent otitis media or hearing loss, and history of bottle propping (a feeding practice whereby babies are put to bed with a bottle).

As outcome, an ear was classified as having chronic OME if middle ear effusion persisted at both the 3 and 6 week visits, or if AOM developed without resolution of middle ear effusion during the 6 week observation. Because subjects had OME for at least 2 weeks at enrolment, those with chronic OME had persistent effusion for at least 8 weeks (between 8 and 10 weeks).

3. STATISTICAL METHODS

In these data each child (or main unit) has one or two subunits (ears affected by OME), and each subunit has a binary response (1 if the outcome is chronic OME and 0 if OME resolves). Consider a child with two affected ears (bilateral cases). Let Z_{ij} denote the binary response from the jth ear ($j = 1, 2$) of the ith such child. A number of probability models have been proposed.[16-18] Using the above notation, we assume the following model:

$$Pr(Z_{ij} = 1) = p_i; \quad 0 \leqslant p_i \leqslant 1$$

$$Pr(Z_{i+} = x) = \begin{cases} \theta(1 - p_i) + (1 - \theta)(1 - p_i)^2 & \text{if } x = 0 \\ 2(1 - \theta)p_i(1 - p_i) & \text{if } x = 1 \\ \theta p_i + (1 - \theta)p_i^2 & \text{if } x = 2 \end{cases}$$

where Z_{i+} represents the number of ears developing chronic OME in the ith subject. The rationale for this model is explained in one of two ways.

The first is that it is obvious from the formulation of $Pr(Z_{i+} = x)$ that if $\theta = 0$ then the two ears respond independently, while if $\theta = 1$ the outcomes in the two ears are completely dependent. Thus θ can be regarded as a 'mixture' parameter in a model where $100(1 - \theta)$ per cent of the population produce independent responses and 100θ per cent produce identical responses from the left and right ears.

The second is that, since $\text{cov}[Z_{i1}, Z_{i2}] = \theta p_i(1 - p_i)$, θ can be regarded as the correlation coefficient, a measure of within-subject agreement. It should be noted that θ may be negative because, in either ophthalmology or otolaryngology, it is conceivable that an insult to one organ (eye or ear) may result in greater resiliency or better health in the other. In these cases, θ does not

represent a mixture parameter; on the other hand, the interpretation of θ as the correlation coefficient between Z_{i1} and Z_{i2} always holds.

In applying this model to solve our risk determination problem, the unknown parameter θ will be assumed constant over subjects, and a logistic model will be assumed to relate p_i to a vector of covariates y_i:[19]

$$\ln \frac{p_i}{1-p_i} = \beta^{\mathrm{T}} y_i,$$

where β is a vector of regression coefficients. Thus in general

$$q_{ix} = Pr[Z_{i+} = x]$$

is a function of θ and the regression coefficients β.

In addition to our formulation, other models have been proposed, including the beta-binomial regression model.[17] Our model above is in the form of a multinomial distribution with three categories. Rosner's R-model,[16] of which the beta-binomial model is an extension, however, is expressed in terms of the marginal and conditional probabilities $Pr(Z_{ij} = 1) = p_i$ $(0 \leqslant p_i \leqslant 1)$ and $Pr(Z_{i2} = 1 \mid Z_{i1} = 1) = Rp_i$. Dallal[20] comments that, because of its parameterization, Rosner's R-model does not fit well when the correlation between ear responses is high because the constant R is dependent on the marginal probability p_i. For example, the same R value, say 2·0, may fit well in cases where $p_i < 0{\cdot}5$ but not when $p_i > 0{\cdot}5$. This problem is avoided with the parameterization in our multinomial model. The beta-binomial model[17] is a powerful approach because it can incorporate ear-specific covariates. In the specific example we discuss, only person-specific covariates are available; our model is suitable and has the advantage that it is easy to incorporate unilateral cases.

Bilateral cases

We first consider the cases which have two subunits available for data analysis; in our example, these are the children who entered the study with bilateral disease. Let the outcome indices be $(\lambda_{i0}, \lambda_{i1}, \lambda_{i2})$, where

$$\lambda_{ix} = \begin{cases} 1 & \text{if } Z_{i+} = x \\ 0 & \text{otherwise} \end{cases}$$

$$\sum_{x=0}^{2} \lambda_{ix} = 1.$$

The likelihood function corresponding to this bilateral subgroup is then

$$L_{\mathrm{B}}(\theta, \beta) = \prod_{i=1}^{n_{\mathrm{B}}} \prod_{x=0}^{2} q_{ix}^{\lambda_{ix}},$$

where n_{B} is the number of bilateral cases.

Unilateral cases

In our study, in addition to children who entered with bilateral disease, there were those who entered with unilateral disease. For each of the unilateral cases, the outcome in only the diseased ear was considered. Let δ_j be the indicator showing outcome at the end of the study period, i.e.

$$\delta_j = \begin{cases} 1 & \text{if chronic OME develops} \\ 0 & \text{if OME resolves.} \end{cases}$$

With an additional indicator representing laterality added to the list of covariates, the likelihood function becomes

$$L(\theta, \beta) = \left\{ \prod_{i=1}^{n_B} \prod_{x=0}^{2} q_{ix}^{\lambda_{ix}} \right\} \left\{ \prod_{j=n_B+1}^{n_B+n_U} p_j^{\delta_j} (1 - p_j)^{1-\delta_j} \right\},$$

where n_U is the number of unilateral cases and $n = n_U + n_B$ is the sample size.

Since no closed-form expressions exist for parameter estimates, an iterative procedure such as the Newton–Raphson method must be employed. Our numerical implementation of an iterative process to obtain point estimates of parameters and their variances was performed using a FORTRAN program in conjunction with IMSL subroutines.[21] We incorporated two procedures in this implementation. First, the likelihood ratio method was used to construct a forward stepwise variable selection process (using entering probability $p < 0{\cdot}10$ according to the chi-square distribution with one degree of freedom). Second, in the final model, tests for a particular regression coefficient are based on the asymptotic normality of the maximum likelihood estimators, so that $Z = \hat{\beta}/\mathrm{SE}(\hat{\beta})$ is referred to the standard normal distribution to determine levels of significance (two-sided p-values). The function $\exp(\beta)$ has the usual odds-ratio interpretation, and 95 per cent confidence intervals for odds ratios are obtained from $\exp[\hat{\beta} \pm 1{\cdot}96\,\mathrm{SE}(\hat{\beta})]$.

The convergence of the iterative process using IMSL subroutine ZXMIN is quite slow. It has been our experience with this subroutine that the point estimates are very accurate, but the variances of the estimates are often less reliable unless the subroutine is used with a high number of digits of accuracy. Specification of high accuracy is the main source of slow convergence. The analysis could be somewhat accelerated if a smaller number of digits of accuracy, say 2 or 3, is specified in the stepwise variable selection process. This is appropriate if the main emphasis is on the likelihood ratio test and not on estimation. This approach could be combined with specifying a much higher number of digits of accuracy, say 5 or 6, for the final model so as to obtain more reliable values for standard errors and confidence intervals.

4. RESULTS AND DISCUSSION

Because of the complexity of the numerical implementation and its slow convergence, univariate analyses were used to screen for factors to be included in the stepwise variable selection process, the acceptance criterion being $p < 0{\cdot}10$. In this stage four variables were selected: bilaterality ($p = 0{\cdot}01$); duration of effusion before enrolment ($p = 0{\cdot}04$); type of otitis media episode before enrolment ($p = 0{\cdot}04$); and day care attendance ($p = 0{\cdot}09$). In the stepwise process, the type of otitis media episode was no longer significant because it was highly correlated with the duration of effusion. We also added to the model containing the three remaining variables, one at a time, the factors which were found not significant in the univariate analysis stage; however, no factors – including age – contributed significantly to the model. Thus the final model included only three risk factors:

(i) Bilateral effusion at enrolment: $p = 0{\cdot}01$, odds ratio = 1·45, 95 per cent confidence limits = (1·09, 1·92).
(ii) Duration of effusion before enrolment (dichotomized as less than or more than 2 weeks): $p = 0{\cdot}03$, odds ratio = 1·25 (1·02, 1·58)
(iii) Day care attendance: $p = 0{\cdot}06$, odds ratio = 1·16 (0·99, 1·36).

The within-subject correlation measure θ was estimated to be 0·59, with 95 per cent confidence limits (0·56, 0·62). In theory, this correlation coefficient θ can be modelled as a function of the

covariate vector; we did try this, considering one factor at a time, and obtained separate estimates of θ for strata with and without the factor under investigation, but no heterogeneity of θ was detected.

From a clinical point of view, the results of our analysis are not very satisfactory. As with other studies of otitis media, we are able to identify a number of risk factors but none is strong enough to base clinical decisions for preventing sequelae. Perhaps the only cases which might benefit from more aggressive intervention are those having all three factors found: children in daycare with bilateral effusion which lasted more than two weeks. In our study, 67 per cent of the 18 children with all three factors developed chronic OME in at least one ear as compared with 36 per cent of the 67 children who lacked all three risk factors.

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