Frailty models for repeated Clinical Mastitis Episodes in Dairy Cows

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Abstract

Clinical mastitis occurs essentially at any time during lactation, with usually a higher incidence in early lactation. Since cows that have had a case of clinical mastitis are more likely to get a second case of clinical mastitis, time-to-event models need to include the within cow correlation between these events. Cows within herds are likely to be more similar than cows between herds. We therefore developed a series of correlated time-to-event models (frailty models) to accurately correct for this within cow correlation. The results indicated that random effects were large when the model was not fully specified. Missing covariates are represented in the random effect. When the model is not fully specified, the omission of random effects may have a large impact on the inference drawn from the data.

Introduction

CM is a major problem on dairies worldwide, causing lower milk production, unsaleable milk due to antibiotic presence, and culling of affected cows. We previously studied the effect of the 1st occurrence of pathogen-specific CM (see for example Gröhn et al. 2005). However, CM can occur several times during a cow's lactation, and the effects may vary with episode. Survival analysis, with a counting process to account for recurrent events, can handle this (Therneau and Grambsch 2000). Our aim in this study was to study the repeated occurrence of clinical mastitis during lactation and to predict the time to clinical mastitis using a set of cow-level covariates.

Materials and Methods

Calving, and health data, including information on all CM episodes, were available for 2573 Holsteins, calving from October 1999 to July 2001, in two New York herds. We used survival analysis, with a Cox proportional hazards model (S-Plus), to estimate the time to occurrence of the clinical mastitis event. We followed cows for one lactation, from calving until culling, subsequent calving, or end of study; cows that did not have the event of interest (mastitis) were either culled or dried off, and in both cases were considered censored. To account for multiple CM occurrences, we used the 'GAP' coding approach whereby the time at risk for a mastitis event is measured. For cows with multiple events, multiple observations are present in the data set. The time at risk for the second case is counted starting the day after the first case. The idea is that cows are only at risk for a second case if they have experienced a first case (Therneau and Grambsch 2000). Each non-CM cow was represented by one observation, having a start time at calving and end time drying off or culling date. A cow with one CM episode was allocated two observations; the first covered the period from calving date to date of 1st CM episode, and the second from date of 1st CM episode to culling or censoring date. A cow with two CM episodes had three observations, covering the following time intervals: 1) calving date to date of 1st CM episode; 2) date of 1st CM episode to date of 2nd CM episode; and 3) date of 2nd CM episode to culling or censoring date. Similarly, cows with three or four CM episodes were allocated four and five observations, respectively. Cow-level covariate that were observed included post-partum diseases (Retained Placenta (=RP), Metritis, Displaced Abomasum, Lameness), parity of the cow (PAR 1, 2, 3 and >3) and milk production at the first test day (MILK).
Our Cox proportional hazard regression model with frailty was of the form:

$$(\text{time at risk}(i))^{*}\text{censor}(0) = \text{disease} + \text{parity} + \text{Milk prod} + \text{at-risk-interval}(i) + z$$

where *time at risk* denotes the time at risk for mastitis case i (i=1…4); *censor* is a censoring indicator (0 is the censoring (not mastitis) value); *disease* represents diseases (other than CM) with significant effects on culling. *Milk Prod* was the milk production in kg at first test day; *at-risk interval* denotes which CM episode (ARint 1, 2, 3, and >3) the observation pertains to; *z* represents the Frailty (random effect for excess risk in a cow). Only cows with clinical mastitis after the first test day were included in this analysis. Herd was included as a stratifying variable in each of the models.

Results and Discussion

2229 cows (81.9%) had no CM episodes during the study lactation, 267 (13%) had one episode, 52 (2.8%) had two episodes, 12 (0.9%) had three episodes, and six cows (0.2%) had four episodes. 20% of the cows were culled. After one CM episode, CM cows had 22% probability of getting a second case. After two episodes, CM cows had 32% probability of getting a third case, and after three episodes the risk of a fourth case was 52%. Median days to clinical mastitis was resp. 244, 98, 57, and 20 for the first, second, third and greater than third case of clinical mastitis. This increased hazard rate is also depicted in Figure 1.

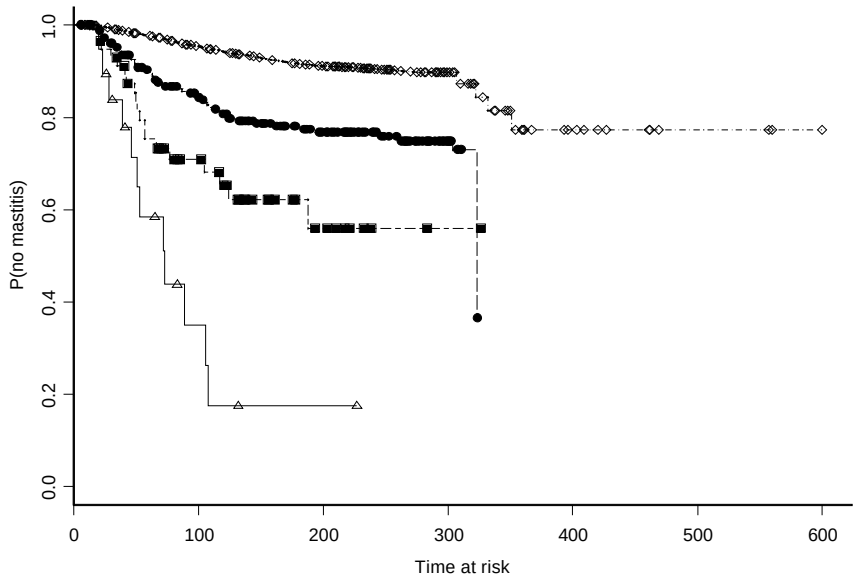

Figure 1 Time to event curves for cows with 1, 2, 3, or ≥4 clinical mastitis episodes during lactation (1 CM episode: --•--; 2 CM episodes: -- --; 3 CM episodes: --•--; ≥4 CM episodes: -•-).

The final model included terms for parity, retained placenta, milk production, milk production*parity and the indicator for the at-risk interval. The frailty parameter (which is the variance of the random effect with a fixed mean of one) was large in the null-model and decreased when more covariates were added to the model. With the inclusion of the indicator variable for at-risk interval, the random effect virtually disappeared.

This reduction in the size of the random effect is depicted in Figure 2.

Table 1 Parameter estimates for the covariates with their standard error in a model with and without random effect. (*) indicates p<.1, * indicates p<.05, ** indicates p<.01

	No Random			Random		
	Exp	Se		Exp	Se	
RP	0.055	0.155		0.054	0.155	
Milk	0.0109	0.01		0.0109	0.01	
Par=1	0.212	0.448		0.212	0.448	
Par=2	-0.992	0.557	(*)	-0.992	0.557	(*)
Par=3	0.7367	0.443		0.737	0.443	
Par1*Milk	-0.0823	0.024	*	-0.0823	0.024	*
Par2*Milk	0.0121	0.0183		0.0121	0.0183	
Par3*Milk	-0.0326	0.0151	*	-0.0326	0.0151	*
ARint1	-2.556	0.237	**	-2.554	0.237	**
ARint2	-1.548	0.252	*	-1.545	0.252	*
ARint3	-1.064	0.294	*	-1.062	0.294	*

Table 1 shows the parameter estimates for the covariates with their standard error in a model with and without random effect. As may be expected from figure 2, since the random effect is very small (and non significant) in this model, relatively little impact is present on the parameters or their standard deviation. Table 2 shows the parameter estimates for the covariates with their standard error in an incomplete model (the indicator variable for at-risk interval is not included). Since the random effect is now relatively large, a substantial impact of the inclusion of the random effect is observed. Parameters change in size and particularly the standard error increase substantially. This has an important impact on the statistical significance of the covariates in the model.

Table 2. Parameter estimates for the covariates with their standard error in an incomplete model with and without random effect. * indicates p<.05, (*) indicates p<.1.

	No Random			Random		
	Exp	Se		Exp	Se	
RP	0.323	0.1522	*	0.288	0.203	
Milk	0.0197	0.0107	(*)	0.0238	0.0144	
Par=1	0.0442	0.4463		0.116	0.551	
Par=2	-1.55	0.5647	*	-1.3	0.683	(*)
Par=3	0.5036	0.4571		0.873	0.595	
Par1*Milk	-0.0773	0.0239	*	-0.0831	0.0277	*
Par2*Milk	0.0261	0.0186		0.014	0.023	
Par3*Milk	-0.0305	0.0156	*	-0.043	0.0203	*

Conclusions

Modeling correlated time to event data requires a detailed analysis of variance components. Ignoring these in the analysis of complex data will lead to improper inference.

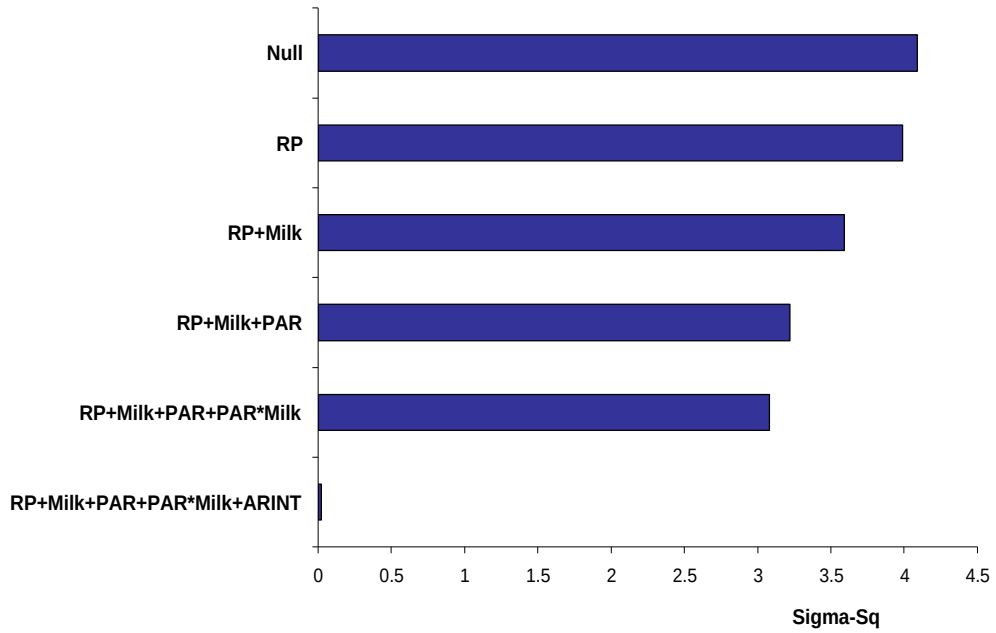

Figure 2. The variance of the random effect (Sigma-Sq) is shown in subsequent regression models.

References

Gröhn, Y. T.; González, R. N.; Wilson, D. J.; Hertl, J. A.; Bennett, G.; Schulte, H.; and Schukken, Y. H. (2005) Effect of pathogen-specific clinical mastitis on herd life in two New York State dairy herds. *Preventive Veterinary Medicine*, 71 (2005), 105-125.

Therneau, T. M. and Grambsch, P. M. (2000) Modeling Survival Data: Extending the Cox Model. Springer-Verlag, New York. 350 pp.