SURVIVAL OF HORSES FOLLOWING STRANGULATING LARGE COLON

VOLVULUS

Keywords: horse, large colon volvulus (LCV), strangulating, survival, colic.

Word Count: 4638
Summary

Reasons for performing study: The pattern of long-term survival and specific factors associated with long-term survival have not previously been evaluated in horses with a strangulating large colon volvulus (LCV).

Objectives: The aims of this study were to provide data on the long-term survival of horses with LCV and to identify pre-, intra- and post-operative variables associated with survival.

Methods: Clinical data and long-term follow up information were obtained from 116 horses with a strangulating LCV (≥ 360°) undergoing general anaesthesia. Two multivariable Cox proportional hazards models for post-operative survival time were developed: Model one included all horses and evaluated pre-operative variables and model two included horses that survived anaesthesia and evaluated pre, intra and post-operative variables.

Results: The study population comprised 116 horses. Eighty-nine (76.6%) survived general anaesthesia. Of these, the percentage that survived until discharge, to one year, and to two years was 70.7%, 48.3% and 33.7% respectively. Median survival time for horses that survived general anaesthesia was 365 days. In model one increased pre-operative packed cell volume (PCV) was significantly associated with reduced post-operative survival (Hazard Ratio [HR] 1.08, 95% confidence intervals [CI] 1.05 – 1.11). However, this effect changed over time. In model two abnormal serosal colour intra-operatively (HR 3.61, 95% CI 1.55 – 8.44), increased heart rate at 48 hours post-surgery (HR 1.04, 95% CI 1.02 – 1.06), and colic during post-operative hospitalisation (HR 2.63, 95% CI 1.00 – 6.95), were all significantly associated with reduced post-operative survival.

Conclusions: Survival time in horses with a LCV was associated with pre-operative PCV, serosal colour, heart rate at 48 hours post-operatively, and colic during post-operative hospitalisation.
Potential relevance: This study provides evidence based information on the long-term survival of horses with LCV and identifies parameters that may assist decision making by clinicians and owners.

Introduction:

Identification of factors that are significantly associated with prognosis following surgical treatment of colic allows clinicians and owners to make informed decisions regarding the management of individual horses [1, 2]. It has been recognised that these key prognostic indicators, and survival patterns following surgery, differ for various types of colic [1, 2, 3]. However, relatively few studies provide information regarding survival patterns following hospital discharge or on key prognostic indicators for specific surgical lesions.

Large colon volvulus (LCV) is one of the most painful and rapidly fatal causes of colic in the horse [4]. LCV represents between 10 and 20% of horses with colic that undergo exploratory laparotomy [5, 6]. Volvulus greater than or equal to 360 degrees has been found to be strongly associated with poor survival [3], with survival to discharge following strangulating LCV reported to lie between 36 and 74% [7, 8, 9]. In a study modelling long-term survival of horses following surgery for large intestinal disease, age, pre-operative PCV and heart rate were found to be significantly associated with post-operative mortality; however, horses with a strangulating LCV represented only 20% of the cases included in this study [3]. Post-operative persistent tachycardia has been previously suggested to indicate a poor prognosis for survival in horses with LCV [10] and in horses undergoing large colon resection and anastomosis (LCRA), increased heart rate at 24 hours post-operatively was significantly associated with post-operative mortality [11]. However, specific determinants of survival for
horses with a strangulating LCV have not been investigated in a large number of cases using survival analysis.

The aims of this study were to provide data on the long-term survival of horses with strangulating LCV and to identify pre, intra and post-operative variables associated with survival.

**Materials and methods:**

**Study population**

The case records of all horses with a LCV, (greater than or equal to 360 degrees), identified at exploratory laparotomy between 1st January 2001 and 31st December 2010 at the Equine Hospital, United Kingdom were reviewed. Horses were included if they underwent general anaesthesia and exploratory laparotomy. Horses that were euthanased during surgery were included, but horses that died or were euthanased prior to anaesthesia were excluded from the study population. Pre-, intra- and post-operative data were extracted from hospital records and entered into a computer database. Short-term survival data whilst in the hospital (reason for death and date of death) were obtained from hospital records. To evaluate long term survival, telephone questionnaires with owners were conducted following discharge from the hospital. The telephone questionnaire asked the date of death and reason for death. Questionnaires were conducted quarterly for the first year following colic surgery and bi-annually thereafter as part of an on-going study on colic survival [3]. This was with the exception of a 30-month period during which questionnaires were suspended due to an alteration in the study’s funding. Owners were re-contacted after this period. All horses remained in the study until they died or were lost to follow up, for
example, following a change of ownership. In cases where the owner was unable to provide
the exact date of death or censorship, this was defined as the mid-point of the week or month
in which the horse was reported to have died or been sold. In this study the term death
includes death due to euthanasia.

Statistical analysis
Descriptive data were generated and survival time was used to construct a Kaplan-Meier plot
of cumulative probability of survival [12]. The study population was divided into two groups.
Group one included the entire study population and evaluated pre-operative variables (model
one). Group two included only those horses that recovered successfully from anaesthesia and
evaluated pre, intra and post-operative variables (model two). Prior to univariable analysis,
all variables were assessed for correlation using Spearman’s rank correlation coefficients.

For both groups association with survival time was modelled using Cox proportional hazards
models [12]. Survival time (days) was measured as a continuous variable starting from the
date of induction of anaesthesia until death or censoring. Potential explanatory variables
were screened for univariable association with survival time. The functional form of the
relationship between continuous variables and survival time was modelled using penalised
Cox models and by generating smoothing splines for each continuous variable [13]. Variables
showing some evidence of univariable association with outcome (P<0.2) were evaluated in a
multivariable Cox proportional hazards model, which was constructed using a backwards,
stepwise elimination procedure [12]. Variables remained in the model if they significantly
improved the fit (p≤0.05) assessed using the likelihood ratio statistic. Variables with >33%
of missing values were excluded from the initial model-building procedure. Biologically
plausible interaction terms for variables remaining in the final model were assessed. As Cox
models assume proportional hazards, (i.e. the effect of a variable on the outcome is constant
over time), model diagnostics performed included Schoenfield residual plots to assess
proportionality throughout survival time. In addition, graphical assessment of log cumulative
hazards plots for categorical variables was performed. Scaled changes in the regression
coefficient for each observation (delta betas) were used to evaluate potential leverage by
individual observations for each variable [12]. The model was rerun excluding observations
with large delta-beta values (>0.4 or <-0.4) to evaluate their influence on parameter
estimates. The critical probability for all analyses was set at 0.05.

Results:
The study population included 116 horses, of which 63 (54%) were mares, 52 (45%) were
geldings and 1(1%) was a stallion. The median age of horses was 11 years (range 1-28 years)
and the median weight was 580kg (range 350-750kg). The median duration of colic signs
prior to surgery was 10 hours (range 3-96 hours). Median heart rate on admission was 60
beats/min (range 32-108 beats/min) and median packed cell volume (PCV) was 45% (range
27-65%). Only two horses underwent a large intestinal resection.

Of the 116 horses, 89 (76.7%) recovered from anaesthesia. Of these horses, the percentage
that survived until discharge, to one year, and to two years was 70.8%, 48.3% and 33.7%
respectively. The reasons for death are shown in table 1. Sixteen horses were lost to follow
up. The study included 67,386 days of survival. Median survival time for all horses was 88
days (Figure 1a) and median survival time for those horses that successfully recovered from
anaesthesia was 365 days (Figure 1b).
The results of univariable relationships of potential explanatory pre-operative variables with survival time as the outcome measure, when all the horses were included (Group one) are shown in Supporting items 1 and 2 (available online). On univariable analysis pre-operative variables significantly associated with increased risk of post-operative death were the degree of pain on admission, pre-operative heart rate and pre-operative PCV. The final Cox proportional hazards model (Model one) included only the variable pre-operative PCV, which was positively and significantly associated with the risk of post-operative death and demonstrated a linearly increasing likelihood of mortality (Figure 2 and Table 2). However, there was evidence of significant non-proportionality of the effect of the variable PCV over time (Figure 3), with reduced risk over time (p<0.007). A PCV*ln(time) interaction term was added to the model (Table 2). The effect of PCV was allowed to interact with time on a natural log scale; this was chosen since it was assumed that the effect of PCV would be greatest in the immediate post-operative period and then reduce as time passed. The PCV*ln(time) interaction term was significant, confirming that the effect of PCV does vary with time. Using this model, the hazard ratio was computed at a number of time points, with the hazard ratio at time t equal to 1.08*0.96^ln(t) (Table 3). The effect of pre-operative PCV decreases until day 7 post-operatively then the effect disappears.

To illustrate these results, a horse with a LCV that has a PCV on admission of 55% has a 4.7 times greater risk of mortality, intra or post-operatively, than a horse with a pre-operative PCV of 35%.
The results of univariable relationships of potential explanatory pre, intra and post-operative variables with survival time as the outcome measure, when only those horses that recovered successfully from anaesthesia were included (group two) are shown in Supporting items 3 and 4 (available online). Categorical variables that were significantly associated with increased risk of post-operative death were colour of large colon serosa (normal/abnormal), colour of mucosa at the enterotomy site (normal/abnormal), haemorrhage at the enterotomy site (present/absent), colic during post-operative hospitalisation (no/yes) and repeat laparotomy (no/yes). Derangements in serosal and mucosal colour and the presence of haemorrhage at the enterotomy site were defined by the surgeon at the time of exploratory laparotomy and recorded in the horse’s surgical report. Continuous variables significantly associated with increased risk of post-operative death were pre-operative heart rate and pre-operative PCV, heart rate at 24 and 48 hours post-operatively, PCV at 24 and 48 hours post-operatively and total protein at 24 and 48 hours post-operatively. The final Cox proportional hazards model included serosal colour intra-operatively (normal/abnormal), heart rate at 48 hours post-surgery and colic during post-operative hospitalisation (no/yes), which were all positively associated with risk of post-operative death (Table 4). Examination of the functional form of the relationship of heart rate at 48 hours post-operatively demonstrated a linearly increasing likelihood of mortality, with no evidence of non-linearity (Figure 4). In model two graphical and statistical evaluation of Schoenfeld residuals for all variables, and graphical assessment of log cumulative hazard plots for categorical, confirmed the assumption of proportional hazards to be valid (Supporting item 5 and Supporting item 6a and Supporting item 6b, available online).
To illustrate the results for model two, a horse with a LCV that has a heart rate of 60 beats per minute at 48 hours post-operatively has a 2.2 times greater risk of post-operative mortality than a horse with a heart rate of 40 beats per minute at 48 hours post-operatively.

For both models removal of influential individual observations with large delta-betas had little effect on coefficients, showing the models were stable and all observations were retained within the models.

Discussion

This study provides information on survival following surgery for a specific type of colic (strangulating LCV) and identifies risk factors for post-operative survival. The results of the study may assist clinicians with decision-making in the management of horses with strangulating LCV and clinicians can utilise this information to provide owners of these horses with evidence-based information regarding their survival following surgery.

Survival to discharge following LCV has been previously reported to lie between 36-74% [7, 8, 9]. This wide range can partially be attributed to differences between hospital populations, the lack of consistency in the definition of a strangulating LCV and the fact that some studies excluded horses that did not survive anaesthesia. Variation in the number of horses euthanised without an opportunity for exploratory laparotomy, due to a poor prognosis, will also influence survival rate. This study included only horses with a volvulus of greater than or equal to 360 degrees in order to ensure all cases of volvulus were strangulating in nature. LCV was found to be associated with considerable post-operative mortality, with over 20% of horses not recovering from anaesthesia. Of those horses that recovered from anaesthesia,
less than 50% were alive one year post-operatively and only a third of horses were alive two years post-operatively.

Two models were created to allow exploration of pre, intra and post-operative parameters. In model one only increased pre-operative packed cell volume (PCV) on admission was significantly associated with increased post-operative mortality. This significant association emphasises the importance of early referral of horses with a suspected LCV, prior to alteration of their PCV. Pre-operative PCV has been shown previously to be significantly associated with long term survival for other colic types [1, 2] and in particular with long term survival following surgery for large intestinal disease [3]. Pre-operative PCV was found to be associated with an increased risk of mortality in the early post-operative period and its influence diminished by day 7. Elevated PCV on admission is likely to reflect the degree of systemic inflammatory response that may develop during hospitalisation, which will affect survival in the immediate post-operative period. Pre-operative PCV was not retained in model two when intra and post-operative variables were included. It is likely that those horses that died or were euthanased on the operating table (and were therefore excluded from model two), had a high PCV on admission, and were excluded from model two.

When pre, intra and post-operative variables were included in a multivariable model, the variables abnormal serosal colour of the large colon intra-operatively, heart rate at 48 hours post-operatively, and colic during post-operative hospitalisation were found to be significantly associated with reduced long term survival. Alteration in serosal colour is indicative of the degree of vascular compromise of the large colon. It may correlate with the degree of the systemic inflammatory response, which occurs as a result of the loss of mucosal
barrier function, and the subsequent trans-mural and trans-vascular migration of microbes and pathogen associated molecular patterns, including LPS (endotoxin), into the peritoneal cavity and circulation [14, 15]. Alternative intra-operative methods of estimating prognosis in cases of LCV, including pulse or surface oximetry, fluorometric evaluation [16, 17] and colonic luminal pressure [18] are often unreliable and may not be readily available. Histopathologic evaluation of an intra-operative biopsy, collected from the pelvic flexure, examining the crypts and interstitial crypt space has been shown to be a highly sensitive and specific predictor of post-operative survival in cases of LCV [19, 20]. However, intra-operative evaluation of a biopsy is often impractical and a more recent study found histopathological evaluation of pelvic flexure biopsies did not accurately predict survival [21].

Post-operative persistent tachycardia has been suggested to indicate a poor prognosis for survival in horses with LCV [10]; however, its effect has never previously been quantified. Post-operative tachycardia is related to the degree of systemic inflammatory response present post-operatively [22], which is likely to determine survival in cases of strangulating LCV. Colic during post-operative hospitalisation may be due to localised sites of ischaemia, adhesion formation or stenosis [23]. Physiological derangements of the large intestine may predispose certain individuals to recurrent LCV or large colon displacement [24]. The risk of post-operative colic is significantly increased in horses with LCV [23] and in this study nearly 20% of this population died as a result of colic following discharge from the hospital. Colic during hospitalisation may contribute to a decision for euthanasia during hospitalisation or in other cases be a marker for colic post discharge from the hospital. Further investigation into the incidence of post-operative colic in horses with LCV is warranted.
Variables with over 33% of missing values were excluded from the initial model building procedure. Whilst much of the data included in this study was collected prospectively some data was missing due to the severity of pain on admission and the obvious requirement for immediate exploratory laparotomy. Adequate and complete follow-up is a prerequisite for the conduct of any survival study [25]. The 30-month period during the study where follow-up questionnaires were suspended was due to an alteration in funding, and may have reduced the accuracy of survival time and increased the number of censored individuals. In addition, as in numerous other veterinary studies evaluating survival time, the censorship of horses that were lost to follow-up, and the lack of differentiation between death and euthanasia, may have resulted in erroneous inferences from the data [26, 27]. Horses that were euthanased on the operating table were not excluded from the study population; it was deemed their inclusion would provide clinicians and owners with more accurate information on the prognosis of horses presenting with a strangulating LCV. However, the inclusion of horses that were euthanased on the operating table allows a surgeon’s judgment and the owner’s financial situation to have a potential influence on survival time. In an attempt to assess the effect of financial constraints on survival, insurance status was assessed within the models, and was found not to be significant (see Supporting items 1 and 3).

Extrapolation of these findings to other populations must be done with caution; over 40% of this population of LCV cases were geldings and the median duration of colic signs prior to admission was 10 hours. The study only included two horses that underwent a large colon resection and anastomosis (LCRA); in our hospital population LCRA has previously been associated with poor survival in horses with large intestinal disease [3]. However, Ellis et al.
[9] demonstrated favourable survival in horses with strangulating LCV that underwent LCRA, in a population comprising 88% mares with a mean duration of colic signs prior to admission of 4 hours. Whether LCRA improves the prognosis of horses with strangulating LCV requires further investigation [9, 11].

In conclusion LCV is associated with considerable post-operative mortality. Median survival time in horses with a strangulating LCV that survived anaesthesia was 365 days. Increased pre-operative PCV was significantly associated with increased post-operative mortality, illustrating importance of early referral, prior to alteration in PCV. Alteration in serosal colour intra-operatively, increased heart rate at 48 hours post-operatively, and colic during post-operative hospitalisation were also significantly associated with increased post-operative mortality. The study provides evidence based information on the survival of horses with LCV and identifies parameters that may assist the clinician when determining the prognosis for survival in individual horses.
Reasons for death or euthanasia during intra and post-operative period.

<table>
<thead>
<tr>
<th>Time post-operatively</th>
<th>Reason for death or euthanasia</th>
<th>Number of horses</th>
<th>% of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>During surgery (n=23)</td>
<td>Euthanased: non viable colon¹</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Euthanased: unable to correct torsion</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Euthanased: second LCV</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Died under anaesthesia</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>During recovery from anaesthesia (n=4)</td>
<td>Euthanased: Unable to stand</td>
<td>2</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Died: Unable to stand</td>
<td>2</td>
<td>2.7</td>
</tr>
<tr>
<td>During hospitalisation (n=26)</td>
<td>Euthanased: Systemic inflammatory response syndrome (SIRS) / pain / colon necrosis</td>
<td>23</td>
<td>30.7</td>
</tr>
<tr>
<td></td>
<td>Euthanased: gastric rupture</td>
<td>2</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Euthanased: concurrent synovial sepsis</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Following hospital discharge (n=22)</td>
<td>Colic</td>
<td>17</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td>Non-colic related</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>2</td>
<td>2.7</td>
</tr>
</tbody>
</table>

¹ Non-viable large colon as defined by surgeon at the time of exploratory laparotomy and recorded in the horse’s surgical report.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>Hazard ratio</th>
<th>95% Confidence intervals</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV on admission (%)</td>
<td>0.08</td>
<td>0.02</td>
<td>1.08</td>
<td>1.05-1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCV*ln(time) interaction effect</td>
<td>-0.04</td>
<td>0.01</td>
<td>0.96</td>
<td>0.95-0.97</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Final, multivariable Cox proportional hazards model (Model one) for post-operative death in 116 horses undergoing anaesthesia and exploratory laparotomy for LCV, including a PCV*ln(time) interaction term.
<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Ln(t)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>1.08</td>
</tr>
<tr>
<td>3</td>
<td>1.10</td>
<td>1.03</td>
</tr>
<tr>
<td>5</td>
<td>1.61</td>
<td>1.01</td>
</tr>
<tr>
<td>7</td>
<td>1.95</td>
<td>0.99</td>
</tr>
</tbody>
</table>

**Table 3.** Calculation of the hazard ratio in the presence of a PCV*time interaction term at different time points, with hazard ratio at time $t$ equal to $1.08^{0.96 \ln(t)}$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>Hazard ratio</th>
<th>95% Confidence Intervals</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate at 48 hours post-operatively</td>
<td>0.04</td>
<td>0.01</td>
<td>1.04</td>
<td>1.02-1.06</td>
<td>0.0005</td>
</tr>
<tr>
<td>(beats/minute)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serosal colour (normal/abnormal)</td>
<td>1.28</td>
<td>0.43</td>
<td>3.61</td>
<td>1.55-8.44</td>
<td>0.003</td>
</tr>
<tr>
<td>Colic during post-operative hospitalisation</td>
<td>0.97</td>
<td>0.50</td>
<td>2.63</td>
<td>1.00-6.95</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Table 4.** Final, multivariable Cox proportional hazards model (Model two) for post-operative death in 89 horses with LCV recovering from general anaesthesia.
Figure 1a and Figure 1b: Kaplan-Meier survival curves for a) 116 horses undergoing general anaesthesia and exploratory laparotomy for LCV and b) 89 horses recovering from anaesthesia following exploratory laparotomy for LCV.

Figure 2: This graph illustrates the shape of the relationship between PCV on admission and the risk of mortality in 116 horses undergoing surgery for LCV. Spline fit (solid line), with 95% confidence intervals (dotted lines) from univariable penalised Cox proportional hazards regression model are illustrated.

Figure 3: Schoenfield residual plots for Model one: PCV. This graph reveals a lack of proportionality over survival time, demonstrating that the effect of pre-operative PCV alters with time (p<0.007).

Figure 4: This graph illustrates the shape of the relationship between heart rate at 48 hours post-operatively and the risk of mortality in 89 horses with LCV that survived anaesthesia. Spline fit (solid line), with 95% confidence intervals (dotted lines) from univariable penalised Cox proportional hazards regression model are illustrated.

References


**Supporting Items**

**Supporting item 1.** Univariable associations of pre-operative categorical variables (Cox proportional hazards model) with post-operative death in 116 horses with a large colon volvulus >360 degrees undergoing exploratory laparotomy.

**Supporting item 2.** Univariable associations of pre-operative continuous variables (Cox proportional hazards model) with post-operative death in 116 horses with a large colon volvulus >360 degrees undergoing exploratory laparotomy.

**Supporting item 3.** Univariable associations of pre, intra and post-operative categorical variables (Cox proportional hazards model) with post-operative death in 89 horses surviving anaesthesia following surgery for large colon volvulus >360 degrees.
Supporting item 4. Univariable associations of pre, intra and post-operative continuous variables (Cox proportional hazards model) with post-operative death in 89 horses surviving anaesthesia following surgery for large colon volvulus >360 degrees.

Supporting item 5. Schoenfield residual plots for Model two: a) Heart rate at 48 hours post-operatively, b) Serosal colour and c) Colic during post-operative hospitalisation. These graphs demonstrate proportionality throughout survival time, with all plots having no significant pattern over time.

Supporting item 6a and Supporting item 6b. Log minus log cumulative hazard plots for categorical variables in the final model Cox proportional hazards regression model (Model two) for survival in 89 horses surviving anaesthesia following surgery with LCV. These graphs demonstrate proportionality throughout survival time.