Bias correction in the hierarchical likelihood approach to the analysis of multivariate survival data

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SUMMARY
Frailty models are useful for measuring unobserved heterogeneity in risk of failures across clusters, providing cluster-specific risk prediction. In a frailty model, the latent frailties shared by members within a cluster are assumed to act multiplicatively on the hazard function. In order to obtain parameter and frailty variate estimates, we consider the hierarchical likelihood (H-likelihood) approach (Ha, Lee and Song, 2001. Hierarchical-likelihood approach for frailty models. Biometrika 88, 233–243) in which the latent frailties are treated as “parameters” and estimated jointly with other parameters of interest. We find that the H-likelihood estimators perform well when the censoring rate is low, however, they are substantially biased when the censoring rate is moderate to high. In this paper, we propose a simple and easy-to-implement bias correction method for the H-likelihood estimators under a shared frailty model. We also extend the method to a multivariate frailty model, which incorporates complex dependence structure within clusters. We conduct an extensive simulation study and show that the proposed approach performs very well for censoring rates as high as 80%. We also illustrate the method with a breast cancer data set. Since the H-likelihood is the same as the penalized likelihood function, the proposed bias correction method is also applicable to the penalized likelihood estimators.

Keywords: Frailty model; Hierarchical likelihood; Multivariate survival; NPMLE; Penalized likelihood; Semiparameric.

1. INTRODUCTION
The frailty model has been widely used for analysis of clustered failure time data to account for potential correlation among failure times within a cluster. In this model, latent frailties, also called random effects, are assumed to be shared by all subjects within a cluster, and they act multiplicatively on the hazard function. In this case, the hazard function typically has 2 components: the nonparametric baseline hazard function, which is usually left unspecified, and the parametric risk function, which describes the effects

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of covariates on the hazard function. The mixed nonparametric and parametric components in a model is called semiparametric. To some extent, frailties that act on the hazard function may be viewed as latent covariates, like smoking and genotypic status of disease susceptibility genes. Because of their latency, a distribution for frailties needs to be assumed: Here, we assume a parametric distribution.

Estimation in the semiparametric frailty model has received much attention under various parametric frailty distributions, for example, the gamma distribution, the log-normal distribution, and the inverse Gaussian distribution (Hougaard, 2000 and references therein). A natural tool for estimating the parameters in the presence of latent variables is to use the expectation–maximization (EM) algorithm (Nielsen and others, 1992; Zeng and Lin, 2007). The parameters of interest are the regression coefficients in the risk function, the baseline hazard function, and the parameters in the frailty distribution. The EM algorithm yields nonparametric maximum likelihood estimators (NPMLEs) when the likelihood used in the M-step treats the cumulative baseline hazard function as an infinite dimensional parameter (Andersen and others, 1993). As in conventional maximum likelihood estimators, the NPMLEs are consistent and most efficient. Another approach is to use the innovation theorem to obtain the observed hazard function at time \( t \) conditional on all information up to time \( t \) (Gorfine and others, 2006, and references therein). In this approach, the unspecified baseline hazard function is estimated by a Nelson–Aalen type of estimator and then plugged in a pseudolikelihood function to yield estimators for the regression coefficients and the parameters in the frailty distribution. The estimators are consistent but not the most efficient because of the plug-in estimators of the cumulative hazard function. However, Gorfine and others (2006) found from an extensive simulation study that on a data set-by-data set basis, the correlation between these pseudolikelihood estimators and the NPMLEs was 0.95 or above. The advantage of this approach is that the variance estimators do not require inversion of a large matrix that includes jumps at all failure times as in the NPMLE estimation. In both approaches, the likelihood may have analytically intractable integrals. When there are multivariate frailties in the model, the multiple numerical integration can be time consuming and is generally not recommended (Breslow and Clayton, 1993).

All aforementioned approaches are focused on parameter estimation, thus the latent frailties are integrated out in order to obtain the parameter estimators. In contrast to these approaches, Ha and others (2001) proposed treating the latent frailties as “parameters” and jointly estimated them with regression coefficients and parameters in the frailty distribution. The approach is based on the hierarchical likelihood (H-likelihood) proposed by Lee and Nelder (1996) for a generalized linear mixed-effects model. By treating the frailties as parameters, this approach avoids integration of unobserved frailties over the frailty distribution. This property is particularly appealing when the frailty distribution is not a conjugate prior or when the complex dependence structure among clustered failure times requires one to assume multiple frailties. Moreover, frailties are also useful to predict cluster-specific failure time distributions such as in genetic counseling where family-specific risk is of keen interest. Because of these appealing properties, we conducted a simulation study and found that the H-likelihood estimators (Ha and others, 2001) for regression coefficients and parameters in the frailty distribution performed well when the censoring rate in the data was low (see Section 3). However, when the censoring rate was high, parameter estimates were substantially biased. This is probably because frailty variate estimators, which are estimated for each cluster, may suffer from information loss due to high censoring and unfortunately do not improve even if the number of clusters goes to infinity. Plugging these poorly estimated frailties into the likelihood can result in a substantial bias in estimates of regression coefficients and parameters in the frailty distribution.

In this paper, we propose a bias correction approach for the H-likelihood estimators (Ha and others, 2001). As described previously, in the H-likelihood, frailties are estimated directly and then plugged into the likelihood when estimating the parameters of interest. It is well known in the measurement error literature that when plugging the estimates of latent variables directly into a nonlinear model, the estimators of the regression coefficients are biased. Many methods have been proposed to correct this bias (see, e.g. Carroll and others, 2006). Among these, the regression calibration approach (Wang and others, 1997) has
been shown to be a simple yet effective approach in real applications. We extend this approach to the H-likelihood estimators and show that the proposed method reduces the bias substantially. In Section 2, we briefly review the H-likelihood and describe the bias correction approach under a shared frailty model. We then extend this method to a multivariate frailty model. Simulation studies were conducted to evaluate the performance of the proposed approach, and the results are given in Section 3. We illustrate the method with a real data set in Section 4 with some remarks in Section 5.

2. Models and estimation

2.1 The univariate frailty model

Consider \( n \) clusters of failure times, where the cluster is indexed by \( i = 1, \ldots, n \), the subject is indexed by \( j \) for \( j = 1, \ldots, m \), and \( m \) is the number of subjects in the \( i \)th cluster. For the \( j \)th subject in the \( i \)th cluster, let \( T_{ij} \) and \( C_{ij} \) be the failure time and censoring time, respectively. However, we only observe \( X_{ij} = T_{ij} \wedge C_{ij} \), the minimum of the failure time and the censoring time, and \( \delta_{ij} = I(T_{ij} \leq C_{ij}) \), the failure status indicator. In addition, we observe a vector of covariates \( Z_{ij} = (Z_{ij1}, \ldots, Z_{ijp})^T \), where superscript \( T \) indicates transpose. Clusters are allowed to have different sizes, which can be achieved by setting \( C_{ij} \) to 0 whenever the \( ij \)th subject is missing. Under the shared frailty model, a common frailty \( \exp(v_i) \) is assumed to be shared by all subjects in the \( i \)th cluster and the \( ij \)th individual hazard function follows an extended Cox proportional hazards model (Cox, 1972). Specifically, conditional on the frailty \( v_i \) and the covariates \( Z_{ij} \), the hazard function for the \( ij \)th subject is given by

\[
\lambda_{ij}(t | Z_i, v_i) = \lambda_0(t) e^{\beta^T Z_{ij} + v_i},
\]

where \( \lambda_0(t) \) is an unspecified baseline hazard function and \( \beta \) is a \( p \times 1 \) vector of regression coefficients associated with \( Z_{ij} \). Frailties \( v_i \)s are assumed to be independently and identically distributed (i.i.d.) according to a parametric distribution. In this paper, we consider the log-normal frailty model, that is, \( v_i \sim N(0, \sigma^2) \), and note that the proposed approach can be applied to other parametric distributions. We assume \( P(\sum_{j=1}^{m} \delta_{ij} \geq 2) > 0 \) to avoid unidentifiability of the model (Nielsen and others, 1992). In addition, we assume the following conditions:

1. Conditional on \( v_i \) and \( Z_i = (Z_{i1}, \ldots, Z_{im}) \), the censoring times for the cluster members are independent of the failure times and noninformative for \( v_i \) and all parameters of interest \( \{\beta, \sigma^2, \Lambda_0(\cdot)\} \). In addition, the frailty \( v_i \) is independent of \( Z_i \).

2. Conditional on \( v_i \) and \( Z_i \), the observational times and failure indicators of the cluster members are independent of each other, that is, \( f(X_{i1}, \delta_{i1}, \ldots, X_{im}, \delta_{im} | Z_i, v_i) = \prod_{j=1}^{m} f(X_{ij}, \delta_{ij} | Z_i, v_i) \).

3. Subject-specific covariates’ effect, that is, \( f(X_{ij}, \delta_{ij} | Z_i, v_i) = f(X_{ij}, \delta_{ij} | Z_{ij}, v_i) \).

2.2 A brief review of the H-likelihood estimators

In this section, we briefly describe the H-likelihood approach for frailty models. A unique aspect of the H-likelihood approach is that instead of integrating out the latent frailty variates when obtaining the parameter estimates, the frailty variates \( v = (v_1, \ldots, v_n)^T \) are treated as parameters and jointly estimated.
along with \( \{\beta, \sigma^2, \Lambda_0(\cdot)\} \). Specifically, under the assumptions (1)–(3), the log-H likelihood, denoted by \( h \), is defined by
\[
h = \sum_{i=1}^{n} \sum_{j=1}^{m} l_{ij}(\beta, \Lambda_0; X_{ij}, \delta_{ij}|Z_{ij}, v_i) + l_{2i}(\sigma^2; v_i).
\]
(2.2)

The first term in (2.2) is the summation of the log-likelihood function of observational times and disease indicators given frailty variates \( v_i \) and covariates \( Z_{ij} \) over all subjects with \( l_{ij}(\beta, \Lambda_0; X_{ij}, \delta_{ij}|Z_{ij}, v_i) = \delta_{ij}\{\log \lambda_0(X_{ij}) + \beta^T Z_{ij} + v_i\} - \Lambda_0(X_{ij})e^{\beta^T Z_{ij} + v_i} \), and \( l_{2i}(\sigma^2; v_i) \) is the logarithm of the density function of \( v_i \) with the parameter \( \sigma^2 \). Given \( v \) and \( \beta \), the nonparametric maximum H-likelihood estimator of the cumulative baseline hazard function \( \Lambda_0(t) \) can then be written as
\[
\hat{\Lambda}_0(t) = \sum_{k:X(k) \leq t} \frac{d(k)}{\sum_{ij \in R(X(k))} e^{\beta^T Z_{ij} + v_i}},
\]
(2.3)

where \( X(k) \) is the \( k \)-th smallest distinct failure time among the \( X_{ij} \)'s, \( R(X(k)) = \{ij: X_{ij} \geq X(k), i = 1, \ldots, n, j = 1, \ldots, m\} \) is the risk set at time \( X(k) \), and \( d(k) \) is the number of failures at \( X(k) \). This estimator has a similar form to the well-known Breslow estimator (Breslow, 1974) for the Cox proportional hazards model.

To estimate \( (\beta, v) \), Ha and others (2001) proposed to use the log-H profile likelihood \( h^* \) by plugging \( \Lambda_0(\cdot) = \hat{\Lambda}_0(\cdot) \) into \( h \) in (2.2). After some simple algebra, one can show that the log-H profile likelihood
\[
h^* \propto \sum_k \left[ \sum_{ij \in D(k)} \beta^T Z_{ij} + \sum_{ij \in D(k)} v_i - d(k) \log \sum_{ij \in R(X(k))} e^{\beta^T Z_{ij} + v_i} \right] + \sum_i l_{2i},
\]
(2.4)

where \( D(k) = \{ij: \delta_{ij} = 1, X_{ij} = X(k), i = 1, \ldots, n, j = 1, \ldots, m\} \) is the set of individuals who fail at \( X(k) \). Given \( \sigma^2 \), the maximum H-likelihood estimators of \( (\beta, v) \) can be obtained by using the Newton–Raphson algorithm to solve the following equations:
\[
\left( \begin{array}{c}
\hat{\beta}^{(i+1)} \\
\hat{\sigma}^{(i+1)}
\end{array} \right) = \left( \begin{array}{c}
\hat{\beta}^{(i)} \\
\hat{\sigma}^{(i)}
\end{array} \right) + J^{-1}(\hat{\beta},\hat{\sigma}) \frac{\partial h^*/\partial \beta}{\partial h^*/\partial \sigma} \bigg|_{(\hat{\beta},\hat{\sigma})=(\hat{\beta}^{(0)},\hat{\sigma}^{(0)})},
\]
(2.5)

where \( J = -\partial^2 h^*/\partial (\beta, v)^2 \) is the \((p + n) \times (p + n)\) observed information matrix. For the explicit forms of the first and second derivatives of \( h^* \), readers are referred to Appendix 3 in Ha and others (2001).

The frailty parameter estimator \( \hat{\sigma}^2 \) can be obtained by maximizing the log of the marginal likelihood, which integrates the H profile likelihood \( \exp(h^*) \) over frailty \( v \), that is, \( \log \int \exp(h^*) dv \). While the estimator is generally unbiased, this marginal likelihood is difficult to use because it involves intractable high dimension integration even for gamma frailty (Ha and others, 2010). Instead an approximation to the log marginal likelihood may be used. Lee and Nelder (2001) used the first-order Laplace approximation to the log marginal likelihood, \( \log \int \int \exp(h^*) dv d\beta \), assuming a uniform prior for \( (\beta; \sigma^2) \). Here, the integration over \( \beta \) is to account for the loss in degrees of freedom from estimating \( \beta \), an idea similar to the restricted maximum likelihood approach (Patterson and Thompson, 1971). The first-order Laplace approximation can be written as \( p_{\sigma^2}(h^*) = \left[ h^* - \frac{1}{2} \log([J/(2\pi)]) \right]_{(\hat{\beta},\hat{\sigma})=(\beta,\sigma^2)} \), where \( [J/(2\pi)] \) is the determinant of the matrix \( J/(2\pi) \). The variance estimator \( \tilde{\sigma}^2 \) can then be obtained by solving the equation \( \partial p_{\sigma^2}(h^*)/\partial \sigma^2 = 0 \), which is given by
\[
\tilde{\sigma}^2 = \frac{1}{n} \left( \sum_{i=1}^{n} \hat{\sigma}^2_i + \text{tr}(K) \right),
\]
(2.6)
follows a normal distribution with mean \( \tau \) is the same for both likelihoods. The main difference between the two methods arises in the estimation for \( \sigma^2 \). For the H-likelihood estimator \( \hat{\sigma}^2 \) in (2.6), \( K \) is the bottom right-hand corner of \( J^{-1} \), whereas for the penalized partial-likelihood \( K \) would first take the bottom right-hand corner of \( J \) and then the inverse (see Section 1 of the supplementary material available at Biostatistics online). Hence, even though the paper is focused on the H-likelihood, the same bias correction procedure also applies to the penalized likelihood. Second, the H-likelihood estimator \( \hat{v}_i \) and its variance are the first-order Laplace approximation to the conditional mean \( E(v_i|\text{obs}) \) and variance \( \text{var}(v_i|\text{obs}) \) of \( v_i \) given observed data (Booth and Hobert, 1998). The details of derivation are given in Section 2 of the supplementary material available at Biostatistics online. This connection suggests that the H-likelihood estimators may also be considered as the Laplace approximation to the EM algorithm for NPMLE.

The H-likelihood is useful in obtaining parameter estimates especially when the frailty variates are multivariate and the integration is analytically intractable since it does not use integration to deal with latent frailties. While it performs well when there is no or low censoring, it yields substantial bias when the censoring rate is high, a situation commonly encountered in family studies of chronic diseases. In the following section, we propose a method that borrows an idea from the measurement error literature to correct the bias in the H-likelihood estimators.

### 2.3 Bias correction in the H-likelihood estimators

There are many approaches for measurement error correction in survival analysis (Nakamura, 1992; Wang and others, 1997, and references therein). Among these, the regression calibration approach proposed by Wang and others (1997) is the simplest and has been shown very effective in a wide range of applications. We therefore propose to use the regression calibration approach to correct the bias in the H-likelihood estimators.

We make a working assumption that \( \hat{v}_i \) given \( v_i \) follows a normal distribution with mean \( v_i \) and variance \( \tau_i^2 \). This assumption is made based on a heuristic argument. That is, as the cluster size \( m \) becomes large, the estimators \((\hat{\beta} - \beta, \hat{\sigma} - \sigma)\) converge to a normal distribution with mean 0 and variance \( \tau^2 \), where \( \beta \) and \( \sigma \) are the true values, and \( \tau^2 \) is the limit of \( J^{-1} \) in the inverse of the observed information matrix in (2.5). Thus, it seems natural to use \( \tau_i^2 \), the \((p + i)\)th diagonal of \( \tau^2 \) to quantify the variance of \( \hat{v}_i \) given \( v_i \).

We want to point out that even though this assumption is made based on a large sample theory argument, our simulation results (Section 3) show that the proposed method works well even when the cluster size is as small as 2.

Now, since \( v_i \sim N(0, \sigma^2) \), \((v_i, \hat{v}_i)\) has a joint normal distribution, \( \left( \frac{v_i}{\hat{v}_i} \right) \sim N(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2 & \sigma^2 \\ \sigma^2 & \sigma^2 + \tau_i^2 \end{pmatrix}) \). We can then derive the conditional distribution \( v_i|\hat{v}_i \sim N(\zeta_i\hat{v}_i, \sigma^2(1 - \zeta_i)) \), where \( \zeta_i = \sigma^2/(\sigma^2 + \tau_i^2) \), and easily calculate the conditional mean of \( v_i \) or function of \( v_i \) given the estimated \( \hat{v}_i \). This becomes rather handy, as the terms involving the latent frailty variates in the log-H likelihood are in the form of either \( v_i \) or \( \exp(v_i) \). In the regression calibration approach, we would then replace \( v_i \) by \( E[v_i|\hat{v}_i] \) and \( \exp(v_i) \) by \( E[\exp(v_i)|\hat{v}_i] \). Under the normal distribution, both \( E[v_i|\hat{v}_i] \) and \( E[\exp(v_i)|\hat{v}_i] \) have explicit forms, which are \( \zeta_i\hat{v}_i \) and \( \exp(\zeta_i\hat{v}_i + \sigma^2(1 - \zeta_i)/2) \), respectively.

When \( \tau_i^2 = 0 \) or near 0, \( \zeta_i \approx 1 \). As a result, \( E[v_i|\hat{v}_i] \approx \hat{v}_i \) and \( E[\exp(v_i)|\hat{v}_i] \approx \exp(\hat{v}_i) \). In other words, if the variance of \( \hat{v}_i \) is small, the regression calibration approach is very similar to the original
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H-likelihood approach, which plugs in \( \hat{\tau}_i \) for each latent frailty variate \( v_i \). However, when \( \tau^2 \) is large, both \( E[v_i|\hat{\tau}_i] \) and \( E[\exp(v_i)|\hat{\tau}_i] \) are further away from the simple plug-in estimates, suggesting simple plug-in estimates may yield biases in the parameter estimates. Since the variance of \( \hat{\tau}_i \) is associated with the censoring rate, the bias correction is more pronounced when the censoring rate is high.

A summary of the proposed estimation procedures, using the H-likelihood estimators with bias correction, is provided in the following. In the \( t \)th iteration,

1. Estimate \((\hat{\beta}^{(t)}, \hat{\sigma}^{(t)})\) by solving (2.5) and update the information matrix \( J \) by plugging the estimates \((\hat{\beta}^{(t)}, \hat{\sigma}^{(t)})\) into \( J \).

2. Estimate \( \hat{\sigma}^{(t)} \) by replacing \( v_i \) with \( E[v_i|\hat{\tau}^{(t)}_i] = \hat{\tau}^{(t)}_i \) in (2.6), where \( \hat{\tau}^{(t)}_i = \hat{\sigma}^{(t-1)}(\hat{\tau}^{(t-1)}_i + \hat{\tau}^{(t)}_i) \). Here, \( \hat{\sigma}^{(t-1)} \) is the variance estimate of \( v_i \) at the \((t-1)\)th iteration, and \( \hat{\sigma}^{(t)}_i \) is the variance of \( \hat{v}^{(t)}_i \) given \( v_i \), which is directly obtained from \( J^{-1} \).

3. Estimate \( \hat{\Lambda}^{(t)}_0(\cdot) \) by replacing \( e^{\theta^T Z_{ij} + v_i} \) with \( e^{\hat{\theta}^{(t)}_i Z_{ij}} E[e^{v_i|\hat{\tau}^{(t)}_i}] = e^{\hat{\beta}^{(t)}_i Z_{ij}} e^{\hat{\sigma}^{(t)}_i v_i + \hat{\tau}^{(t)}_i} \) in (2.3).

4. Update \( h^* \) by replacing \( v_i \) with \( E[v_i|\hat{\tau}^{(t)}_i] \) and \( e^{v_i} \) with \( E[e^{v_i|\hat{\tau}^{(t)}_i}] \).

5. Iterate (1)–(4) until all estimates \( \{\hat{\beta}, \hat{\sigma}^2, \hat{\Lambda}^{(t)}_0(\cdot)\} \) converge.

2.4 H-likelihood estimators for a multivariate frailty model

In the H-likelihood approach, it is straightforward to extend the frailty model to accommodate multivariate frailties. Let \( v_i = (v_{i1}, \ldots, v_{iL})^T, i = 1, \ldots, n \), be unobserved \( L \)-dimensional multivariate frailty random variables for \( n \) clusters, where \( v_{ij} \) is the frailty for the \( l \)th subset of cluster members and the subsets are mutually exclusive. The size of subsets should be \( >1 \) with at most one subset having size 1. For the univariate frailty model described in Section 2.1, it is easy to see that \( v_i \) is a scalar. We assume that \( v_i \) is i.i.d. according to a parametric distribution \( g(\theta) \), where \( \theta \) is a vector of parameters governing the variance–covariance structure of \( v_i \). For ease of presentation, we define \( w_i = (w_{i1}, \ldots, w_{im})^T \), where if \( j \)th member belongs to the \( l \)th subset, \( w_{ij} = v_{ij} \). As in Section 2.1, the clusters are allowed to have different sizes. Assume that the hazard function for the \( ij \)th individual given the covariates \( Z_{ij} \) and the frailty \( w_{ij} \) follows model (2.1), now with \( v_i \) replaced by \( w_{ij} \). We make the same assumptions (1) and (2) as for the univariate frailty model but need to modify the subject-specific covariates’ effect assumption, that is, \( f(X_{ij}, \delta_{ij}|Z_{ij}, w_i) = f(X_{ij}, \delta_{ij}|Z_{ij}, w_{ij}) \). Under these assumptions, the log-H likelihood \( h^* \) and the log-H profile likelihood \( h^* \) can be written as (2.2) and (2.4) with \( v_i \) and \( \sigma^2 \) replaced by \( w_{ij} \) and \( \theta \).

Set \( v = (v_1^T, \ldots, v_n^T)^T \). We can follow the same procedure under the univariate frailty model and obtain \( \hat{\beta} \) and \( \hat{\sigma} \) using the Newton–Raphson algorithm and then \( \hat{\theta} \) by using \( p_\theta(h^*) \), the first-order Laplace approximation to the log of the marginal likelihood, \( \log \int \int \exp(h^*) dv \ d\beta \). The explicit forms for the first and second derivatives of \( h^* \) are provided in Section 3 of the supplementary material available at Biostatistics online. The size of the observed information matrix is \((p + q) \times (p + q)\), where \( q \) is the total number of unobserved frailty random variables. For instance, if there are two frailty variables in each cluster, then \( q = 2n \). As in the univariate frailty model, no integration is involved in the algorithm here for the multivariate frailty variates.

Assume a multivariate normal distribution for \( v_i \sim N(\mathbf{0}, \Sigma) \), where \( \mathbf{0} \) is the \( L \times 1 \) zero vector, and \( \Sigma \) is the \( L \times L \) covariance matrix indexed by \( \theta \). Then we estimate \( \theta \) by solving the score equation, \( \partial p_\theta(h^*)/\partial \theta = 0 \), where

\[
\frac{\partial p_\theta(h^*)}{\partial \theta} = \sum_{i=1}^{n} \left[ -\frac{1}{2} \text{tr} \left\{ \Sigma^{-1} \left( \frac{\partial \Sigma}{\partial \theta} \right) \right\} + \frac{1}{2} v_i^T \Sigma^{-1} \frac{\partial \Sigma}{\partial \theta} \Sigma^{-1} v_i \right] - \frac{1}{2} \text{tr} \left\{ J^{-1} \left( \frac{\partial J}{\partial \theta} \right) \right\}.
\]
To make it more concrete, below we provide an example of a bivariate frailty model, that is, \( L = 2 \). Let \( \mathbf{v}_i = (v_{i1}, v_{i2})^T \), where \( v_{i1} \) is the frailty for one subset of cluster and \( v_{i2} \) is the frailty for the rest of the cluster members. Assume \( \mathbf{v}_i = (v_{i1}, v_{i2})^T \) follows a bivariate normal distribution \( N(\mathbf{0}, \Sigma) \), where \( \mathbf{0} \) is a zero vector, and \( \Sigma \) is a \( 2 \times 2 \) covariance matrix with \( \sigma_1^2 \) and \( \sigma_2^2 \) as variances and \( \rho \) as the correlation coefficient. Then, the H-likelihood estimators are as follows: \( \hat{\sigma}_1^2 = \frac{1}{n} (\sum_{i=1}^n v_{i1}^2 + M_1) \), \( \hat{\sigma}_2^2 = \frac{1}{n} (\sum_{i=1}^n v_{i2}^2 + M_3) \), \( \hat{\rho} = \frac{1}{n\sigma_1\sigma_2} (\sum_{i=1}^n v_{i1}v_{i2} + M_2) \), where \( M_1, M_2, \) and \( M_3 \) are provided in Section 4 of the supplementary material available at Biostatistics online.

2.5 Bias correction in the H-likelihood estimators for the multivariate frailty model

As in the univariate frailty model, we use the regression calibration approach (Wang and others, 1997) to correct the bias in the H-likelihood estimators. We make a working assumption that \( \mathbf{v}_i \) given \( v_i \) follows a multivariate normal distribution with mean \( \mathbf{v}_i \) and covariance matrix \( \Xi_i \).

Here, \( \Xi_i \) is the direct estimate of the covariance matrix of \( \mathbf{v}_i \) from the observed information matrix \( J \) in the H-likelihood estimators. Since \( v_i \sim N(\mathbf{0}, \Sigma) \), \((v_i, \mathbf{v}_i)\) has a multivariate normal distribution: \( \left( \begin{array}{c} v_i \\ \mathbf{v}_i \end{array} \right) \sim N\left( \left( \begin{array}{c} \mathbf{0} \\ \Sigma \end{array} \right), \left( \begin{array}{cc} \Sigma & \Sigma \\ \Sigma & \Sigma + \Xi_i \end{array} \right) \right) \). Thus, we have \( v_i|\mathbf{v}_i \sim N(\Sigma(\Sigma + \Xi_i)^{-1}\mathbf{v}_i, \Sigma - \Sigma(\Sigma + \Xi_i)^{-1}\Sigma) \). Similar to the univariate frailty model, we replace \( \mathbf{v}_i \) and \( \exp(v_i) \) by \( E[\exp(v_i)|\mathbf{v}_i] \) in the H-likelihood function. It is worth noting that the regression calibration approach for other parametric frailty distributions also works.

To continue the bivariate frailty model example of Section 2.4, we provide the explicit forms for the estimators \( E[v_i|\mathbf{v}_i] \) and \( E[\exp(v_i)|\mathbf{v}_i] \). From the observed information matrix \( J \), we can obtain the covariance matrix of \( \hat{\mathbf{v}}_i \): \( \Xi_i = \left[ \begin{array}{cc} J^{-1}(2i + p - 1, 2i + p - 1) & J^{-1}(2i + p - 1, 2i + p) \\ J^{-1}(2i + p, 2i + p - 1) & J^{-1}(2i + p, 2i + p) \end{array} \right] \). Set \( \bar{\mu}_i = \Sigma(\Sigma + \Xi_i)^{-1}\mathbf{v}_i \) and \( \bar{\Sigma}_i = \Sigma - \Sigma(\Sigma + \Xi_i)^{-1}\Sigma \). Then, we obtain \( E[v_i|\mathbf{v}_i] = \bar{\mu}_i \), and \( E[\exp(v_i)|\mathbf{v}_i] = \exp\{ \bar{\mu}_i + \frac{1}{2} \text{diag}(\bar{\Sigma}_i) \} \). The estimation procedure for the multivariate log-normal frailty model is essentially same as for the univariate frailty model. To save space, we omit the algorithm.

3. Simulation studies

We conducted simulation studies to evaluate the finite sample performance of the proposed H-likelihood bias correction approach (H-corr est) and compare it with the NPMEs (Nielsen and others, 1992; Zeng and Lin, 2007) and the H-likelihood estimators (H-est) (Ha and others, 2001). Our first simulation study examines the performance of these three estimators under a univariate frailty model. We generated failure times of 300 clusters with two members in each cluster according to the hazard function (2.1), where \( v_i \sim N(0, 1) \), \( \lambda_0(t) = 0.04 \), \( \beta = \log(2) \), and the binary covariate \( Z_{ij} \) is 0 for the first half of the clusters and 1 for the remaining half. For each subject, we also generated a censoring time \( C_{ij} \) from Uniform\([0, 80]\) and set the end of study time \( \mathbf{s} \), so the censoring time is \( \min\{C_{ij}, s\} \). We chose \( s = 70, 10, 2 \), which gives censoring rates of 28%, 55%, and 84%, respectively.

Table 1 summarizes the mean and standard deviations of \( \hat{\beta}, \hat{\sigma}^2 \) and \( \hat{\lambda}_0 \) at three different time points over 1000 simulated data sets. The three time points \( t_k \) are the first, second, and third quartile of the duration of the study \([0, s]\), that is, \( t_k = (ks)/4 \). The results in Table 1 show that the H-est \( \hat{\beta} \) and \( \hat{\sigma}^2 \) are underestimated, while \( \hat{\lambda}_0(\cdot) \) are overestimated, and the bias increases with the censoring rate. We also find that the bias does not reduce when the number of clusters increases (results not shown). In contrast, the proposed H-corr est reduces the bias substantially and the bias, if there is any, is minimal, for all the censoring rates that we considered. The NPMEs, as expected, are largely unbiased except for \( \hat{\sigma}^2 \) when
Table 1. Summary of simulation results for NPMLE, H-est, and H-corr est under a univariate frailty model

<table>
<thead>
<tr>
<th>Cens. rate (%)</th>
<th>Parameter</th>
<th>True</th>
<th>NPMLE</th>
<th>H-est</th>
<th>H-corr est</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>MSE</td>
<td>Mean</td>
</tr>
<tr>
<td>28</td>
<td>$\beta$</td>
<td>0.693</td>
<td>0.686</td>
<td>0.168</td>
<td>0.657</td>
</tr>
<tr>
<td></td>
<td>$\sigma^2$</td>
<td>1</td>
<td>0.958</td>
<td>0.215</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_1)$</td>
<td>0.7</td>
<td>0.706</td>
<td>0.088</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_2)$</td>
<td>1.4</td>
<td>1.404</td>
<td>0.182</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_3)$</td>
<td>2.1</td>
<td>2.098</td>
<td>0.291</td>
<td>0.085</td>
</tr>
<tr>
<td>55</td>
<td>$\beta$</td>
<td>0.693</td>
<td>0.692</td>
<td>0.184</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>$\sigma^2$</td>
<td>1</td>
<td>0.962</td>
<td>0.246</td>
<td>0.062</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_1)$</td>
<td>0.1</td>
<td>0.102</td>
<td>0.018</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_2)$</td>
<td>0.2</td>
<td>0.204</td>
<td>0.032</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_3)$</td>
<td>0.3</td>
<td>0.305</td>
<td>0.044</td>
<td>0.002</td>
</tr>
<tr>
<td>84</td>
<td>$\beta$</td>
<td>0.693</td>
<td>0.700</td>
<td>0.271</td>
<td>0.073</td>
</tr>
<tr>
<td></td>
<td>$\sigma^2$</td>
<td>1</td>
<td>0.928</td>
<td>0.349</td>
<td>0.127</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_1)$</td>
<td>0.02</td>
<td>0.021</td>
<td>0.006</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_2)$</td>
<td>0.04</td>
<td>0.042</td>
<td>0.011</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_3)$</td>
<td>0.06</td>
<td>0.063</td>
<td>0.016</td>
<td>0.000</td>
</tr>
</tbody>
</table>

NPMLE refers to the nonparametric maximum likelihood estimators. H-est and H-corr est refer to the H-likelihood estimators and the proposed H-likelihood bias corrected estimators, respectively. Cens. rate is the censoring rate in the simulated data. Mean and SD are the mean and standard deviation of the estimates over 1000 simulated data sets. MSE is the mean squared error. Each data set consists of 300 clusters with two individuals in each cluster.

The censoring rate is high. The efficiency of $\hat{\beta}$ and $\Lambda_0(\cdot)$ are comparable between the H-corr est and the NPMLE, however, the H-corr est $\hat{\sigma}^2$ has a much larger variance than the NPMLE. The same trend is observed for the mean squared errors (MSE) of the estimators.

As requested by the reviewers, we also examined the performance of the bias correction method for relatively small sample sizes with no censoring rate ($n = 50$, $m = 2$; $n = 50$, $m = 4$; $n = 100$, $m = 2$; $n = 100$, $m = 4$; Table S2 in the supplementary material available at Biostatistics online), even though our main purpose is to handle the bias issue in the high censoring case. Our method yields comparable frailty variance estimator with similar bias and efficiency, but much better estimators for $\Lambda_0$ compared to the H-est in these scenarios.

When the sample size is very small and the censoring rate is high (e.g. $n = 100$, $m = 2$, and censoring rate $\approx 80\%$), the H-corr est encountered some convergence problems in estimating parameters due to few failures in the data. About 13% of simulated data sets failed to converge. However, the nonconvergence rate was reduced to 5% or less when the cluster size is increased to 4 or the number of clusters to 300. We did not experience the nonconvergence problem in the NPMLE or the H-est.

We also evaluated the robustness of $\hat{\beta}$ under misspecified log-normal frailty distribution. We generated data from three well-known frailty distributions: Gamma, Inverse Gaussian, and Positive Stable distributions (Hougaard, 2000), where the Gamma frailty distribution is perhaps most commonly used in the literature. We used Kendall’s (Kendall, 1938) coefficient of concordance ($\tau$) as the common measure of dependency to determine the parameter values in the various frailty distributions (Hsu and others, 2007). Table 2 describes the parameter values used in each frailty distribution for Kendall’s $\tau = 0.10$ and $\tau = 0.30$, representing small and strong dependency between cluster members.

Table 3 summarizes the percent bias and the standard deviations of $\hat{\beta}$ of the H-corr est. When the dependency is small, that is, $\tau = 0.10$, the percent bias in $\hat{\beta}$ ranges from 0.5 to 4.5 across all three
Table 2. Parameter values used in the simulation study when the frailty distribution is misspecified. Refer to Hsu and others (2007) for the models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Kendall’s τ = 0.10</th>
<th>Kendall’s τ = 0.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma</td>
<td>0.22</td>
<td>0.86</td>
</tr>
<tr>
<td>Inverse Gaussian</td>
<td>0.55</td>
<td>4.07</td>
</tr>
<tr>
<td>Positive stable</td>
<td>0.90</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Table 3. Summary of bias and standard deviation of $\hat{\beta}$ when the frailty distribution is misspecified

<table>
<thead>
<tr>
<th>τ</th>
<th>Cens. rate (%)</th>
<th>Gamma</th>
<th>Inverse Gaussian</th>
<th>Positive stable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bias (%)</td>
<td>SD</td>
<td>Bias (%)</td>
</tr>
<tr>
<td>0.10</td>
<td>80</td>
<td>1.7</td>
<td>0.200</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.8</td>
<td>0.148</td>
<td>-0.8</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>-0.5</td>
<td>0.121</td>
<td>-1.5</td>
</tr>
<tr>
<td>0.30</td>
<td>80</td>
<td>-3.9</td>
<td>0.221</td>
<td>-5.9</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>-4.1</td>
<td>0.172</td>
<td>-5.6</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>-4.3</td>
<td>0.159</td>
<td>-4.8</td>
</tr>
</tbody>
</table>

τ is the Kendall’s τ. Cens. rate is the censoring rate in the simulated data. Bias(%) is calculated by $100 \times (E[\hat{\beta}] - \beta)/\beta$, where $\beta = \log(2) \approx 0.693$. SD is the standard deviation for the estimates over 1000 simulated data sets. Each data set consists of 300 clusters with two individuals in each cluster.

Frailty distributions. Not surprisingly, the bias in $\hat{\beta}$ increases when the dependency becomes stronger ($\tau = 0.30$). However, the percent bias for most scenarios is still around 5% or below except when the true frailty distribution is Positive Stable and the censoring rate is high. In this situation, the percent bias are 8.2 and 13.9 when the censoring rate is 60% and 80%, respectively. This is because the Positive Stable distribution has a very strong time-dependent correlation with correlation high in the early failure time (Hougaard, 2000). When censoring is high, $\hat{\sigma}^2$ will be driven mainly by the early failures and hence is likely biased upward. As a result, $\hat{\beta}$ is underestimated. Generally speaking though, it seems that the log-normal frailty model is fairly robust against model mis-specification and can be a reasonable choice in real data analysis.

We also considered the more complicated bivariate frailty model. We generated failure times for 200 clusters each with six members by letting $w_{ij} = v_{il} I(j \in l\text{th subset}), l = 1, 2$, and $\lambda_0(t) = 0.04$. We assume $v_i$ follows a bivariate normal distribution with mean 0 and covariance matrix with $\sigma_1^2 = 1$, $\sigma_2^2 = 2$, and $\rho = 0.5$. We set $v_{i1}$ for the first individual and $v_{i2}$ for the remaining members in cluster $i$, mimicking the situation of a family study where the first individual is a mother and all other cluster members are her daughters. The rest of the data were generated in the same way as in the first simulation study.

Table 4 summarizes the results for $\{\hat{\beta}, \hat{\sigma}_1^2, \hat{\sigma}_2^2, \hat{\rho}, \hat{\Lambda}_0\}$ over 500 simulated data sets. These results show that the H-corr est performs very well for the bivariate frailty model. The H-est performs reasonably well when the censoring rate is low, however, when the censoring rate is high, the biases are quite substantial. The NPMLE also performs well, however, as in the univariate frailty model case, the variance estimators $\hat{\sigma}_1^2$ and $\hat{\sigma}_2^2$ are substantially biased. For example, the true value for $\sigma_1^2$ is 1, but the mean for the NPMLE is 0.492 (SD = 0.218) when the censoring rate is 81%. In contrast, the H-corr est is 0.877 (SD = 0.552). The small sample bias in the frailty variance for the NPMLE has previously been reported (Barker and Henderson, 2005). They suggested that the bias is due to the discrete estimator of the baseline hazard function, which may cause bias in the tail in the no censoring case (and to a similar extent, high censoring...
Table 4. Simulation results for a bivariate frailty model

<table>
<thead>
<tr>
<th>Cens. rate (%)</th>
<th>Parameter</th>
<th>True</th>
<th>NPMLE</th>
<th>H-est</th>
<th>H-corr est</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>MSE</td>
</tr>
<tr>
<td>29</td>
<td>$\beta$</td>
<td>0.693</td>
<td>0.697</td>
<td>0.174</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>$\sigma_1^2$</td>
<td>1</td>
<td>0.764</td>
<td>0.247</td>
<td>0.117</td>
</tr>
<tr>
<td></td>
<td>$\sigma_2^2$</td>
<td>2</td>
<td>1.855</td>
<td>0.237</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>$\rho$</td>
<td>0.5</td>
<td>0.524</td>
<td>0.135</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_1)$</td>
<td>0.7</td>
<td>0.702</td>
<td>0.190</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_2)$</td>
<td>1.4</td>
<td>1.385</td>
<td>0.237</td>
<td>0.123</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_3)$</td>
<td>2.1</td>
<td>2.062</td>
<td>0.280</td>
<td>0.080</td>
</tr>
<tr>
<td>53</td>
<td>$\beta$</td>
<td>0.693</td>
<td>0.689</td>
<td>0.190</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>$\sigma_1^2$</td>
<td>1</td>
<td>0.554</td>
<td>0.211</td>
<td>0.244</td>
</tr>
<tr>
<td></td>
<td>$\sigma_2^2$</td>
<td>2</td>
<td>1.818</td>
<td>0.241</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td>$\rho$</td>
<td>0.5</td>
<td>0.590</td>
<td>0.164</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_1)$</td>
<td>0.1</td>
<td>0.108</td>
<td>0.016</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_2)$</td>
<td>0.2</td>
<td>0.213</td>
<td>0.031</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_3)$</td>
<td>0.3</td>
<td>0.316</td>
<td>0.045</td>
<td>0.002</td>
</tr>
<tr>
<td>81</td>
<td>$\beta$</td>
<td>0.693</td>
<td>0.695</td>
<td>0.239</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td>$\sigma_1^2$</td>
<td>1</td>
<td>0.492</td>
<td>0.218</td>
<td>0.305</td>
</tr>
<tr>
<td></td>
<td>$\sigma_2^2$</td>
<td>2</td>
<td>1.719</td>
<td>0.292</td>
<td>0.165</td>
</tr>
<tr>
<td></td>
<td>$\rho$</td>
<td>0.5</td>
<td>0.539</td>
<td>0.291</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_1)$</td>
<td>0.02</td>
<td>0.022</td>
<td>0.005</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_2)$</td>
<td>0.04</td>
<td>0.045</td>
<td>0.009</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>$\Lambda_0(t_3)$</td>
<td>0.06</td>
<td>0.067</td>
<td>0.013</td>
<td>0.000</td>
</tr>
</tbody>
</table>

NPMLE refers to the nonparametric maximum likelihood estimators. H-est and H-corr est refer to the H-likelihood estimators and the proposed H-likelihood bias corrected estimators, respectively. Cens. rate is the censoring rate in the simulated data. Mean and SD are the mean and standard deviation of the estimates over 500 simulated data sets. MSE is the mean squared error. Each data set consists of 200 clusters with 6 individuals in each cluster.

with small sample size). Methods such as using local likelihood or smoothing for the baseline hazard to borrow information across failure times have been shown to reduce bias in the variance estimators considerably (see, e.g. Rondeau and others, 2003; Barker and Henderson, 2005). If we increase the number of clusters to 1000, the bias in the NPMLEs for $\sigma_1^2$ and $\sigma_2^2$ is much reduced (see Table S3 in the supplementary material available at Biostatistics online). As in the case of the univariate frailty model, the efficiencies of $\hat{\beta}$, $\hat{\Lambda}_0(t)$, and $\hat{\rho}$ are comparable between the NPMLE and the H-corr est. However, the efficiencies for $\hat{\sigma}_1^2$ and $\hat{\sigma}_2^2$ are much better for the NPMLE than that for the H-corr est. We also examined the performance of these three estimators with other configurations of different sample sizes and cluster sizes: $n = 200$, $m = 2$; $n = 200$, $m = 3$; $n = 1000$, $m = 2$; $n = 1000$, $m = 3$; $n = 1000$, $m = 6$. The relative performance of the three estimators in each of these configurations is consistent with what is shown in Table 4, though with different variances. To save space, we do not report the results here.

We evaluated the performance of the bootstrapping method for conducting statistical inference. Given the intensive computation, we examined two selected scenarios; $n = 200$, $m = 2$ ~ 4 with the censoring rate 55% and $n = 300$, $m = 2$ ~ 4 with the censoring rate 84%. We used 25 bootstrap samples with cluster as a sampling unit. As expected, the standard errors calculated from bootstrap samples were very close to the standard deviations of the estimates from simulated data sets. The coverage probabilities were 92–94% when the censoring rate was 55%, and 89–95% when the censoring rate was 84%.
We analyzed the data from the Washington Ashkenazi Kin-Cohort Study (WAS) (Struewing and others, 1997) to illustrate our proposed method. Ashkenazi Jewish volunteers living in Washington D.C. area were asked about the cancer history of their relatives. For illustration, we considered only a subset of the data, which consists of female volunteers and their mother and sisters to evaluate the age at diagnosis for breast cancer. There are 3571 volunteers, each having 1 ∼ 6 relatives. In total, there are 9771 individuals, and the censoring rate is 89%.

We found, by the Kaplan–Meier estimator, that the age at onset of breast cancer in the volunteers appears to be lower than that of their mothers or sisters (results not shown). A possible explanation for this difference is that subjects who had cancer were more motivated to participate in the study than those who had not. To account for this potential ascertainment bias, we included a binary covariate to indicate whether the subject is volunteer (=1) or not (=0).

We fit both univariate and bivariate frailty models to the WAS data. In the univariate frailty model, we assume mother and daughters within a family share the same frailty value, whereas in the bivariate frailty model, we assume mother and daughters have separate frailties and the frailties are correlated. The standard errors of the parameter estimates were calculated using 50 bootstrap samples with family as a sampling unit. Table 5 summarizes the parameter estimates obtained from the NPMLE, the H-est, and the H-corr est. As expected from the simulation results, the $\hat{\sigma}^2_1$ from the H-est are overestimated compared to the NPMLE and the H-corr est, but the variance and correlation estimates are smaller. The NPMLE and the H-corr est are fairly consistent with each other on both estimates and standard errors. However, $\hat{\sigma}^2_2$ in the H-corr est is smaller than in the NPMLE. The trend is somewhat different from the simulation results in Table 1. We investigated this issue by conducting further simulations using the similar parameter value obtained here, that is, $\sigma^2 = 0.5$. Interestingly, we found that $\hat{\sigma}^2_2$ from the H-corr est is smaller than from the NPMLE when the true variance is small. The H-corr est $\hat{\sigma}^2_2$ were 0.435 and 0.472, whereas the

<table>
<thead>
<tr>
<th>Table 5. Analysis of the Washington Ashkenazi Kin-Cohort Study (Struewing and others, 1997)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Univariate</td>
</tr>
<tr>
<td>Frailty model</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

$\hat{\sigma}^2_1$ and $\hat{\sigma}^2_2$ are the first-order Laplace approximations to the log marginal likelihoods for univariate and bivariate frailty model, respectively.
NPMLE est were 0.445 and 0.497 for \((n = 300, m = 2)\) and \((n = 1000, m = 2)\), with censoring rate \(\approx 87\%\), respectively.

We performed likelihood ratio (LR) tests to test two null hypotheses: (I) \(H_0: \sigma^2 = 0\), that is, no shared frailty among mothers and daughters and (II) \(H_0: \sigma_1^2 = \sigma_2^2, \rho = 1\), that is, frailties are common for both mother and daughters. By following the suggestion by Ha and others (2007), we used the original H-likelihood function (Ha and others, 2001) for the LR test, as the regression calibration bias correction approach does not provide proper likelihood. The LR statistic is twice the difference of the first-order Laplace approximation to the log marginal likelihoods between the full and reduced model. For hypothesis I, the full model is the univariate frailty model and the reduced model is no frailty. Under the null, the expected distribution is a 50:50 mixture of \(\chi^2_0\) and \(\chi^2_1\). For hypothesis II, the full model is the bivariate frailty model and the reduced model is the univariate frailty. The expected distribution under the null is a 50:50 mixture of \(\chi^2_1\) and \(\chi^2_2\). We conducted simulations and showed that both test statistics follow the expected distributions (see Section 6 of the supplementary material available at Biostatistics online). For the WAS data, the LR test statistic under hypothesis I was 29.2, indicating that the dependence within a family is highly significant \((p = 3e^{-8})\). The LR test statistics under hypothesis II was 2.8 \((p = 0.17)\). There is little evidence to support that mother and daughters have different frailties.

In summary, based on the H-corr est, volunteers may have an earlier age at onset than their female relatives \((\exp(\beta) = 1.137, 95\%\ CI: 0.991–1.304)\), although the effect is not statistically significant at 0.05. The \(\hat{\sigma}^2\) in the univariate model is 0.516 \((95\%\ CI: 0.334–0.698)\), corresponding to Kendall’s \(\tau = 0.18\). Even though the bivariate frailty model did not significantly improve the univariate frailty model, there are some interesting observations. The frailties for mother and daughters are highly correlated with \(\hat{\rho} = 0.654\) \((95\%\ CI: 0.511–0.797)\). In addition, the dependence between daughters (Kendall’s \(\tau = 0.25\)) is stronger than the dependence between mother and daughter (Kendall’s \(\tau = 0.13\)), suggesting that there may be a stronger childhood environment effect or dominant deviation from additive genetic effects on breast cancer risk.

5. DISCUSSION

In this paper, we propose a bias correction method for the H-likelihood estimators (Ha and others, 2001) by using the regression calibration approach. The H-likelihood approach is useful particularly when the frailty distribution is multivariate because it avoids integration over frailty distribution. It generally performs well except when the censoring rate is high. Our correction method overcomes this issue. The efficiency of the proposed estimators for \(\beta\) and \(\Lambda_0(\cdot)\) are comparable to the NPMLE, although the efficiency of \(\hat{\sigma}^2\) appears to be less. This is probably because the Laplace approximation to the marginal likelihood for \(\sigma^2\) loses some information.

For the hierarchical generalized linear models, Noh and Lee (2007) proposed a different strategy, which uses the first-order Laplace approximation to the marginal likelihood to estimate the fixed effects, and the second-order Laplace approximation to estimate the dispersion parameters. The same scheme may be considered for reducing bias in H-likelihood estimators for the log-normal frailty distribution. An anonymous reviewer shared unpublished results of this approach, and the bias of the variance estimator appears to be reduced. Another recently proposed approach (Ha and others (2011)) is to incorporate \(\frac{\partial \hat{\beta}}{\partial \sigma^2}\) in estimating \(\sigma^2\). Their simulation studies under the setting of multicenter clinical trials give good results with censoring rate up to 50%. A further comparison of the proposed method with these new approaches would be worthwhile.

In the R package, the penalized likelihood function is implemented for fitting the shared frailty model. Like the H-likelihood, it also yields biased parameter estimates under the log-normal frailty when the censoring rate is high. The proposed bias correction procedure is simple and easy to implement.
Frailty models are very useful in predicting cluster-specific risk. For example, in the WAS data, there is a strong heterogeneous effect in the age at diagnosis of breast cancer between families. It would be useful to provide an estimate for the background risk that is family specific and use it to assess a subject’s risk for developing breast cancer. Further work on using frailty models in risk prediction would be fruitful.

SUPPLEMENTARY MATERIAL

Supplementary material is available at http://biostatistics.oxfordjournals.org.

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