Equine vet. J. (2002) **34** (5) 438-443

Long-term survival of equine surgical colic cases. Part 2: Modelling postoperative survival

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Keywords: horse; colic; survival analysis; penalised Cox regression; random effects modelling

Summary

Colic surgery is a frequently performed operation with high postoperative mortality. This study was undertaken to identify variables associated with decreased postoperative survival. We used data from 321 horse years of postoperative survival time to model the probability of survival following recovery from colic surgery. Continuous variables were modelled using a 6 variable, penalised Cox regression model. This demonstrated approximately linear relationships between survival and the following variables: increase in packed cell volume (PCV), intestinal resection length, time to surgery (interval between onset of colic and surgery) and duration of surgery. No significant decrease in survival was demonstrated with increasing age of the patient or with heart rate. The only categorical variable to be significantly associated with decreased survival was epiploic foramen entrapment. The final, fixed effects Cox proportional hazards model of postoperative survival included the variables epiploic foramen entrapment, PCV, resection length and duration of surgery, each variable adjusted for the nonlinear relationship with time to surgery. Residual variation in postoperative survival attributable to professional personnel (referring veterinary surgeon, anaesthetist and surgeon) was explored by fitting each as a random effects term in the model. Little of the residual variation could be attributed to any category of personnel. Model diagnostics indicated little influence by individual outliers on model parameters and little evidence of subjects poorly predicted by the final model. The study highlights factors influencing the long-term survival of horses recovering from colic surgery and proposes a model that can be used to inform prognosis.

Introduction

The management of horses with colic is a major challenge to equine veterinary surgeons. The term 'colic' encompasses a wide range of disease entities, all of which have a similar clinical presentation. Prognosis however, varies greatly between the different diseases and according to the treatment regimen selected. A further complication in the assessment of colic cases is the large number of clinical parameters that can be measured and the variability of each parameter. Recent advances in epidemiology and statistical modelling enable the detailed exploration of complex relationships between explanatory variables and specific outcomes (e.g. survival, hernia formation, postoperative ileus). Furthermore, the co-relationships between explanatory variables can be studied and accounted for (Reeves and Curtis 1989).

Multivariable modelling has been used in a number of studies of equine colic (reviewed by Reeves and Curtis 1989). The most common application has been the development of prognostic models (Parry *et al.* 1983; Puotunen-Reinert 1986; Orsini *et al.* 1988; Reeves *et al.* 1989, 1990, 1992; Pascoe *et al.* 1990; Furr *et al.* 1995). None of these models have gained widespread acceptance in clinical practice. Reasons for this include the apparent complexity of the models (Reeves and Curtis 1989), but also difficulties in validating models developed on data from one hospital for use in a different hospital with different prevalences of surgery, death and different colic types.

Estimating prognosis in surgical cases prior to surgery necessarily precludes information gained at the time of surgery e.g. nature of the lesion, length of ischaemic bowel, duration of surgery. All of these factors may have a profound influence on the probability of survival. Exploratory laparotomy is a diagnostic procedure as much as a therapeutic one. For this reason we wanted to evaluate the prognostic importance of intra-operative variables.

The present study uses data derived from a 3 year, prospective study of postoperative survival of colic cases (Proudman *et al.* 2002). Specific objectives of data modelling are the development of simple models of postoperative survival, hypothesis generation and the description of the functional form of the relationships between continuous variables and the probability of survival. Random effects models (Aalen 1988) are used to evaluate, in a nondivisive manner, the influence of professional personnel on the outcome of colic surgery.

Materials and methods

Study population and data collection

Data from the study described by Proudman *et al.* (2002) were used. In brief, the clinical details from 341 horses that recovered from colic surgery were recorded on a computer database. All horses eligible were recruited between March 1998 and August

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TABLE 1: Comparison of age, heart rate, PCV and time to surgery between horses surviving colic surgery and those dying or undergoing euthanasia prior to recovery

	Survivors		Nonsurvivors	
	Median	s.d.	Median	s.d.
Age (years)	10	6.4	13	5.6
Heart rate (beats/min)*	50	19.0	78	22.0
PCV (l/l)*	0.38	0.08	0.50	0.11
Time to surgery (h)	15.3	25.3	18.5	70.6

*IP<0.05 for Wilcoxon two-sample test.

2000. Postoperative progress was rigorously followed during hospitalisation and by means of periodic telephone and postal questionnaire, after discharge. A total of 321 horse years of postoperative survival were documented. The study population was a subpopulation of all surgical colic cases as horses were only recruited onto the study upon successful recovery from anaesthesia following surgery. Table 1 provides summary data for some clinical parameters for the study population (n = 311, excluding grass sickness cases), and for the 32 colic cases, that were anaesthetised for surgery during this period, that failed to recover from anaesthesia and were, therefore, ineligible for recruitment into the study.

Data analysis

Descriptive data for surgical survivors and nonsurvivors was compared with the Wilcoxon 2 sample test. Critical probability was set at P<0.05. The shape of the relationship between continuous variables (e.g. heart rate at admission, age, length of resection) and mortality was explored using penalised Cox regression models[1] (Therneau and Grambsh 2000). These are extensions of Cox regression models that fit nonparametric functions (p-spline smoothers) to estimate the relationships between outcome and explanatory variables (Anon 2001). The results can be displayed graphically to illustrate the multivariable functional form of these relationships (e.g. linear, quadratic or cubic). Penalised Cox regression modelling in S-Plus[1] has the additional advantage of testing fitted functions for linearity and the significance of nonlinearity. Final models were constructed using backwards elimination procedures and an assessment of the effect of variable inclusion on parameter estimates. A critical probability of 0.05 was used to assess effect. Model diagnostics explored the influence of individual observations on regression coefficients using plots of the scaled change in regression coefficient for each observation. Changes in coefficient greater than 0.4 of s.e. can be interpreted as exerting disproportional influence (Therneau 1994). A deviance plot was also generated, indicating the ability of the model to differentiate survivors and non-survivors. The combined effect of pairs of variables on the probability of mortality up to 100 days was explored by plotting 3-dimensional graphs of the smoothed relationships generated by generalised additive models (Hastie and Tibshirani 1990).

Residual variability in survival that could be attributed to random effects was tested by including variables such as referring clinician, surgeon and anaesthetist as frailty (gamma) terms in the model (Aalen 1988). A critical probability of 0.05 was used to determine significant effects.

TABLE 2: Variables explored as potential explanatory variables for postoperative survival

Continuous variables	Categorical variables
Age	Breed
Heart rate at admission	Gender
Duration of colic prior to surgery	Laparotomy diagnosis
Packed cell volume at admission	Resection (yes/no)
Resection length	Anastomosis type (jejuno-caecal vs. jejuno-jejunal)
Duration of surgery	Anastomosis method (stapled vs. handsewn)
	Anaesthetic induction agent
	Anaesthetic gaseous agent

Results

Continuous variables

Six continuous variables thought *a priori* to influence postoperative survival were modelled in a 6 variable, penalised Cox regression model using p-spline smoothers. Figure 1 illustrates the multivariable smoothed relationships between these variables and mortality risk (log hazard). It is apparent that age and heart rate at admission show no marked or consistent association with mortality. However, packed cell volume at admission (PCV), resection length and duration of surgery all show reasonably linear increases in mortality with increasing values. P values for linearity for PCV, resection length, duration of surgery and time to surgery (time between onset of colic and surgery) are all less than 0.05 indicating a significant linear component to their relationship with mortality. Of these 4 variables, only time to surgery has a P value for non linearity approaching 0.05, suggesting a significant non linear component to this p-spline fit.

Figure 2 illustrates the combined effect of PCV and duration of surgery and of PCV and resection length on the probability of death before 100 days. It is apparent that horses with high values of 2 variables had a significantly greater probability of death. For example, a horse with a PCV of 0.45 l/l at admission and no intestine resected had a probability of death of approximately 0.2 (20% of horses at risk). Whereas one with a similar PCV and 30 feet of intestine resected had a probability of approximately 0.45 (45% of horses at risk), rising to 0.6 if 35 feet of intestine were resected. No significant multiplicative interaction between variables was detected. Table 1 provides summary data for 4 continuous variables in survivors and nonsurvivors of colic surgery. Heart rate and PCV for these 2 groups are significantly different.

Categorical variables

Survival was categorised by a number of variables (listed in Table 2) and the influence of each on postoperative survival examined using Cox proportional-hazards modelling. Only epiploic foramen entrapment emerged as a significant variable. Probability of survival of epiploic foramen entrapment cases is significantly different to that of ileal impaction and pedunculated lipoma cases (RR = 2.1, 95% CI 1.4, 2.8, P = 0.033). Kaplan-Meier plots comparing the cumulative probability of survival after surgery for different small intestinal lesions are shown in Proudman *et al.* (2002).

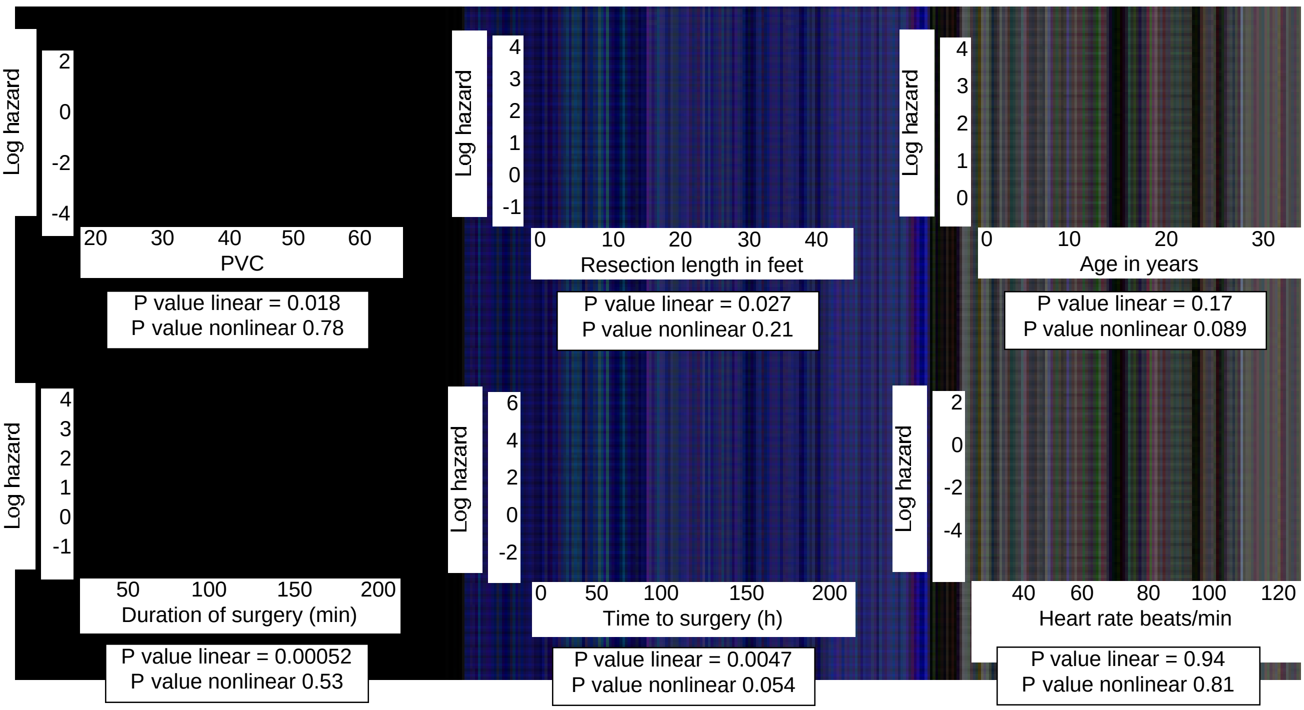


Fig 1: Plot of p-spline smoothers for the 6 continuous variables considered for inclusion in the fixed effects model. Results of significance tests for linearity and nonlinearity shown for each variable.

Model construction

Based on the results described above, a Cox proportional-hazards model for postoperative survival was constructed including PCV, resection length, time to surgery, duration of surgery and epiploic foramen entrapment. Due to the nonlinear relationship between time to surgery and mortality, this variable was fitted as a p-spline with 5 degrees of freedom (the most parsimonious fit). Table 3 gives details of parameter values for the model, adjusted for the nonlinear relationship with time to surgery.

Random effects

The residual variation due to referring clinician, surgeon and anaesthetist was explored by inclusion of each as a random effect (frailty) term in the fixed effects model. The *a priori* hypothesis being tested was that some referring clinicians, surgeons and anaesthetists were associated with better long-term survival. The variance estimates for these effects are given in Table 4 and it is apparent that residual variation attributable to anaesthetist, surgeon or referring veterinary surgeon in this hospital was nonsignificant.

TABLE 3: Parameter values for a fixed effects model of postoperative survival (adjusted for nonlinear relationship with time to surgery)

Variable	Coefficient (ß)	s.d.	P value
Fixed effects model			
Resection length (increment per foot)	0.029	0.014	0.0310
Duration of surgery (increment per min)	0.012	0.004	0.0011
PCV (increment per 1%)	0.046	0.018	0.0088
Epiploic foramen entrapment (y/n)	0.75 (RR = 2.11; 1.42, 2.79)	0.350	0.0330

y/n = yes/no.

Model diagnostics

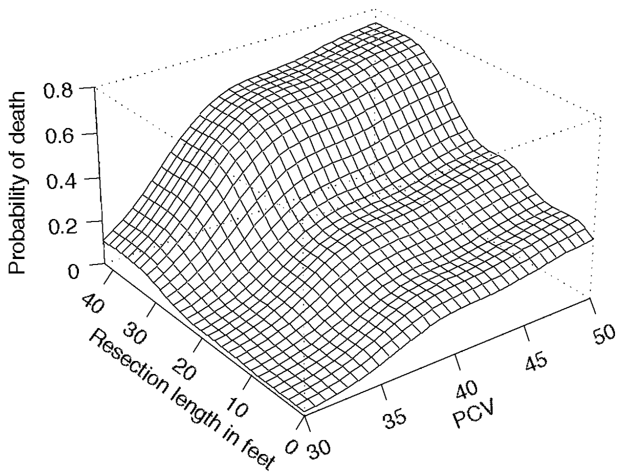
Apart from 4 observations on the regression coefficient for the variable 'time to surgery,' the scaled residuals are less than 0.4 of s.e. (Fig 3) indicating that individual observations have relatively little influence on the parameters in the final model. The plot of deviance residuals from the final model shows little evidence of poorly predicted subjects.

Discussion

The model described above differs radically from previous models of colic survival because it deals with the long-term survival of horses undergoing colic surgery. Previous prognostic models (Parry *et al.* 1983; Puotunen-Reinert 1986; Orsini *et al.* 1988; Reeves *et al.* 1989, 1990, 1992; Pascoe *et al.* 1990; Furr *et al.* 1995) have sought to use pre-operative clinical data to predict short-term outcome. The

TABLE 4: Variance estimates for random effects terms in the fixed effects model

Variable	Variance estimate	P value
Random effects		
Referring veterinary surgeon	0.00	0.93
Surgeon	0.06	0.15
Anaesthetist	0.14	0.25



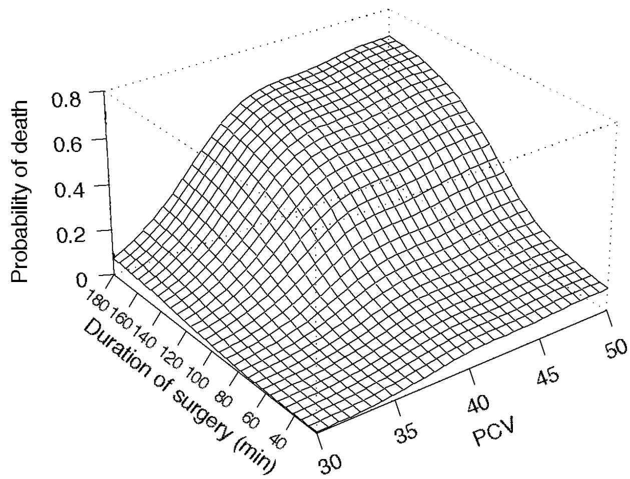


Fig 2: Three-dimensional graphs illustrating the combined effect of PCV and resection length (above), and PCVand duration of surgery (below) on the probability of death by 100 days.

modelling techniques used in our study also differ from those employed previously. In particular, evaluation of the functional form of relationships between continuous variables and mortality, and the use of penalised Cox models, have not previously been applied to postoperative colic data.

There are clear differences between our study population (horses surviving colic surgery) and the population of surgical nonsurvivors not eligible for inclusion in this study (Table 1). Median heart rate and PCV are higher than for the surgical survivor group. This suggests that our case definition (recovery from surgery) excludes many severely endotoxaemic horses which are unlikely to survive surgery. Clinical parameters indicating endotoxaemia have been identified previously as important prognostic indicators in horses prior to colic surgery (Orsini *et al.* 1988; Reeves *et al.* 1989, 1990, 1992; Pascoe *et al.* 1990; Furr *et al.* 1995; Thoefner *et al.* 2001).

The current approach acknowledges that much of the variability in survival is due to the different disease processes that cause colic. Of the 5 significant variables, only one is a preoperative clinical parameter. The other 4 variables (time to surgery, epiploic foramen entrapment, duration of surgery and resection length) are contingent upon surgery having taken place. This study suggests that trying to predict postoperative survival without these data would exclude much useful information. It is also questionable how necessary it is to use models to predict survival preoperatively. Blikslager and Roberts (1995) demonstrated that clinicians were reasonably accurate at predicting survival on the basis of clinical examination. They cite positive predictive values of 83–91%. A more important prediction might be the need for surgical intervention in colic cases. This has been addressed by Reeves *et al.* (1992) who developed a logistic regression model to predict the need for surgery. This model included seven clinical variables. Validation of the model indicated that the model fitted the data poorly. In the light of these previous studies and the reluctance of clinicians to use predictive models incorporating preoperative data only, our study was designed to evaluate data derived at surgery as well as preoperatively, and to identify variables associated with long-term survival of those horses successfully recovering from surgery.

The relationships between continuous variables and survival are illustrated by the output from the 6 variable, penalised Cox regression model. This suggests that PCV, resection length and duration of surgery have an approximately linear association with decreased survival (mortality). Increasing values of ‘time to surgery’are associated with a significant increase in mortality but this relationship is significantly nonlinear. It is of interest that age shows no marked association with survival. Although the smoothing spline indicates increased mortality in horses over age 20 years, the confidence interval is wide due to the small number of observations and suggests that any difference is non-significant. This study offers little evidence that older horses recovering from colic surgery have a worse prognosis than younger ones.

The observed relationship between heart rate and survival indicates no increase in mortality with increasing heart rate. This is apparently contrary to the findings of Reeves *et al.* (1990, 1992) who found that a number of variables relating to cardiovascular compromise (PCV, heart rate, capillary refill time, pulse quality) were significantly associated with survival. This apparent difference can be explained by the different study populations. Our study focussed on surgical survivors only, largely excluding severely endotoxaemic horses (with high heart rate, PCV, poor pulse quality) as they were unlikely to survive surgery. Freeman *et al.* (2000), in a study of exclusively small intestinal colic cases, also reported no effect of heart rate.

The 3 dimensional plots, illustrating the combined effect of changes in 2 variables on the probability of death, highlight the need for a multivariable approach to modelling survival in postoperative colic cases. Single variables, considered in isolation, will not give an accurate estimate of the probability of survival in individual cases. Although the 3 dimensional plots consider the influence of 2 variables, the final model contains 5 variables that should be considered in combination when estimating the probability of death.

Modelling postoperative survival serves to highlight the variables with the greatest influence on postoperative survival. The results of our study suggest that both duration of surgery and length of intestinal resection are surgical variables with considerable prognostic value. Efforts to improve long-term survival should be focussed on decreasing surgery time and on understanding the mechanisms underlying the association

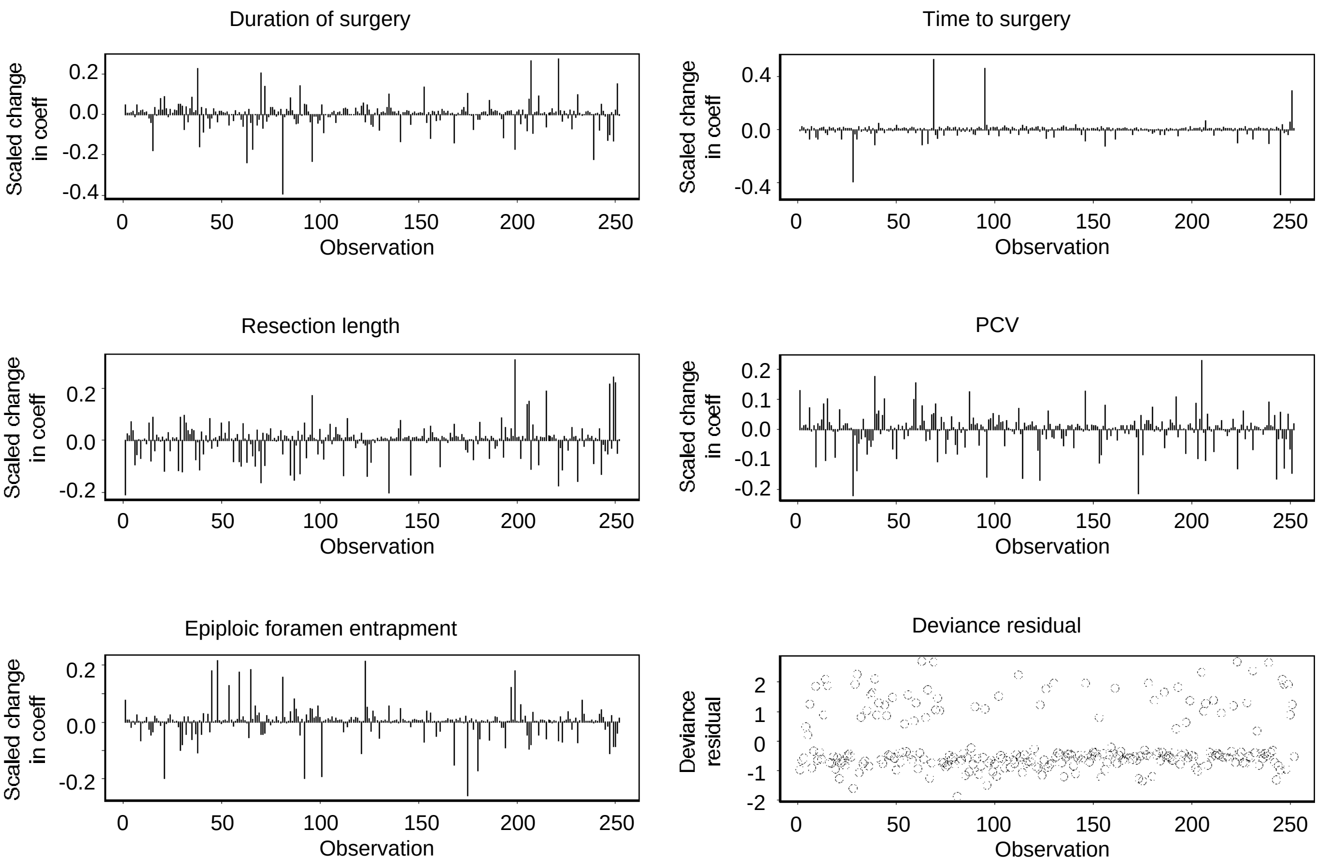


Fig 3: Plots of scaled residuals for each variable in the final model. Values of >0.4 for individual observations indicate outliers that may exert disproportional influence on the regression coefficient. The deviance residual plot indicates the ability of the model to differentiate survivors from nonsurvivors.

between length of resected bowel and risk of mortality. While some of the causes of prolonged surgery time are beyond the control of the surgeon (e.g. length of bowel involved, accessibility of diseased bowel), others are within his/her control. Examples of such include quick identification of the lesion and rapid surgical decision making. Whether it is possible to reduce the length of bowel resected in specific cases needs further investigation. At present, intestinal viability following strangulation is assessed subjectively. The advent of more objective measures of intestinal viability may allow resection to be minimised, or avoided altogether, in order to maximise the probability of long-term survival.

The influence of professional personnel on the postoperative survival of our colic cases was one that the investigators were keen to assess. However, we were also keen to perform the analysis in a non divisive manner in order to prevent direct comparisons between individuals. This was achieved by investigating the influence of our personnel as a random effect term in the model. Therefore a summary statistic, representing the contribution to residual variation (i.e. variation not explained by the terms in the model) made by professional personnel, was generated. This variation was small in magnitude and no further analysis was therefore necessary. Had this model suggested that differences in personnel made a major contribution to variation in survival, then the investigators would have been justified in exploring further. Freeman *et al.* (2000) reported a reduced probability of survival in horses operated on by surgeons with experience of less than 9 colic operations. Our database included 3 surgeons that met this criterion but no effect was demonstrated. This may reflect a genuine lack of effect or may be due to low statistical power. The authors suggest that random effects modelling is an effective screening method for conducting non divisive surgical audit amongst groups of professional personnel. If a significant effect is identified, further analysis might be justified to identify individuals associated with worse postoperative prognosis.

Surgery, involving both human and animal patients, is notoriously difficult to evaluate scientifically. Surgeons have traditionally taken an anecdotal approach to evaluating their own performance, with case series predominating (Horton 1996). A further problem associated with evaluation of surgical success is the artificial categorisation of follow-up as ‘during hospitalisation’ or ‘after discharge from the hospital’. In the veterinary literature this has lead to an over-emphasis on immediate postoperative success and a failure to account for mortality or postoperative complications that occurred after discharge. It is hoped that further prospective studies such as ours, with rigorous monitoring of animals after discharge, will generate high quality data about a range of surgical procedures. This will allow accurate descriptions of postoperative progress to be made and the development of models describing the risk of survival and the risk of developing postoperative complications. The results described in this study relate specifically to one hospital, they should not be taken as representative of all equine hospitals.

Variables not recorded in this study may also be of prognostic value. Differences in prognosis and in significant prognostic variables may arise from different populations of horse, different professional personnel and different surgical procedures.

This study has described the relationship between certain continuous variables and long-term postoperative survival following recovery from colic surgery. It has highlighted the association of epiploic foramen entrapment with reduced long-term survival and has described a multivariable model for postoperative survival. The influence of professional personnel (referring clinician, anaesthetist and surgeon) on the probability of long-term survival was found to be small.

Acknowledegements

This study is funded entirely by The Home of Rest for Horses. The authors thank their anaesthetist colleagues and residents in the Phillip Leverhulme Large Animal Hospital for their assistance with data collection. The willing co-operation of referring veterinary surgeons and horse owners is gratefully acknowledged. Some of the data presented in this paper were first presented at the Annual Conference of The Society for Veterinary Epidemiology and Preventive Medicine, 2001.

Manufacturer's address

[1]Insightful Corporation, Seattle, USA.

References

Aalen, O.O. (1988) Heterogeneity in survival analysis. *Stats. in Med.* **7**, 1121-1137.

Anon (2001) Penalised Cox models. In: *S-Plus 6 Guide to Statistics*. **2**. Insightful Corporation, Washington. pp 373-383.

Blikslager, A.T. and Roberts, M.C. (1995) Accuracy of clinicians in predicting site and type of lesion as well as outcome in horses with colic. *J. Am. vet. med. Ass.* **207**, 1444-1447.

Freeman, D.E., Hammock, P., Baker, G.J., Goetz, Foreman, J.H., Schaeffer, D.J., Richter, R.-A., Inoue, O. and Magid, J.H. (2000) Short- and long-term survival and prevalence of postoperative ileus after small intestinal surgery in the horse. *Equine vet. J., Suppl.* **32**, 42-51.

Furr, M.O., Lessard, P. and White, N.A. (1995) Development of a colic severity score for predicting the outcome of equine colic. *Vet Surg.* **24**, 97-101.

Hastie, T. and Tibshirani, R. (1990) *Generalized Additive Models*, Chapman and Hall, London.

Horton, R. (1996) Surgical research or comic opera: questions, but few answers. *Lancet* **347**, 984-985.

Orsini, J.A., Elser, A.H., Galligan, D.T., Donawick, W.J. and Kronfeld, D.S. (1988) Prognostic index for acute abdominal crisis (colic) in horses. *Am. J. vet. Res.* **49**, 1969-1971.

Parry, B.W., Anderson, G.A. and Gay, C.C. (1983) Prognosis in equine colic: a comparative study of variables used to assess individual cases. *Equine vet. J.* **15**, 211-215.

Pascoe, P.J., Ducharme, N.G., Ducharme, G.R. and Lumsden, J.H. (1990) A computer-derived protocol using recursive partitioning to aid in estimating prognosis of horses with abdominal pain in referral hospitals. *Can. J. vet. Res.* **54**, 373-378.

Proudman, C.J., Smith, J.E., Edwards, G.B. and French, N.P. (2002) Long-term survival of equine surgical colic cases. Part 1: Mortality and morbidity. *Equine vet. J.* **34**, 432-437.

Puotunen-Reinert, A. (1986) Study of variables commonly used in examination of equine colic cases to assess prognostic value. *Equine vet. J.* **18**, 275-277.

Reeves, M.J. and Curtis, C.R. (1989) "By the seat of your pants" or multivariable predictive modelling. *Equine vet. J.* **21**, 83-84.

Reeves, M.J., Curtis, C.R., Salman, M.D. and Hilbert, B.J. (1989) Prognosis in equine colic patients using multivariable analysis. *Can. J. vet. Res.* **53**, 87-94.

Reeves, M.J., Curtis, C.R., Salman, M.D. Reif, J.S. and Stashak, T.S. (1990) A multivariable model for equine colic patients. *Prev. vet. Med.* **9**, 241-257.

Reeves, M.J., Curtis, C.R., Salman, M.D., Stashak, T.S. and Reif, J.S. (1992) Validation of logistic regression models used in the assessment of prognosis and the need for surgery in equine colic patients. *Prev. vet. Med.* **13**, 155-172.

Therneau, T.M. (1994) *A Package for Survival Analysis in S,* Technical Report, Mayo Clinic.

Therneau, T.M. and Grambsh, P.M. (1998) Penalised models. In: *Modeling Survival Data*, Springer-Verlag, New York. pp 120-126.

Thoefner, M.B., Ersboll, A.K., Jensen, A.L. and Hesselholt, M. (2001) Factor analysis of the interrelationships between clinical variables in horses with colic. *Prev. vet. Med.* **48**, 201-214

Received for publication: 17.10.01
Accepted: 7.2.02