Analysis of Survival of Pigs Challenged with the Porcine Reproductive and Respiratory (PRRS) Virus

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Introduction

Porcine reproductive and respiratory syndrome (PRRS) has been one of the most devastating viral diseases in commercial pig herds, resulting in total annual costs to the US pork industry estimated at $560 million USD (Petry *et al*., 2006). PRRS virus (PRRSV) affects reproduction through abortions and higher proportions of non-viable pigs as well as respiratory health, causing higher mortality and poor performance in growing pigs. Improving resistance or tolerance to PRRSV through breeding is a high priority goal in swine genetic research. Under normal commercial conditions, where presence of PRRSV cannot be completely eliminated, selection should be aimed at decreased mortality and smaller impact on performance in the case of PRRSV infection. In this paper, we investigate genetics of survival in pigs experimentally challenged with a highly virulent strain of PRRSV by means of survival analysis.

Material and Methods

Animals and Experiment: The animals originated from two genetic nucleus farms declared free of PRRS. The experiment was conducted from Summer 2006 through Spring 2007, in five batches of 200-250 pigs each. At the age of about three weeks, animals were delivered to an experimental facility and randomly assigned to pens. After a 7 day acclimation period, each pig was challenged by nasal administration of an inoculum prepared from a well-characterized strain of the PRRSV commonly found in North American commercial production systems. The pigs were kept at the facility for at least 35 days after the challenge and observed daily. Death was recorded if an animal was found dead or had to be euthanized.

The data set used in the analysis contained 1081 animals, sampled approximately equally from each of two different genetic lines. The animals originated from 38 sires, 254 dams, and 261 litters. The average number of offspring per sire was 27.7, ranging from 1 to 118. The average number of animals per litter was 4.1 (1-10). Animals were considered uncensored (dead) if death or euthanasia was recorded on their observation sheet. Animals were treated as censored if they survived until 35 days of trial. In addition, a small number of animals that died of causes other than PRRS were considered censored. Pedigree was traced up to 9 generations back and comprised a total of 4033 individuals.

Statistical Analyses: The following semi-parametric Cox model was used for the analysis of PRRS challenge survival data:

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$$h(t,\mathbf{x_m}) = h_0(t)\ \exp\{l_i + s_j + fb_k + p_l + wt_m + a_m + litt_n\}$$

where $h(t,\mathbf{x_m})$ is the risk of dying at t days after PRRS challenge of animal m, $h_0(t)$ is the non-parametric baseline hazard function, l_i is the fixed effect of genetic line (2 levels), s_j is the fixed effect of sex (2 levels), fb_k is the combined effect of farm of origin and batch (10 levels), p_l is the fixed effect of pen (16 levels), wt_m is the effect of starting weight used as a linear covariate, a_m is the random effect of animal, and $litt_n$ is the random effect of litter. The animal effect was assumed to follow a multivariate normal distribution with mean zero and variance $\sigma^2_a A$, where A is the additive relationship matrix. The litter effect was assumed to follow a loggamma distribution, with the variance $\sigma^2_l = \Psi^{(l)}\hat{\gamma}_{litt}$ where $\Psi^{(l)}\hat{\gamma}_{litt}$ is the trigamma function of the parameter γ_{litt} estimated from the data. All effects were assumed time-independent.

Data analysis was performed using the software The Survival Kit V. 3.12 (Ducrocq and Sölkner, 1998). The analysis was first conducted without random effects to obtain significance of the fixed effects and determine the percentage of total variance explained by the model. The estimates of genetic and litter variance were obtained in a subsequent analysis as described in Ducrocq and Cassela (1996). The heritability was estimated as

$$h^2 = \frac{\hat{\sigma}_a^2}{\hat{\sigma}_a^2 + \psi^{(1)}\hat{\gamma}_{litt} + \frac{\pi^2}{6}}$$

Where $\hat{\sigma}_a^2$ and $\psi^{(1)}\hat{\gamma}_{litt}$ are estimated additive genetic and litter variance, respectively, and $\pi^2/6$ is the error variance, defined as the variance of the extreme value distribution.

Results and Discussion

At the end of the 35-d trial, 429 pigs were dead (uncensored) and 652 (60.3%) were treated as censored records. The average survival time for uncensored pigs was 18.6 days. The censoring time was 34.5 days, because only a small proportion of pigs were defined as censored before the end of the experiment. Most deaths occurred between days 14 and 21. The Kaplan-Meier survivor function (Figure 1) shows flat profile until approximately 10 days into the trial. After that, the profile becomes increasingly steep, until approximately 21 days, when it flattens again. Similarly, the hazard rate (Figure 2), which reflects number of deaths recorded each day, peaks initially around days 10 and 11 and is the highest between days 14 and 21 of the trial.

Fixed effects: The fixed effects in the model explain 7.3% of the variance in survival times. The most significant effects ($P<0.001$) were farm x batch combination, starting weight, and sex. Line effect was significant, but only at the 5% level, whereas effect of pen was not significant and could have been removed from the model.

To facilitate interpretation, the results are expressed as relative risk, defined as the ratio between the estimated risk of dying under the influence of a certain environmental or genetic

effect [exp($\hat{\beta}$)], and the average risk, which is set to 1 [exp(0)]. Lower relative risk reflects lower probability of dying of PRRS and is considered desirable from the selection point of view. For fixed effects, the level with the highest number of uncensored records was set to 0 and assumed to be the average risk. This level was used for comparison with all other levels of the effect.

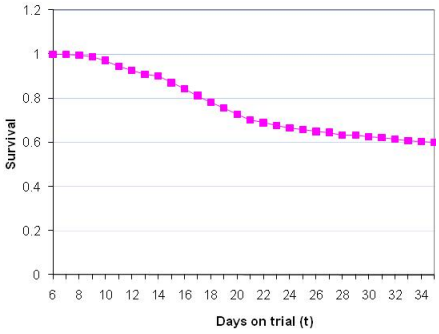

Figure 1: Kaplan-Meier survivor function

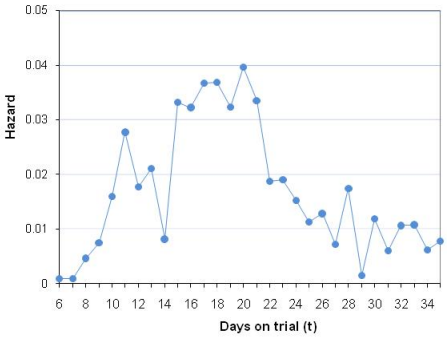

Figure 2: Instantaneous hazard rate for 1081 pigs during 35 days of trial

Figure 3 shows relative risk for 2 genetic lines used in the trial. Line 2 had lower relative risk than line 1 indicating existence of genetic differences in resistance to disease. Figure 4 shows relative risk of dying for male and female animals. Estimated relative risk for female animals was 30% lower than the risk for males, likely indicating higher susceptibility to this disease syndrome in male animals. Figure 5 illustrates relative risk for the combination of farm and batch, presented separately for each farm. Similar trend in relative risk from one batch to another can be observed for both farms, suggesting higher mortality in batches 3 and 4, i.e. during late fall and winter months. The regression coefficient of survival on starting weight was estimated at -0.052, showing that higher weights are associated with lower risk of dying.

Random effects and genetic parameters: The estimates of litter and genetic parameters are given in Table 1. The estimate of the gamma parameter for the litter effect was 6.794. The estimated additive genetic variance was 0.629 with the corresponding heritability of 0.259. The estimated heritability was much higher than heritability of survival under "normal conditions" reported in literature (e.g., Cecchinato *et al*., 2008). The estimated relative risk for individual animals ranged from 0.29 to 3.44. The average estimated relative risk was 1.29 and 0.70 for uncensored and censored animals, respectively. Estimated relative risk for sires of the challenged animals ranged from 0.29 to 3.4, with the lowest risk sire having zero uncensored records and the highest risk sire having 88% (15 of 17 total) uncensored records.

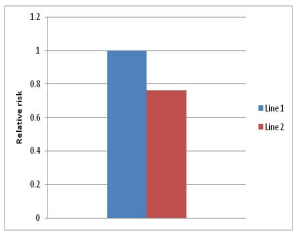

Figure 3: Estimated relative risk by genetic line

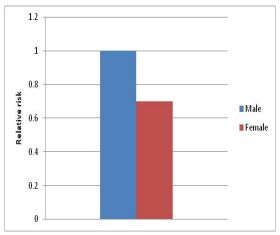

Figure 4: Estimated relative risk by sex

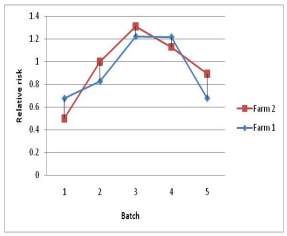

Figure 5: Estimated relative risk of dying by farm x batch combination

Table 1: Estimates of genetic and litter variance parameters

Effect	Estimated parameter	Estimate	h^2
litter	gamma	6.794	
animal	variance	0.629	0.259

Conclusions

The most important factors influencing survival of pigs challenged with PRRSV were sex, farm x batch, starting weight, and genetic factors, both between and within genetic lines. The relatively high heritability of survival and large differences in estimated relative risk among animals imply that mortality caused by PRRS could effectively be reduced by breeding. However, selection and breeding under disease conditions are not practical. Therefore, it is necessary to apply other methods, such as marker assisted selection, to successfully target the genetic component of disease tolerance.

References

Cecchinato, A., Bonfatti, V., Gallo, L. and Carnier, P. (2008): *J. Anim. Sci.* 86:2486-2495.

Ducrocq, V. and Sölkner, J. (1998): in *Proc. 6th WCGALP*, volume 27, pages 447–450.

Ducroq, V. and Casella, G. (1996)*: Genet. Sel. Evol.* 28:505–529.

Petry, D., Johnson, R. and Lunney J. (2006): *2006 Nebraska Swine Report*:53-56.