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Evaluation of Clinical and Laboratory Variables as Prognostic Indicators in Hospitalised Gastrointestinal Colic Horses

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Ihler CF, Larsen J and Skjerve E: Evaluation of clinical and laboratory variables as prognostic indicators in hospitalised gastrointestinal colic horses. Acta vet. scand. 2004, 45, 109-118. – The present prospective study included 106 horses referred to the Department of Large Animal Sciences, The Norwegian School of Veterinary Science, as non-responders to the initial colic treatment in general practise. In 14 of these cases a required surgical treatment was not performed due to economical or other reasons and were excluded from the study. Clinical and laboratory data were obtained at the arrival in the hospital. The outcome for all analyses was survival/ non-survival. A multivariable logistic regression was performed. The analyses were used in medically (46 horses) and surgically treated cases (46 horses) separately. The same analyses were also run for all 92 horses in a simulated "field" situation, where only clinical variables and D-dimer values were included. The fraction of survivors was 78% in the medical and 48% in the surgical cases. In total 63% of the horses survived. In the final multivariable logistic regression model packed cell volume (PCV) was the only important predictor for medically treated cases, and heart rate and presence of hyperaemic or cyanotic mucous membranes were the predictors in the surgically treated cases as well as in the simulated "field" situation. In conclusion, traditional variables as heart rate, mucous membranes and PCV were the important predictors for the outcome in hospitalised colic cases.

horse; colic; prognosis; clinical and laboratory variables; hospital; logistic regression; epidemiology.

Introduction

Equine colic caused by gastrointestinal disorders is often encountered in general equine practise and may lead to severe clinical conditions and death. The incidence of colic is estimated in several studies. From USA *Kaneene et al.* (1997) and *Tinker et al.* (1997) reported an incidence of 3.5 and 10.5 colic cases per 100 horse-years, respectively. From Norway *Larsen & Flåøyen* (1997) estimated the incidence to be 4.8 colic cases per 100 horse-years. The case fatality rate is by *Kaneene et al.* (1997) and *Tinker et al.* (1997) reported to be 13 and 7%, respectively.

Acute cases often need immediate surgical treatment. Such treatment is expensive and the mortality is relatively high, reported to be between 31 and 44% in different studies (*Morris* 1991, *Sandholm et al.* 1995, *Kaneene et al.* 1997).

In general, a correct diagnosis is necessary to predict a reliable prognosis. In colic cases, however, a correct clinical diagnosis of the site and

type of the intestinal lesion is often difficult (*Blikslager & Roberts* 1995). The identification of significant clinical and laboratory variables for the prognosis might therefore be useful when taking the decision whether to let the patient undergo further treatment or not.

From an animal welfare point of view a reliable prognosis is also important when veterinarians in general practice consider transportation of severe clinical colic cases long distances for further treatment in hospitals.

From a multivariable model *Parry et al.* (1983) concluded that variables assessing cardiovascular function were good prognostic guides. From other studies clinical and laboratory variables such as heart rate, packed cell volume (PCV), colour of mucous membranes, capillary refill time (CRT), acid- base variables and plasma lactate are valuable prognostic predictors (*Pascoe et al.* 1990, *Reeves et al.* 1990, *Sandholm et al.* 1995, *Furr et al.* 1995, *Thoefner et al.* 2000). The fibrin degradation product, D-dimer, is valuable in assessment of the cardiovascular status. Increased levels indicate that excessive amount of fibrin is formed within the vascular system as a result of disseminated intra-vascular coagulation. D-dimer is of special interest because the values can be measured as a horse side test. *Sandholm et al.* (1995) concluded that D-dimer values in plasma were valuable as a predictor for outcome in equine gastrointestinal colic cases.

The purpose of the present study was to evaluate clinical and laboratory variables as prognostic indicators in medically and surgically treated colic cases in a hospital situation.

Materials and methods

Cases

The present study was a prospective study consisting of 106 horses with colic symptoms caused by gastrointestinal disorders referred to The Norwegian School of Veterinary Science, by veterinarians in general practise for further examination and treatment from March out December 1997 (50 horses) and 1999 (56 horses). In the 2 periods of the study all referred colic cases were included. The horses were all non-responders to the initial treatment in general practise such as non-steroid anti-inflammatory drugs (NSAIDs), fluid therapy and laxatives.

In 14 horses, for which the clinical examination indicated that surgical treatment was required, such treatment was not performed due to economical or other reasons. These horses were euthanised and excluded from the study.

Of the final 92 horses 30 horses were warmblooded riding horses, 15 Norwegian coldblooded trotters, 15 Standard-bred trotters, 16 Thoroughbreds and 16 horses of different pony and pleasure horse breeds. The age ranged from 6 months to 25 years (median = 8.0 years).

Horses discharged from the hospital in good general condition without any signs of colic were classified as survivors. For survivors the hospitalisation period ranged from 3 to 16 days. Non-survivors were all euthanised when considered to be at the terminal stage, where no response to treatment of the life threatening clinical situation, was detected. This was done to prevent unnecessary suffering.

Clinical examination

All horses were clinically examined immediately after arrival in the hospital according to a standard protocol. Rectal temperature (°C), degree of abdominal pain (1-3), heart and respiratory rate (per min), colour of mucous membranes (normal, abnormal), CRT (sec), abdominal auscultation (no sounds, decreased, normal and increased activity), rectal examination findings and any reflux of gastro-intestinal content through a naso-pharyngeal tube (0-1) were recorded. The colour of the mucous membranes was assessed using the gingival membrane and classified as normal or abnormal (hy-

Table 1. Clinical and laboratory variables in the study.

Clinical variables
Heart rate /min
Respiratory rate /min
Rectal temperature °C
Mucous membranes (normal/abnormal)
Capillary refill time (CRT) sec
Pain (no pain/moderate/severe)
Abdominal activity (no sounds/decreased/normal/increased)
Distended small intestine by rectal examination (yes/no)
Pain by rectal examination (yes/no)
Reflux through naso-pharyngeal tube (yes/no)
Laboratory variables
Packed cell volume (PCV) %
Haemoglobin g/l
Total protein g/l
α-, ß- and γ-globulin g/l
Albumin g/l
Fibrinogen g/l
Anion Gap ($Na^+ + K^+$-(Cl^-+ HCO_3)) mmol/l
Na^+ mmol/l
K^+ mmol/l
Cl^- mmol/l
Total Ca mmol/l
Mg^{++} mmol/l
Lactate mmol/l
HCO_3^- mmol/l
Arterial pO_2 kP_a
Arterial pCO_2 kP_a
Standard Base Excess (SBE) mmol/l
PH
D-dimer mg/l

peraemic or cyanotic as pallor and jaundice were not recorded). Abdominal paracentesis was not systematically performed, and the protein content and cytology of the abdominal fluid were therefore not used in the statistical analyses.

Decisions whether the patients should be treated surgically or medically were primarily based on the clinical variables. The criteria for surgical treatment were: (i) Recurrent pain despite heavy analgesic treatment and/or (ii) Rectal findings of distended small intestines and/or (iii) Rectal findings corresponding to displacement of the large intestines. Non-responders to the medical treatment were continuously evaluated for surgical intervention.

The different clinical variables used in this study are presented in Table 1.

Laboratory analyses

Packed cell volume (PCV) was analysed by a capillary micro centrifuge using venous blood from the jugular vein. Haematological variables were analysed on Technicon H 1 Analyser (Miles Inc., Tarrytown, NY, USA).

For blood gas analysis approximately 1 ml of blood was collected from the transverse facial artery into a Pico 70 heparinised arterial blood sampler (Radiometer Medical A/S, Copenhagen, Denmark) for immediate acid-base and blood gas evaluation on a Radiometer ABL 625 acid-base laboratory (Radiometer Medical A/S, Copenhagen, Denmark). Values were adjusted to body temperature.

Total serum protein was measured with a refractometer (Atago SPR-NE, Atago Co LTD, Japan). Serum electrophoresis to measure albumin, α-, ß- and γ-globulin fractions was performed using Paragon Electrophoresis System (Beckman Instruments Inc, Brea CA, USA). Fibrinogen was measured indirectly by calculating the difference of total protein in EDTA-plasma and serum. Serum sodium was measured with an ion-selective electrode,[1] serum chloride was measured with a colorimetric method,[2] and plasma lactate was measured enzymatically.[3]

[1] AVL 982 Electrolyte analyzer, AVL List GmbH, Graz, Austria.

[2] Technicon RA-1000, Miles Inc., Tarrytown, NY.

[3] Lactate fully enzymatic, Boehringer Mannheim, Germany.

Table 2. Survivors and non-survivors of different diagnosis and treatment in 92 colic cases.

	Survivors (n)	Non-survivors (n)	% Survivors
Diagnosis[1]			
Non-specific colic	10	1	91
Large colon impaction	25	4	86
Displacement large colon	16	9	64
Strangulation small intestine	2	10	17
Enterocolitis	5	3	63
Peritonitis	0	7	0
Total	58	34	63
Treatment			
Medically treated cases	36	10	78
Surgically treated cases	22	24	48

[1] For survivors: Clinical diagnosis. For non-survivors: Diagnosis based on necropsy.
n = number of observations.

Plasma D-dimer values were assessed by the Nycomed NycoCard D-Dimer test (Axis-Shield PoC AS, Oslo, Norway) on citrated venous plasma. The test is based on an immunofiltration of citrated plasma through a membrane attached with monoclonal antibody followed by colloidal gold-labelled monoclonal antibody staining (*Gogstad et al.* 1993). The intensity of colour was measured semi quantitatively using a NycoCard Reader (Axis-Shield PoC AS, Oslo, Norway). In addition, the D-dimer test was used in 20 healthy horses as controls. Two cut-off values, 0.5 and 1.5 mg/l were tested in the statistical analysis.

The different laboratory variables used in this study are presented in Table 1.

All clinical variables and blood samples were obtained immediately after arrival at the hospital according to a standard protocol. Further, clinical and laboratory variables obtained during the stay in hospital were used as the basis of further treatment of the patient and not used in the statistical analysis.

Statistical methods

Initially, survivors and non-survivors were compared with respect to year of inclusion (1997 or 1999), breed, age, gender and clinical and laboratory variables using Wilcoxon/Kruskal Wallis Rank Sum Test for continuous variables and Fischer Exact Test for nominal or ordinal variables was performed using JMP for Windows version 4.02 (SAS Institute Inc, USA). Rectal findings were not used as a variable in the analysis because the variable was essential in the classification of surgically and medically treated cases.

To handle collinearity, a correlation analysis of the various explanatory variables was performed for surgically and medically treated cases separately. When variables showed strong correlation (Spearman þ >0.5) the variable with the lowest p-value in the univariable analyses was selected. These selected variables and the other variables showing $p < 0.15$ in the univariable analysis were used in a multivariable logistic model (*Hosmer & Lemeshow* 2000) to associate survival/non-survival with clinical an laboratory variables for surgically and medically treated horses. The same procedure was also used for all cases to simulate a "field situation " where clinical variables and D-dimer, as a horse-side test, were the only available variables.

Table 3. Descriptive analyses of clinical and laboratory variables in medically and surgically treated colic cases demonstrating p-values < 0.15 in either Wilcoxon/Kruskall Wallis Rank Sum test for continuous variables or Fisher Exact test for nominal variables.

Variables	Survivors		Non-survivors	
	n	Median(range) or no/ (%)	n	Median (range) or no (%)
Medically treated colic cases:				
Heart rate /min	36	48 (32-96)	10	72 (32-120)
Respiratory rate /min	35	20 (8-50)	10	28 (15-34)
CRT sec	36	2 (2-4)	9	3 (2-6)
Rectal temperature °C	36	37.9 (36.6-38.8)	10	38.4 (37.9-39.6)
Abnormal mucous membrane	36	16 (44%)	10	7 (70%)
PCV %	36	34 (22-50)	10	48 (33-69)
HGB g/l[1]	34	122 (82-181)	10	180 (123-248)
Fibronogen g/l	33	3 (2-7)	9	3 (1-5)
Alfa- globulin g/l	36	9 (6.9-14.3)	9	7.7 (2.9-12.4)
Gamma- globulin g/l	36	7.8 (4.2-14.7)	9	5.8 (3.5-13.7)
Lactate mmol/l	36	1.2 (0.5-11.1)	9	3.7 (1.1-13.1)
Total Ca mmol/l	34	3.0 (1.5-3.4)	9	2.7 (2.1-2.9)
Surgically treated colic cases:				
Heart rate /min	22	44 (36-80)	24	79 (36-148)
Breath rate /min[2]	22	20 (12-40)	24	30 (15-72)
Temperature difference from 38 °C	20	0.3 (0.0-1.0)	24	0.6 (0.0-2.5)
Abnormal mucous membrane	22	5 (23 %)	24	19 (79%)
No abdominal sounds[2]	22	2 (9%)	24	14 (58%)
CRT sec[2]	22	3 (2-3)	24	4 (2-7)
PCV %[2]	22	38 (29-43)	24	42 (28-56)
HGB g/l[2]	22	138 (106-163)	24	153 (112-199)
Beta-globulin g/l	20	10.5 (7.7-20.0)	23	12.2 (7.4-19.8)
Gamma- globulin g/l	20	8.7 (3.2 -12.1)	23	7.6 (2.2-12.6)
Cl mmol/l	22	99 (89-108)	24	95 (87-108)
K mmol/l	22	3.5 (2.3-4.5)	24	3.8 (2.6-5.2))
Lactate mmol/l[2]	20	1.6 (0.8-7.1)	24	3.6 (1.1-13.0)
D-dimer > 1.5 mg/l	22	2 (9%)	24	12 (50%)
D-dimer > 0.5 mg/l	22	7 (33%)	24	17 (71%)

[1] Excluded from further analysis due to high correlation to PCV.
[2] Excluded from further analysis due to high correlation to heart rate.
n = number of observations.

The final multivariable model was built using logistic regression in a forward selection procedure as described by *Hosmer & Lemeshow* (2000) using Intercooled Stata for Windows 7.0 (Stata Corporation, College Station, TX, USA). Model fit was assessed using the overall Pearson fit, the Hosmer-Lemeshow test and the Receiver Operating Characteristic (ROC) curve. Possible outliers were identified using the Δß and Δ deviance test (*Hosmer & Lemeshow* 2000). The sensitivity and specificity for various probability cut-offs were graphically assessed.

Linearity for continuous variables was also assessed comparing the continuous variable grouped into quartiles and with a graphical ap-

Table 4. Final multiple logistic regression models for surgically and medically treated colic cases and "simulated field situation" based upon variables presented in Table 3. Results are given as estimates (95 % confidence limits) and Odds Ratio (95 % confidence limits).

Treatment group	Variable	Estimate	Odds Ratio
Surgically treated cases	Heart rate	0.11 (0.04-0.18)	3.00 (1.49-6.05)*
	Abnormal mucous membranes	2.90 (0.73-5.07)	18.23 (2.08-159)
Medically treated cases	PCV	0.20 (0.07-0.32)	1.22 (1.07-1.37)**
Simulated field situation	Heart rate	0.07 (0.04-0.11)	2.05 (1.62-2.88)*
	Abnormal mucous membranes	1.18 (0.03-2.34)	3.25 (1.03-10.3)

* Per increase of 10 units
**Per increase of 1 unit

proach using the kernel smoothing graph procedure in Intercooled Stata for Windows 7.0 (Stata Corporation, College Station, TX, USA). Interactions were not evaluated due to a limited number of horses.

Results

Fifty-eight horses (63%) of the total 92 colic cases survived. Forty-six horses where treated medically (survival 78%) and 46 were treated surgically (survival 48%). The numbers of sur-

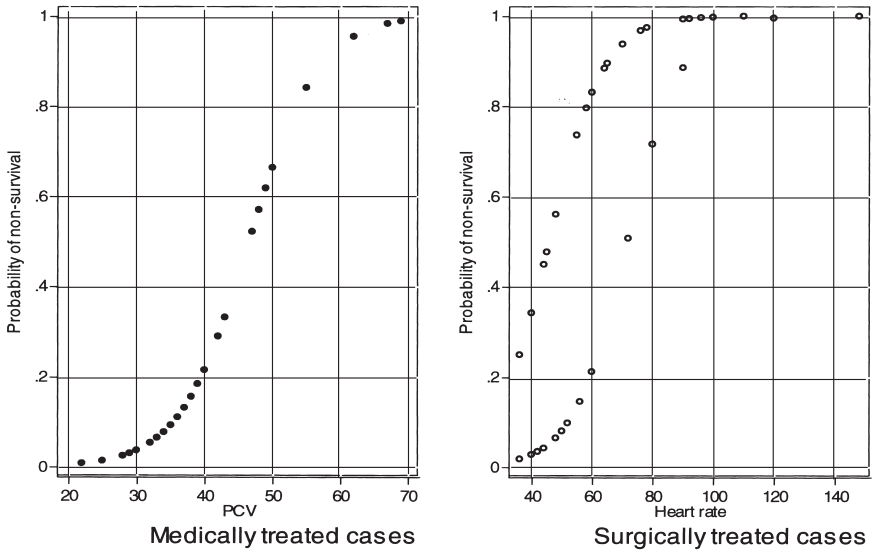

Figure 1. Estimated probability of non-survival for medically and surgically treated colic cases based upon the final logistic models in Table 4. For surgically treated horses the left curve represents horses with abnormal mucous membranes and the right curve represents horses with normal mucous membranes.

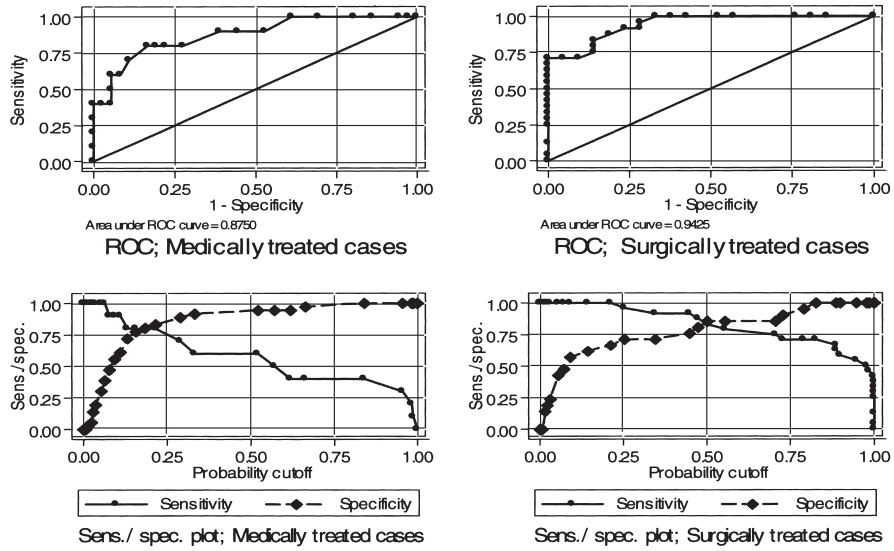

Figure 2. Sensitivity/specificity curves and Receiver Operating Characteristic (ROC) curves for the final logistic model for medically treated cases and surgically treated cases.

vivors and non-survivors according to diagnosis and treatment are presented in Table 2.

D-dimer values of the 20 controls of healthy horses all showed D-dimer values < 0.5 mmol/l.

Univariable analysis of age, breed, gender and year of inclusion (1997 or 1999) did not show any statistical difference between survivors and non- survivors for either medically or surgically treated cases. Neither breed nor gender revealed any difference between surgical and medical cases. The median age was however lower (p= 0.035) in the surgically treated horses (6.5 and 8.0 years, respectively).

The results of the univariable analysis of clinical and laboratory variables showing p-values <0.15 between survivors and non-survivors are given in Table 3.

The univariable analysis of other blood parameters as Mg, Na, total protein, albumin, arterial pH, arterial pO_2 and pCO_2, HCO_3 and Standard Base Excess (SBE) all revealed p-values >0.15 for both medically and surgically treated cases. The univariable analysis of the clinical dichotomous variable intestinal reflux also showed a p-value >0.15 for both treatment groups. The degree of abdominal pain at the time of arrival to the hospital did not differ statistically between the survivors and non-survivors in the 2 treatment groups.

As a result of a high correlation in the medically treated cases the variable haemoglobin (þ=0.99 to PCV) were excluded in the following logistic regression procedure. In the surgically treated cases the variables abdominal sounds, breath rate, CRT, PCV, haemoglobin and lactate were excluded due to high correlation to heart rate (heart rate/abdominal sounds þ=0,52, heart rate/ respiratory rate þ=0.53, heart rate/CRT þ=0.61, heart rate/PCV þ=0.67, heart rate/ HGB þ=0.63 and heart rate/lactate þ=0,59).

The final multiple logistic model included PCV as the only significant predictor in medically

treated cases and heart rate and abnormal mucous membranes as significant predictors in surgically treated cases (Table 4). In the simulated "field" situation the final model also included heart rate and abnormal mucous membranes (Table 4). The prediction curves for the 2 treatment groups are presented in Fig. 1, while the ROC curves and sensitivity and specificity curves are illustrated in Fig. 2.The ROC curve described an area under curve of 87% for medical cases and 94% for surgical cases.

No influential outliers were found in the regression diagnostics. Grouping the continuous variables into quartiles gave no better model fit than analysing the variables as continuous ones. Supplementary tests also indicated (kernel smoothing) linearity of the continuous variables.

Discussion

Material and methods

As all horses in the present study are referred cases as non-responders to initial treatment(s) in the general practice, they represent a selected material compared to colic cases in general. That means that neither colic cases with their origin in simple spastic intestines and mild obstructions nor severe colic cases, in which the pain was not possible to reduce to an acceptable level before transportation to the hospital, are represented in the study.

The exclusion of cases that required surgery but were euthanised of economical or other reasons was necessary to ensure that all horses were euthanised at the terminal stage of the disease. However, it may be difficult to classify a patient to be at the terminal stage. To avoid unnecessary suffering when all possible further treatment was performed was very important when classifying non-survival.

The study was performed over 2 periods of time (1997 and 1999). Year of inclusion might have influenced the results. The same protocol for clinical and laboratory examination throughout the study was used to avoid such bias. In the statistical analysis no association between year of inclusion and survival was detected.

Results

The survival percentage of 63 for all colic cases in the present study is on the same level as reported from other studies on hospitalised colic cases (*Ebert* 1994, *Sandholm et al.* 1995). The probabilities of survival in surgically and medically colic cases (48 and 78%, respectively) also correspond to previous studies (*Sandholm et al.* 1995, *Siebke* 1995).

In the present study there was no association between age and gender and outcome while some studies have reported that older horses have a higher risk of non-survival (*Orsini et al.* 1988, *Reeves et al.* 1989). In line with the present study, *Reeves et al.* (1990) and Thoefner et al. (2000) reported no association between age and the outcome in colic cases.

Thoefner et al. (2000) reported an increased risk of death in cold-blooded ponies compared to a heterogeneous group of warm-blooded horses. In the present study no association between breed and survival was found. In agreement with *Thoefner et al.* (2000) and *Reeves et al.* (1990) no association between gender and outcome was found.

The degree of pain (pain score 1-3) at the initial examination in the hospital did not show any association with the outcome of the colic cases. This is in disagreement with *Thoefner et al.* (2000), *Puotonen-Reinert* (1986) and *Reeves et al.* (1990). In the present study most horses were given analgesics and/or NSAID before and for some horses during the transportation. When given NSAIDs and analgesics at different times before the clinical evaluation the initial pain at arrival might not give the correct picture of the real clinical situation and further might explain why pain did not influence the

outcome. Recurrent pain despite analgesics or NSAIDs was, however, one of the criteria for surgery, and since surgically treated cases in the present study had a higher mortality, pain might indirectly relate to the outcome.

Thoefner et al. (2000) found that a temperature deviation from 38 °C was a significant variable in the multivariable logistic regression model expressing the outcome of a colic case. In the present study we did not find such a relationship when temperature deviation from 38 °C was included in the model.

Heart rate and the presence of abnormal mucous membranes were the only statistically significant variables in the multivariate model for surgical cases. Even if the initial laboratory variables did not directly relate to the outcome, they were of importance in the decision making of supportive therapy such as fluid therapy and correction of acid-base disturbances. In this way they might indirectly influence the outcome.

The classification of the mucous membranes was based on presence of hyperaemia and cyanosis. Since pallor or jaundice was not recorded in any horse in this study the authors chose a dichotomous classification (normal/abnormal) for mucous membranes.

In medical cases PCV was the only explanatory variable in the final logistic model. Also PCV represents a variable expressing the cardiovascular status in the patient.

The final models gave an excellent fit by an area under the ROC curve of 0.94 in surgically and 0.88 in medically treated cases, respectively. The ROC curve plots the probability of deflecting a true signal (sensitivity) and a false signal (specificity) for the entire range of possible outpoints. While the ROC curve assess the overall performance of the model, the prediction curves in Fig. 1 give the magnitude of the probability of death given various levels of the predictor variables.

In the simulated "field" situation, where only clinical variables and D-dimer were used, the only reliable predictors for survival were heart rate and the presence of abnormal mucous membranes. The D-dimer values did not give any additional information in explaining the outcome. This is in agreement with *Thoefner et al.* (2000). *Sandholm et al.* (1995), however, found that D-dimer was included in the final logistic model together with the variables heart rate and chloride. The reason for this might be that *Sandholm et al.* (1995) did not use other clinical variables than heart rate and respiratory rate in their statistical procedure. D-dimer, as the condition of the mucous membranes, is an indicator of cardiovascular status. During our logistic regressions D-dimer was excluded from the final model. This supports that the evaluation cardiovascular variables as the mucous membrane in addition to heart rate tell more about the outcome than the D-dimer value.

In conclusion, traditional clinical variables as heart rate and presence of abnormal mucous membranes in surgical and PCV in medical colic cases were the significant predictors for the outcome. The other variables were, however, important in establishing supportive treatment of the patients.

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Sammendrag

Kliniske parametere og laboratorieparametere som prognostiske indikatorer hos hospitaliserte kolikkhester.

Kliniske parametere og laboratorieparametere fra 106 kolikkhester innsendt til Norges veterinærhøgskole ble statistisk undersøkt som mulige prognostiske indikatorer. Ingen hester hadde respondert på den initiale behandlingen i felt. Fjorten kasus, hvor kirurgisk behandling var påkrevd, men ikke utført på grunn av økonomiske eller andre årsaker, ble utelukket i studien. Alle parametere ble registrert rett etter ankomst og statistisk behandlet med hensyn på overlevelse ved hjelp av en univariabel analyse med etterfølgende korrelasjonsanalyse og multivariabel logistisk regresjon. Overlevelsesprosenten var 78% for de medisinsk behandlede kolikker og 48% for de kirurgisk behandlede. I den multivariable logistiske modellen var hematokrit den eneste viktige variabel for overlevelse for de medisinsk behandlede kolikkene, mens pulsfrekvens og abnormale slimhinner var de beste prediktorene for de kirurgisk behandlede. Studien konkluderer med at tradisjonelle kliniske parametere som pulsfrekvens, slimhinneforandringer og hematokrit var de eneste viktige prognostiske indikatorer ved kolikk hos hospitaliserte hester.

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