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Bayesian nested frailty model for evaluating surgical management of patulous Eustachian tube dysfunction

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Abstract

Background The nested frailty model, a random effects survival model that can accommodate data clustered at two hierarchical levels, has been rarely used in practice. We aimed to evaluate the utility of the Bayesian nested frailty modeling approach in the context of a study to examine the effects of various surgical procedures for patients with patulous Eustachian tube dysfunction (PETD).

Methods A nested frailty model was employed to account for the correlation between each pair of ears within patients and the correlation between multiple event times within each ear. Some patients underwent multiple different surgical treatments in their affected ears. We incorporated two nested lognormal frailties into the Cox proportional hazards model. The Bayesian Monte Carlo Markov Chain approach was utilized. We examined the consequences of ignoring a multilevel structure of the data.

Results The variances of patient-level and ear-level random effects were both found to be significant in the nested frailty model. Shim insertion and patulous Eustachian tube reconstruction using Alloderm or cartilage were associated with a lower risk of recurrence of PETD symptoms than calcium hydroxyapatite injection.

Conclusions Bayesian nested frailty models provide flexibility in modeling hierarchical survival data and effectively account for multiple levels of clustering. Our study highlights the importance of accounting for all levels of hierarchical clustering for valid inference.

Keywords Bayesian analysis, Multilevel survival analysis, Nested frailty model

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Background

Patulous Eustachian tube dysfunction (PETD) is a condition in which the Eustachian tube (ET) remains intermittently open, causing a sensation of ear fullness and a loud echoing sound of one's voice and nasal breathing [1, 2]. In about half of patients with PETD, both ears can be affected [2]. Persistent symptoms of PETD can severely impair patients' quality of life. Most patients with PETD have a concave defect in the anterolateral wall of the ET that prevents complete closure of the valve [1]. PETD is a difficult condition to treat and currently, there is no standard treatment [3, 4]. Patients are treated initially with lifestyle changes and topical medications; however, patients with severe symptoms who are refractory to conservative management eventually may require surgical treatment. We recently examined surgical treatments of PETD [5]. This was the first large study to compare various surgical procedures on symptom resolution in patients with PETD. The study presented several challenges in the statistical analysis. It required analysis of time-to-event data that involved two levels of hierarchal clustering at the levels of the patient and the affected ear. For patients with bilateral PETD, the outcomes between paired ears are expected to be correlated. Furthermore, some patients experienced a recurrence of PETD symptoms and required multiple different surgeries in an affected ear. Multiple event times within the affected ear are expected to be correlated. Finally, PETD severe enough to require surgery is an uncommon condition and a relatively limited number of patients made it challenging to model multilevel clustered survival data.

Multilevel models are commonly used for the analyses of continuous and binary outcomes, though less frequently for survival analysis. A frailty model, which is considered a random effects survival model, can be employed for clustered survival data to account for the correlation between observations within a cluster [6, 7]. The frailty model has been applied in various ways in medical research. For example, the frailty model has been used in multicenter studies to account for the clustering of patients within centers. Clustering can also occur within an individual. The frailty model has been used to study similar paired or multiple organs such as ears, eyes, or teeth. The frailty model is also commonly used for recurrent events data to account for the correlation of repeated event times within the same individual. The frailty model can be extended to account for multiple levels of clustering. Sastry (1997) has proposed the nested frailty model, which is a three-level hierarchical survival model. Rondeau et al. (2006) applied a semi-parametric maximum penalized likelihood estimation procedure to a nested frailty model to account for two levels of geographical clustering. Manda et al. (2005) used the nested gamma frailty model in the Bayesian framework in a study of amalgam restoration to account for two levels of clustering at the tooth and subject levels. Others have used the nested frailty model in the multicenter study of recurrent infections in patients with chronic granulomatous disease [8–11]. However, the magnitude of clustering in one of the clusters was negligible in prior studies [8, 9, 12, 13]. Thus, the importance of using such a complex hierarchical model is uncertain, especially because the model has been rarely used in practice.

We used a Bayesian approach to the nested frailty model because of several advantages. The Bayesian paradigm provides a natural framework for incorporating prior knowledge and updating it based on the observed data. Moreover, the Bayesian approach offers an intuitive interpretation of parameter uncertainty by expressing probability as a degree of belief. One of the major strengths of adopting a Bayesian perspective is its flexibility in modeling hierarchical data [11, 14, 15]. The likelihood function for the two random effects in the nested frailty model involves high dimensional integration that cannot be solved analytically and makes it difficult to use a three-level hierarchal model in the frequentist framework. Even when the frequentist approach is used, it may underestimate the variability of the random effects and lead to biased results [16]. However, the Bayesian Monte Carlo Markov Chain (MCMC) approach draws inference from the posterior distribution and overcomes high dimensional problems. One of the criticisms of Bayesian statistics has been its incorporation of prior belief, which can be subjective and sensitive to the chosen prior probabilities. However, we considered noninformative priors, which have minimal influence on the posterior, in our study.

We aimed to evaluate the utility of the Bayesian nested frailty modeling approach in the context of a study to examine the effects of various surgical procedures for patients with PETD. We incorporated two nested lognormal frailties in parametric and semiparametric proportional hazards models. We also compare models with and without frailties to examine the importance of accounting for the hierarchical structure of the data.

Methods

Surgical management of patulous Eustachian tube dysfunction

We reanalyzed the study evaluating the effectiveness of surgical procedures for PETD. Details of the study have been published [5]. The study was approved by the Institutional Review Board at Boston Children's Hospital. Patients who were refractory to medical therapy and underwent transnasal-transoral endoscopic procedures for PETD from 2004 to 2016 were evaluated. The primary outcome was defined as a time to recurrence of any symptoms of PETD in the affected ear. Surgical procedures included 1) insertion of a shim into the ET lumen, 2) injection of calcium hydroxyapatite (HA), 3) patulous ET reconstruction (PETR), or 4) permanent obliteration of the ET lumen.

PETR technique varied widely; however, all procedures aimed to restore the normal convexity of the anterolateral wall of the ET. Shim placement procedure involves an insertion of an angiocatheter filled with bone wax in the ET. HA injection method was performed by injecting calcium HA cement submucosally intramurally along the lumen of the ET. PETR involved partial obliteration of the ET lumen by insertion of grafting material and temporary suture ligation of the ET orifice. Alternatively, grafting materials were inserted into the anterolateral or the posteromedial wall. Materials for PETR included cartilage grafts, acellular dermal matrix (Alloderm), fat, or other materials to decrease the diameter of the ET lumen. Permanent obliteration of the ET lumen was performed only as the last resort. All eleven patients who underwent total ET obliteration had complete symptom resolution; thus, we did not include this procedure in the current analysis. In addition to assessing the effect of surgical procedures on symptom resolution, the current study examined whether patient characteristics, such as age, gender, duration of symptoms before surgery, and potential underlying etiologies of PETD, affect the risk of symptom reappearance.

Nested frailty model

The nested frailty model incorporates two nested frailties in a proportional hazards model. We assumed frailty effects to be lognormally distributed. One of the advantages of using lognormal frailties is that the logarithm of the frailty terms can be incorporated into linear components of the proportional hazards model as random effects, which can be considered as an extension of multilevel generalized linear mixed models. Others have assumed gamma, inverse Gaussian, or log-t distribution for the frailty term [7, 10].

A nested frailty model was employed to account for clustering at the levels of the affected ear and the patient. A patient-level frailty (cluster level) accounts for the correlation between paired ears within the patient. An ear-level frailty (sub-cluster level) accounts for the correlation between recurrent event times within the ear. We denoted $\lambda_{ijk}(t)$ as the hazard of symptom reappearance of PETD at time t for the kth occasion in the jth side of the ear of ith patient. The gap time was used for the timescale because our primary interest was to assess the effect of the surgical procedure. After each procedure, a patient starts at time 0 and the time to the next event corresponds to the time it took until the patient experiences a reappearance of symptoms consistent with PETD.

The time until symptom reappearance was not observed for all occasions because of right censoring. We denoted T_{ijk} as the time until the symptom reappearance for the kth occasion in the jth side of the ear of ith patient, and C_{ijk} as the corresponding right censoring time. The observed time is written as $Y_{ijk} = \min\{T_{ijk}, C_{ijk}\}$. The indicator of censoring is denoted as δ_{ijk}, where $\delta_{ijk} = 1$ indicates that T_{ijk} was observed and $\delta_{ijk} = 0$ indicates right censoring.

We denoted $\lambda_{ijk}(t)$ as the hazard of symptom reappearance of PETD at time t for the kth occasion in the jth side of the ear of ith patient. The nested frailty model can be written as,

$$\lambda_{ijk}(t) = \lambda_0(t) \exp\left(\boldsymbol{\beta}'\boldsymbol{x}_{ijk} + \upsilon_i + \omega_{ij}\right) \tag{1}$$

where $\lambda_0(t)$ is the baseline hazard function, $\boldsymbol{x}_{ijk}$ is the vector of values of p explanatory variables for the kth observation, and $\boldsymbol{\beta}$ is the vector of their unknown coefficients. Random effects are assumed to be normally distributed; the random effects from the ith cluster, $\upsilon_i \sim N(0, \gamma^2)$ and the random effects from the jth subcluster of cluster i, $\omega_{ij} \sim N(0, \sigma^2)$.

Weibull nested frailty model can be written as,

$$\lambda_{ijk}(t) = \mu\rho t^{\rho-1} \exp\left(\boldsymbol{\beta}'\boldsymbol{x}_{ijk} + \upsilon_i + \omega_{ij}\right) \tag{2}$$

where μ being scale parameter and ρ being shape parameter for the Weibull distribution.

Bayesian inference

In Bayesian statistics, we are interested in updating knowledge based on the observed data. The updated summary of knowledge about the parameters in the model is reflected in the posterior distribution, which can be obtained by combining the likelihood function based on the observed data and the prior distribution of the parameters. The posterior distribution of $\boldsymbol{\theta}$ is given by

$$\pi(\boldsymbol{\theta}|\boldsymbol{D}) \propto L(\boldsymbol{\theta}; \boldsymbol{D})\pi(\boldsymbol{\theta}) \tag{3}$$

where $\boldsymbol{\theta}$ represents the set of all model parameters and $\boldsymbol{D}$ is the observed data.

The joint posterior distribution for the Bayesian nested frailty model is written by

$$\pi(\boldsymbol{\beta}, \boldsymbol{\upsilon}, \boldsymbol{\omega}|\boldsymbol{D}) \propto L(\boldsymbol{\beta}, \boldsymbol{\upsilon}, \boldsymbol{\omega}; \boldsymbol{D})\pi(\boldsymbol{\beta})\pi(\boldsymbol{\upsilon}|\gamma)\pi(\boldsymbol{\omega}|\sigma)\pi(\gamma, \sigma) \tag{4}$$

The conditional data likelihood for the nested frailty model is given by

$$\begin{aligned} L(\boldsymbol{\beta}, \boldsymbol{\upsilon}, \boldsymbol{\omega}; \boldsymbol{D}) = \prod_{i=1}^{I}\prod_{j=1}^{J_i}\prod_{k=1}^{K_{ij}} \left\{\lambda_0(y_{ijk}) \exp\left(\boldsymbol{\beta}'\boldsymbol{x}_{ijk} + \upsilon_i + \omega_{ij}\right)\right\}^{\delta_{ijk}} \\ \times \exp\left[-\int_0^{y_{ijk}} \left\{\lambda_0(t) \exp(\boldsymbol{\beta}'\boldsymbol{x}_{ijk} + \upsilon_i + \omega_{ij})\right\} dt\right] \end{aligned} \tag{5}$$

Bayesian Cox proportional hazards model with nested frailties

One of the commonly used methods for the semiparametric Bayesian analysis of the Cox proportional hazards model is the piecewise constant hazard model [14]. It provides flexibility in modeling the baseline hazard function and accommodates various shapes of the hazard function. We constructed the piecewise constant hazard model by partitioning the time axis into L intervals $(s_0, s_1], (s_1, s_2], ..., (s_{l-1}, s_l]$ where s_l exceeds the maximum observed time. The baseline hazard is assumed to be constant over each interval.

$$\lambda_0(t) = \lambda_l, \text{ for } t \in (s_{l-1}, s_l], l = 1, ..., L. \quad (6)$$

By increasing the number of time intervals (L), we can have a more flexible baseline hazard function; however, this may lead to unstable estimates of piecewise hazards. To determine the optimal choice of L, we fitted three different time intervals ($L = 4$, 8, and 12) and assessed the fit of the model using the deviation information criterion (DIC). An approximately equal number of events was ensured when partitioning the time scale.

The conditional data likelihood for the piecewise constant hazards model with nested frailties, $\mathcal{L}(\boldsymbol{\beta}, \boldsymbol{\lambda}, \boldsymbol{\upsilon}, \boldsymbol{\omega}; \boldsymbol{D})$, is given by,

$$\prod_{i=1}^{I}\prod_{j=1}^{J_i}\prod_{k=1}^{K_{ij}}\prod_{l=1}^{L}\left\{\lambda_l \exp(\boldsymbol{\beta}'\boldsymbol{x}_{ijk} + \upsilon_i + \omega_{ij})\right\}^{\eta_{ijkl}\delta_{ijk}} \times \exp\left[-\eta_{ijkl}\left\{\lambda_l(y_{ijk} - s_{l-1}) + \sum_{g=1}^{l-1}\lambda_g(s_g - s_{g-1})\right\}\exp(\boldsymbol{\beta}'\boldsymbol{x}_{ijk} + \upsilon_i + \omega_{ij})\right] \quad (7)$$

where $\eta_{ijkl} = 1$ if the kth subject from the jth subcluster in the ith cluster failed or was censored in the lth interval, and 0 otherwise. This interval-specific indicator η_{ijkl} is required to define the likelihood function properly.

The joint posterior distribution of all model parameters for the Bayesian Cox proportional hazard model with nested frailties is given by

$$\pi(\boldsymbol{\beta}, \boldsymbol{\lambda}, \boldsymbol{\upsilon}, \boldsymbol{\omega}|\boldsymbol{D}) \propto L(\boldsymbol{\beta}, \boldsymbol{\lambda}, \boldsymbol{\upsilon}, \boldsymbol{\omega}; \boldsymbol{D})\pi(\boldsymbol{\beta})\pi(\boldsymbol{\lambda})\pi(\boldsymbol{\upsilon}|\gamma)\pi(\boldsymbol{\omega}|\sigma)\pi(\gamma, \sigma) \quad (8)$$

Noninformative priors were assumed for all the parameters. We assumed that $\boldsymbol{\beta}$ are independent and $\beta_p \sim N(0,\ 10^4)$ for $p = 1, 2, ...P$. For the baseline hazard, a gamma distribution with a large variance was assumed ($\lambda_l \sim G(0.01, 0.01)$ for $l = 1, 2, ...L$) [11, 15].

The joint prior density of random effects can be written as

$$\pi(\boldsymbol{\upsilon}|\gamma) = \prod_{i=1}^{I}\frac{1}{\sqrt{2\pi\gamma^2}}\exp\left(-\frac{\upsilon_i^2}{2\gamma^2}\right) \quad (9)$$

$$\pi(\boldsymbol{\omega}|\sigma) = \prod_{i=1}^{I}\prod_{j=1}^{J_i}\frac{1}{\sqrt{2\pi\sigma^2}}\exp\left(-\frac{\omega_{ij}^2}{2\sigma^2}\right) \quad (10)$$

We can assume priors $\gamma \sim U(0, 100)$ and $\sigma \sim U(0, 100)$. Alternatively, because the observations are nested within individuals in our study, we allowed two random effects to be correlated, following Congdon's approach [11], which used the uniform shrinkage prior proposed by Daniel (1999) [17]. The uniform shrinkage prior is noninformative and leads to proper posterior distributions in hierarchical models. Given these favorable properties, we specified uniform $U(0,\ 1)$ prior on the shrinkage parameter, $r = (\gamma^2/(\gamma^2 + \sigma^2))$. The total variance $V = \gamma^2 + \sigma^2$, and a uniform prior $V \sim U(0, 100)$.

Bayesian Weibull model with nested frailties

For the parametric approach, a nested frailty model with a Weibull baseline hazard was considered. The conditional data likelihood for the Weibull nested frailty model is

$$L(\boldsymbol{\beta}, \mu, \rho, \boldsymbol{\upsilon}, \boldsymbol{\omega}; \boldsymbol{D}) = \prod_{i=1}^{I}\prod_{j=1}^{J_i}\prod_{k=1}^{K_{ij}}\left\{\mu\rho y_{ijk}^{\rho-1}\exp(\boldsymbol{\beta}'\boldsymbol{x}_{ijk} + \upsilon_i + \omega_{ij})\right\}^{\delta_{ijk}} \times \exp\left\{-\mu y_{ijk}^{\rho}\exp(\boldsymbol{\beta}'\boldsymbol{x}_{ijk} + \upsilon_i + \omega_{ij})\right\} \quad (11)$$

We defined $\beta_0 = \log\mu$ and assumed that a-priori $\beta_0 \sim N(0,\ 10^4)$ and $\rho \sim G(1, 0.001)$.

MCMC methods

We implemented Gibbs sampling, one of the MCMC algorithms. Gibbs sampler iteratively draws samples from the conditional posterior distribution of each parameter conditional on all the other parameters from the most recent draws. Posterior distributions were obtained from three chains of 20,000 simulations after convergence was achieved from an initial 5000 simulations of burn-in period. We monitored the convergence of all model parameters following the Rubin and Gelman diagnostic methods [18]. The 95% credible intervals (CI) were based on the 2.5th and 97.5th percentiles of the posterior distribution. Bayesian 95% CI can be simply interpreted as the interval containing the true parameter with 95% probability.

Bayesian survival models were implemented using JAGS software. R2jags package was used to run JAGS within R. WinBUGS is an alternative Gibbs sampling program that can be used for Bayesian survival analysis.

Model comparison

The deviation information criterion (DIC) and the conditional predictive ordinate (CPO) are the most common methods to compare models from a Bayesian perspective. The DIC combines a measure of model fit with a penalty for the model complexity and can be viewed as a Bayesian version of Akaike information criterion [19]. The DIC is obtained by $\text{DIC} = \overline{\text{D}} + \text{p}_\text{D}$ where $\overline{D}$ is the posterior expectation of the deviance and $p_D = \overline{D} - D(\overline{\boldsymbol{\theta}})$ is the effective number of model parameters to capture model complexity. $D(\overline{\boldsymbol{\theta}})$ is the deviance evaluated at the posterior mean of the parameters. A smaller value of DIC suggests a better fit of the model.

The CPO is a cross-validation predictive method that evaluates how well the observation i can be predicted by a model based on the data from all other observations [20]. The CPO statistic for the ith observation is defined as

$$\mathrm{CPO_i} = \int \mathrm{f}(\mathrm{y_i}|\boldsymbol{\theta})\pi\left(\boldsymbol{\theta}|\boldsymbol{D}^{(-\mathrm{i})}\right)\mathrm{d}\boldsymbol{\theta} \tag{12}$$

where $\boldsymbol{D}^{(-i)}$ is all the data except the ith observation and $\pi(\boldsymbol{\theta}|\boldsymbol{D}^{(-i)})$ is the posterior density of $\boldsymbol{\theta}$ based on the data $\boldsymbol{D}^{(-i)}$. The log pseudo-marginal likelihood (LPML) is usually used for summary statistics of the $\mathrm{CPO_i}$ values. LPML is defined as $\mathrm{LPML} = \sum_{\mathrm{i}=1}^{\mathrm{n}} \log(\widehat{\mathrm{CPO_i}})$. A larger value of LPML implies a better fit of the model.

Results

A total of 230 procedures were performed on 119 ETs of 78 patients (Table 1). The mean number of procedures per patient was 3.0 (SD 2.8; range: 1 to 16 procedures per patient). Forty-one patients (52.6%) underwent bilateral procedures. Kaplan-Meier plot was used to describe the time to reappearance of PETD by procedure and patient characteristics (Fig. 1). Placement of a shim was associated with a lower risk of failure by 59% than calcium hydroxyapatite injection (Hazard Ratio [HR] 0.41; 95% CI: 0.24, 0.73; Table 2). Patulous ET reconstruction procedures using cartilage or Alloderm were associated with a lower risk of symptom reappearance by 45% than HA injection (HR 0.55; 95% CI: 0.30, 0.99). Patulous ET reconstruction using fat or other materials did not provide a better outcome than HA injection (HR 0.81; 95% CI: 0.41, 1.53).

Patient factors such as age, gender, and duration of symptoms before surgery were not associated with the risk of symptom reappearance. Use of oral contraceptives was associated with an increased risk of symptom reappearance (HR 2.64; 95% CI: 1.06, 6.79); however, the majority of other potential etiologic factors did not affect the outcome. Results based on the Weibull nested frailty model were essentially identical to results based on the Cox nested frailty model. Posterior densities of model parameters based on the Cox nested frailty model are shown in Fig. 2.

We evaluated three choices of L = 4, 6, and 8 for the piecewise constant hazard model. The model based on L = 4 provided a better fit (DIC criteria = 1129.2) than the model based on L = 6 (DIC = 1236.6) or L= 8 (DIC = 1339.9); thus, we assumed L = 4 intervals to model the baseline hazard. The cut points were placed at 1, 4, 12, and 24.

The estimated standard deviations (SD) for the random effects for patient-level (cluster $\gamma = 1.01$; 95% CI: 0.19, 1.95) and ear-level (sub-cluster $\sigma = 0.30$; 95% CI: 0.05, 0.71) were both significant in the Cox nested frailty model (model 3; Table 3). The model without frailty (model 1) gave overly narrow intervals and erroneous estimates as they do not account for any cluster. Parameter estimates for treatment effects tend to be larger (i.e., further from zero) in the nested frailty model (model 3) than the model without frailty (model 1). We found that parameter estimates for treatment effects and width of credible intervals were moderately different between the nested frailty model (model 3) and the patient-level frailty model (model 2). These findings were similarly found in Weibull models (Table 4). In the piecewise constant hazard model, the hazard rate gradually declined from 0.178 to 0.039 over the study period. That was also the case with the Weibull nested frailty model. The shape parameter of the Weibull distribution (ρ) was 0.66, indicating a decline in the hazard function over time ($\rho < 1$).

We then compared the predictive performance of the models based on the log pseudo-marginal likelihood (LPML) criteria and the deviation information criterion (DIC; Table 5). As suggested by larger values of LPML,

Table 1 Characteristics of patients with PETD

	n (%) or mean (SD)
Patient characteristics	(*n*=78)
Age, years	38.5 (17.5)
Gender, female	35 (44.9%)
Symptom duration, years	6.8 (8.3)
Affected	
Unilateral	37 (47.4%)
Bilateral	41 (52.6%)
Potential etiologies	
Environmental allergies	29 (37.2%)
Weight loss	28 (36.4%)
Gastroesophageal reflux disease	27 (34.6%)
Oral contraceptive use	11 (14.1%)
Others	17 (21.8%)
Procedure	(*n*=230)
Shim insertion	115 (50.0%)
Hydroxyapatite injection	38 (16.5%)
Patulous ET reconstruction	77 (33.5%)
PETR technique	
Partial obliteration	37 (16.1%)
Anterolateral wall	23 (10.0%)
Posteromedial wall	6 (2.6%)
Others	11 (4.8%)
PETR materials	
Cartilage	28 (12.2%)
Alloderm	18 (7.8%)
Fat	22 (9.6%)
Others	9 (3.9%)

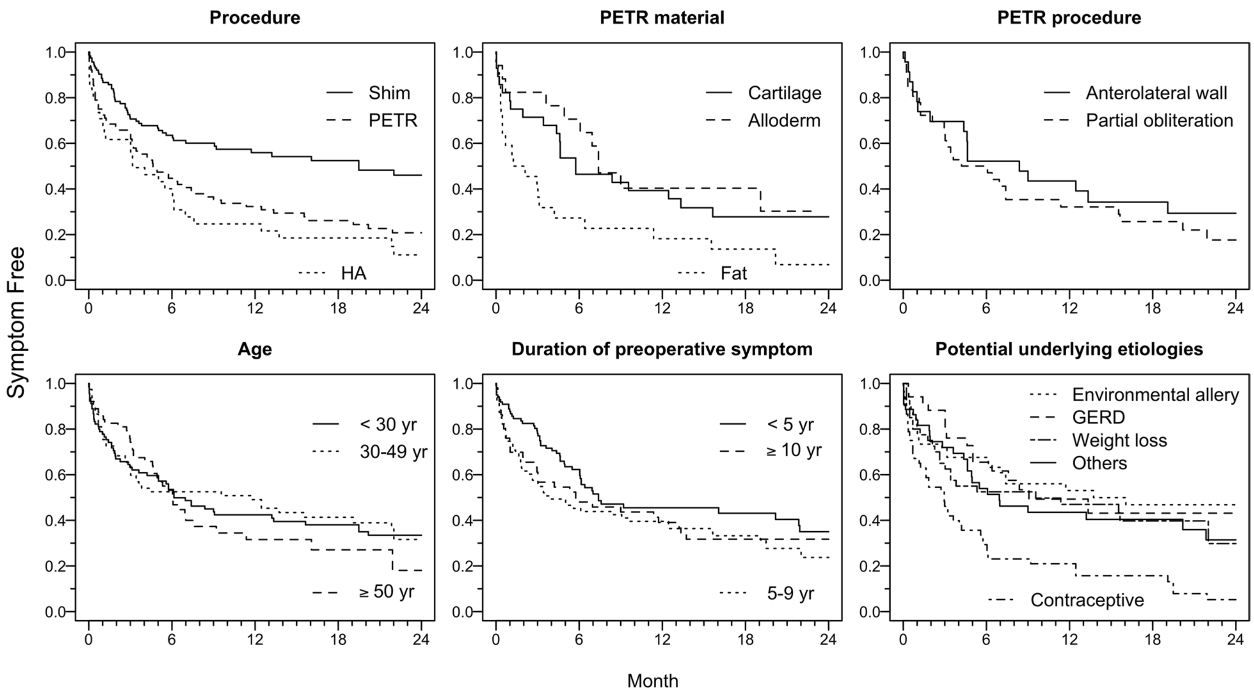

Fig. 1 Kaplan-Meier plot describing the time to reappearance of PETD by procedure and patient characteristics

Table 2 Bayesian Cox nested frailty model and Weibull nested frailty model

	Cox nested frailty model		**Weibull nested frailty model**	
	HR	**(95% CI)**	**HR**	**(95% CI)**
Procedure				
Shim insertion	0.41	(0.24, 0.73)	0.42	(0.25, 0.73)
PETR (cartilage/alloderm)	0.55	(0.30, 0.99)	0.56	(0.31, 1.00)
PETR (fat/others)	0.81	(0.41, 1.53)	0.82	(0.43, 1.53)
HA injection	Reference		Reference	
Age	1.00	(0.98, 1.02)	1.00	(0.98, 1.02)
Female	1.12	(0.51, 2.57)	1.11	(0.54, 2.33)
Symptom duration	1.00	(0.95, 1.04)	1.00	(0.95, 1.04)
Oral contraceptive use	2.64	(1.06, 6.79)	2.59	(1.14, 6.30)

the frailty model and the nested frailty model were a better fit than the Cox model without frailty. Further, Weibull models fit better than Cox models based on the LPML criteria. The DIC values were smaller for the Weibull models than the Cox models, suggesting a better fit as the Weibull models required fewer parameters to model the baseline hazard. The DIC criteria did not suggest that the nested frailty model is a better fit than the model without frailty. As Gustafson commented previously, DIC criteria may not work well for comparing frailty models [21]. Frailty models had lower deviance values than the model without frailty; however, frailty models seem to have been penalized disproportionally for model complexity.

Discussion

We evaluated the effectiveness of surgical procedures for PETD using the Bayesian nested frailty model. We found that the variance of patient-level and ear-level random effects were both significant, indicating the importance of accounting for the hierarchical structure of the data and utilizing the Bayesian nested frailty model for valid inference.

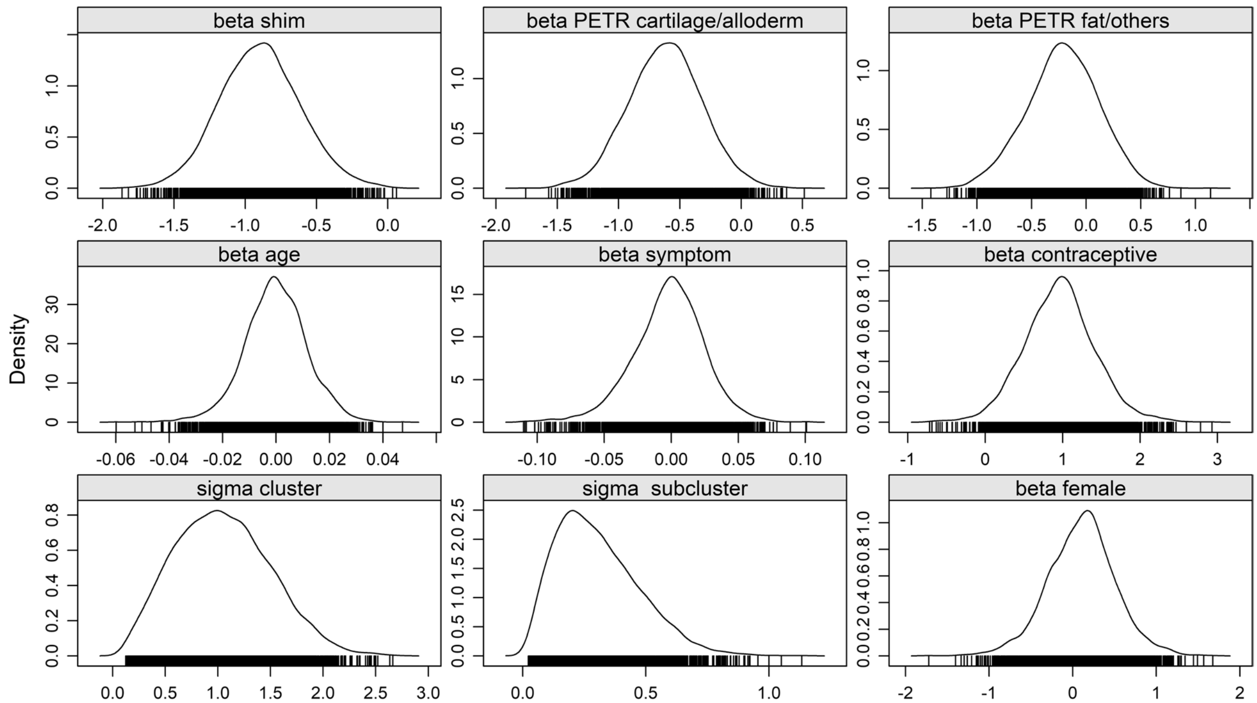

Fig. 2 MCMC density plot for Cox proportional hazards model with nested frailties

Table 3 Bayesian Cox models without frailty (model 1), with one frailty (model 2) and with nested frailties (model 3)

	Model 1		**Model 2**		**Model 3**	
Parameter	**Mean**	**(SE)**	**Mean**	**(SE)**	**Mean**	**(SE)**
β_1 (shim)	−0.992	(0.232)	−0.825	(0.287)	−0.888	(0.281)
β_2 (petr cartilage/alloderm)	−0.540	(0.264)	−0.566	(0.305)	−0.599	(0.308)
β_3 (petr fat/others)	−0.041	(0.273)	−0.192	(0.325)	−0.211	(0.329)
β_4 (age)	0.001	(0.006)	−0.001	(0.013)	0.000	(0.012)
β_5 (female)	0.175	(0.215)	0.101	(0.437)	0.109	(0.411)
β_6 (contraceptive use)	0.814	(0.211)	0.989	(0.513)	0.972	(0.465)
β_7 (symptom duration)	0.005	(0.013)	−0.005	(0.029)	−0.002	(0.025)
λ_1	0.270	(0.067)	0.154	(0.066)	0.178	(0.074)
λ_2	0.121	(0.030)	0.073	(0.032)	0.084	(0.035)
λ_3	0.068	(0.018)	0.051	(0.022)	0.056	(0.023)
λ_4	0.041	(0.013)	0.036	(0.017)	0.039	(0.018)
Variance of random effects						
σ (subcluster)					0.301	(0.174)
γ (cluster)			1.304	(0.398)	1.007	(0.456)

A wide range of surgical techniques have been described previously for treating patients with PETD; however, this was the first study to compare the effects of surgical procedures for PETD [4, 22–24]. Consistent with our prior study, patients who underwent shim insertion had sustained PETD symptom resolution compared with those who received calcium hydroxyapatite injection [5]. Shim placement is a minimally invasive surgical procedure and it can result in symptom resolution for the majority of patients, although some patients may later develop otitis media with effusion. Patulous ET reconstruction (PETR)

Table 4 Bayesian Weibull models without frailty (model 4), with one frailty (model 5) and with nested frailties (model 6)

	Model 4		Model 5		Model 6	
Parameter	Mean	(SE)	Mean	(SE)	Mean	(SE)
β_1 (shim)	−0.994	(0.241)	−0.833	(0.287)	−0.879	(0.281)
β_2 (petr cartilage/alloderm)	−0.537	(0.255)	−0.544	(0.302)	−0.580	(0.296)
β_3 (petr fat/others)	−0.053	(0.271)	−0.175	(0.317)	−0.201	(0.318)
β_4 (age)	0.001	(0.006)	0.000	(0.012)	0.000	(0.011)
β_5 (female)	0.159	(0.211)	0.108	(0.425)	0.104	(0.374)
β_6 (contraceptive use)	0.825	(0.214)	0.977	(0.476)	0.951	(0.426)
β_7 (symptom duration)	0.004	(0.013)	−0.001	(0.026)	−0.001	(0.023)
μ	0.254	(0.061)	0.155	(0.062)	0.167	(0.061)
ρ	0.601	(0.043)	0.669	(0.052)	0.664	(0.050)
Variance of random effects						
σ (subcluster)	-		-		0.277	(0.156)
γ (cluster)	-		1.148	(0.361)	0.927	(0.344)

Table 5 Model comparison

	LPML	DIC	$\overline{D}$	p_D
Model 1 Cox	−484.91	980.71	969.83	10.89
Model 2 Cox frailty	−447.80	1088.12	895.61	192.51
Model 3 Cox nested frailties	−453.71	1129.19	907.41	221.78
Model 4 Weibull	−443.22	895.43	886.44	8.99
Model 5 Weibull frailty	−411.78	985.56	823.56	162.00
Model 6 Weibull nested frailties	−417.95	1044.40	835.91	208.49

techniques varied widely; therefore, we examined the resolution of symptoms by technique and insertion material. When we examined by insertion material, PETR procedure using cartilage or Alloderm provided a better outcome than PETR using fat or HA injection. PETR technique involved partial obliteration or insertion of cartilage graft into the anterolateral or posteromedial wall. It was difficult to determine which PETR technique provided optimal outcomes and more studies are needed. As reflected in the variance of patient-level random effects in the nested frailty model, treatment effects varied by patients. However, patient factors such as age, gender, duration of symptoms before surgery, and most underlying etiologies of PETD did not explain the variation in the effects of treatment.

Bayesian methods provide flexibility in modeling hierarchical survival data and appropriately account for multiple levels of hierarchal clustering. In our study, the point estimate of the treatment effects and width of credible intervals were moderately different between the nested frailty model and the frailty model that only accounts for patient-level clusters. Therefore, not accounting for those clusters can lead to misleading inferences. Some patients underwent multiple different surgical treatments in their affected ear; thus, it was important to account for the correlated multiple event times within the same side of the ear. Moreover, the Bayesian approach provided flexibility in building hierarchical models and adjusting for multiple potential confounding factors. Although the Weibull model fitted well in our study, the Cox proportional hazards model (piecewise constant hazards model) is generally a robust choice to model the baseline hazard in most settings.

Conclusions

Our study shows the importance of accounting for all levels of hierarchal clustering for accurate inference. We accounted for the patient and ear level clustering using the Bayesian nested frailty model. Shim insertion and patulous ET reconstruction provide optimal symptom resolution for the surgical management of PETD. Bayesian nested frailty models provide flexibility in examining the effects of multiple surgical treatments while accounting for multiple levels of hierarchal clustering.

Abbreviations

PETD	Patulous Eustachian tube dysfunction
MCMC	Monte Carlo Markov Chain
ET	Eustachian tube
HA	Hydroxyapatite
PETR	Patulous Eustachian tube reconstruction
CI	Credible interval
DIC	Deviation information criterion
CPO	Conditional predictive ordinate
LPML	Log pseudo-marginal likelihood

Authors' contributions

KK, BW, JT, and DP made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data. KK drafted the manuscript and BW, JT, and DP critically reviewed the manuscript. All authors approved the final manuscript.

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Data availability
The dataset used for analysis during the current study is not publicly available due to privacy restrictions; however, the dataset and the code are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board (IRB) at Boston Children's Hospital (IRB-P00010498). The IRB at Boston Children's Hospital waived the requirement for patients' informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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