Received: 25 May 2023 | Accepted: 2 October 2023
DOI: 10.1111/evj.14032

ORIGINAL ARTICLE

Equine Veterinary Journal WILEY

Survival rates and factors associated with survival and laminitis of horses with acute diarrhoea admitted to referral institutions

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Abstract

Background: Clinicopathological findings and their association with the outcome and development of laminitis in horses with acute diarrhoea has not been investigated in a multicentre study across different geographic regions.

Objectives: Describe and compare clinicopathologic findings of diarrhoeic horses between different geographic regions, survival rates and factors associated with non-survival and laminitis.

Study design: Multicentre retrospective case series.

Methods: Information from horses with acute diarrhoea presenting to participating institutions between 2016 and 2020 was collected, and clinicopathological data were compared between surviving and non-surviving horses and horses that did and did not develop laminitis. Survival rates and seasonal and geographic differences were also investigated.

Results: One thousand four hundred thirty-eight horses from 26 participating institutions from 4 continents were included; 76% survived to discharge with no differences identified between geographic regions. The survival proportion of horses with SIRS and creatinine concentrations > 159 μmol/L was 55% (154/279) compared with 81% (358/437) for those with SIRS and creatinine concentrations < 159 μmol/L ($p < 0.001$). The survival proportion of horses with SIRS that had an L-lactate concentration > 2.8 mmol/L was 59% (175/298) compared with 81% (240/296) in horses with SIRS and L-lactate concentration < 2.8 mmol/L ($p < 0.001$). The proportion of horses that developed laminitis was lower in Europe (4%, 19/479) compared with North America (8%, 52/619), Australia (8%, 12/138) and Latin America (11%, 16/146) ($p < 0.05$). More horses developed laminitis in the summer (46%, 39/85) compared with winter (18%, 15/85), spring (18%, 15/85) and fall (19%, 16/85) ($p < 0.01$). Horses with laminitis had greater odds of non-survival than those without laminitis (OR: 3.73, 95% CI: 2.47–5.65).

The MEDS group (see names and affiliations in Supplementary Item 1).

Main limitations: Not all variables were available for all horses due to the retrospective nature.

Conclusions: Clinicopathological findings in horses with acute diarrhoea and their association with survival are similar across geographic regions. However, developing laminitis secondary to diarrhoea is less common in Europe. In addition, factors associated with non-survival were indicative of disease severity and subsequent cardiovascular compromise.

KEYWORDS

diarrhoea, enterocolitis, horse, laminitis, systemic inflammation, typhlocolitis

1 | INTRODUCTION

In 2019, the first Dorothy Russell Havemeyer Foundation workshop on acute colitis was held in Niagara-on-the-lake, Ontario, Canada. The goal of this workshop was '…*to review the current understanding of acute colitis in the adult horse and to identify key areas for collaborative research into this neglected illness*'.[1] This meeting uncovered many gaps in the knowledge of colitis in the horse, including the absence of a consensus definition of colitis and lack of knowledge on the global incidence, morbidity, mortality and risk factors for non-survival of horses with acute colitis. In addition, the workshop revealed a lack of comprehensive information regarding the most common causes of colitis worldwide and how they differ depending on the geographic areas and an apparent heterogenicity in the diagnostic and therapeutic approach for horses with colitis,[1] which has been confirmed in a recent Canadian nationwide study.[2]

Answering several questions about the epidemiology, diagnostic and treatment approaches to equine colitis requires collaborative studies, mainly due to the low number of horses with colitis presented to individual referral veterinary hospitals.[1] Most studies on equine colitis have focussed on the factors associated with mortality at single facilities involving fewer than 150 horses.[3–8] The true incidence of colitis in horses is difficult to determine from those studies; however, these studies have identified several risk factors associated with mortality. Specifically, age, a history of antimicrobial therapy, tachycardia, haemoconcentration, hypoproteinaemia and the development of azotemia during hospitalisation were all associated with mortality in horses with diarrhoea.[6,7]

A scoring system of colitis severity is required to conduct a comparative assessment of the beneficial effects of existing or novel therapies used in different institutions, given the required large sample size to make valuable conclusions. The most common system used to classify critically ill horses is establishing the presence or absence of systemic inflammatory response syndrome (SIRS), which is associated with an increased risk of death in horses suffering from gastrointestinal diseases.[9] Furthermore, the combination of SIRS criteria, hyperlactataemia (blood lactate concentrations > 2 mmol/L) and alteration in the mucous membranes is a better predictor of mortality in horses with gastrointestinal diseases than SIRS alone.[9] These classification systems have not been assessed in horses with acute diarrhoea; however, the findings suggest that SIRS criteria in combination with markers of organ injury or failure and cardiovascular deficiencies can better indicate decreased chances of survival than SIRS alone in diarrhoeic horses.

The primary objective of this retrospective multicentre exploratory study was to describe the epidemiology, selected clinicopathological findings, morbidity, fatality rate and risk factors associated with the survival of diarrhoeic horses and the development of laminitis (factors were investigated as prognostic factors[10]). The secondary objective was to report the fatality rates of horses with acute diarrhoea that meet SIRS criteria. We hypothesised that the proportion of hospitalised horses with acute diarrhoea, expressed as a percentage of the total case number, and the survival proportion, regardless of the aetiology, varies among institutions worldwide. We also hypothesised that clinical and clinicopathologic findings associated with the non-survival of diarrhoeic horses or the development of laminitis would be similar to those previously reported for horses with gastrointestinal diseases.

2 | MATERIALS AND METHODS

Participating institutions were identified by contacting veterinarians via email. A minimum of 30 records *per* institution from 2016 to 2020 were initially requested. Inclusion criteria were horses > 1-year-old admitted to the institutions for evaluation of acute (<48 h in duration) diarrhoea or developed diarrhoea within the first 24 h after admission. Horses that underwent surgery and developed diarrhoea >24 h after being admitted to the hospital were excluded. The total number of horses admitted per year was recorded from each hospital. The proportion of horses admitted for acute diarrhoea was calculated as the number of cases diagnosed in each institution in a specified timeframe.

Recorded information included signalment (sex, breed, age), month and year of presentation. The admission season was also recorded for institutions located in the temperate zones of the Northern and Southern hemispheres (23.5° to 66.5° North and South of the Equator, 0°). For institutions from the Northern hemisphere seasons were classified as winter (December, January and February), spring

(March, April and May), summer (June, July and August) and autumn (September, October and November), while in the Southern hemisphere, winter corresponded to the months of June, July and August, spring to the months of September, October and November, summer to the months of December, January and February, and autumn to the months of March, April and May. Historical information before admission (duration of clinical signs, history of antimicrobial or anti-inflammatory drugs and reasons for administration, history of surgery or any disease before the onset of diarrhoea and history of fever, diarrhoea, or colic) and the presenting complaint was also recorded.

The following physical examination findings (determined by the attending clinician) were collected: attitude (bright, obtunded, stuporous), temperature (T, Celsius), heart rate (HR, beats per minute, bpm), respiratory rate (RR, respirations per minute, rpm), mucous membranes appearance (pink, pale, injected, icterus, muddy and cyanotic), capillary refill time (CRT, seconds), hydration status (normal, mild, moderate or severe dehydration), and the presence of a toxic line, diarrhoea, colic, reflux, and laminitis on admission (all recorded as present/absent).

Data extracted from a complete blood cell count (CBC) and biochemistry profile performed on admission included the packed cell volume (PCV, %), total white blood cell (WBC, cells/μL), neutrophil count (cells/μL), total calcium (tCa, mmol/L), ionised calcium (iCa, mmol/L), total protein (TP, g/dL) and creatinine concentrations (μmol/L). In addition, when a total protein concentration was unavailable from the biochemistry, total solids concentrations (TS) were recorded.

The presence or absence of SIRS on presentation was determined based on previously published SIRS criteria in horses[9] where SIRS is defined by the presence of 2 or more of the following criteria: HR > 40 bpm, RR > 20 rpm, T > 38.5 or <36.5°C, and WBC count < 5300 or >14 800 cells/μL. Results of aetiological testing for infectious (e.g., *Salmonella* spp., *Clostridioides difficile*, *Neorickettsia risticii*, equine coronavirus [ECoV]) and non-infectious (sand-associated diarrhoea) causes of diarrhoea were documented. Sand enterocolitis was diagnosed based on the physical exam findings and radiographic examination of the horse's abdomen. Horses that developed diarrhoea during antimicrobial therapy for a different disease process were considered to have antimicrobial-associated diarrhoea (AAD). Complications during treatment (e.g., laminitis, peritonitis, rectal prolapse, neurological abnormalities, phlebitis/thrombophlebitis) and outcome (survival to discharge or non-survival) were also recorded.

2.1 | Data analysis

Data normality was assessed using normal probability Q–Q plots and the Kolmogorov–Smirnov test, and data were analysed accordingly. Descriptive statistics included mean and standard deviation (SD) or median and ranges. Categorical variables were compared between groups using a X^2 or Fisher's exact test, while continuous variables were compared with the student's *t*-test or the Wilcoxon test. Generalised linear mixed models were built (Proc GLIMMIX), incorporating the institution as a random effect, to evaluate the variables associated with the outcomes of non-survival and laminitis. Initially, factors known to be associated with the survival of horses with colitis (HR, colic signs, creatinine, PCV and TP)[2] or laminitis (PCV, and L-lactate[11]) were offered to the model. Thereafter, potential risk factors (season, breed, age [days], sex, mentation [normal or abnormal], degree of dehydration, mucus membranes colour, CRT, a toxic line, gastric reflux, diarrhoea, colic signs, and the RR, T, WBC, neutrophils, and lactate and creatinine concentrations) were introduced and removed using a stepwise manual approach considering interactions and appropriate quadratic terms. Variables with a *p*-value <0.05 remained in the final model. The cause of missing values was considered 'completely at random' because most of the missing data results from not measuring a given variable in a specific institution, and the reason for missing data was unrelated to the outcome. Therefore, analysis was conducted based on complete cases.[12] Statistical analyses and figures were performed using statistical software (SAS 9.4 Institute Inc.) and JMP 16 (SAS Institute Inc.). Survival rates were computed for horses affected by colitis, both in cases that meet (or not) SIRS criteria. The survival rates for horses with colitis and SIRS, alongside alterations in L-lactate and creatinine concentrations, were calculated to provide diagnostic information from the results obtained in the linear mixed model for survival. Receiver operating curves (ROC) were constructed,[13] and cut-offs for blood creatinine and L-lactate concentration were identified using the value whose sensitivity and specificity were the closest to the value of the area under the ROC curve and the absolute value of the difference between the sensitivity and specificity values was minimum (Youden's J statistics).[14]

3 | RESULTS

3.1 | Participating institutions

Initially, 56 institutions were contacted via email, 40 agreed to participate, and 16 did not respond. Ten institutions indicated that they did not have enough cases to contribute, three stated that they did not have time to collect the information, and one submitted a small number of cases with limited data for analysis and was excluded from the study. Therefore, the medical records of horses admitted to 26 institutions located in 14 different countries (USA [$n = 9$], Australia [$n = 4$], Canada [$n = 2$], Chile, Colombia, Denmark, England, France, Ireland, Italy, Japan, Mexico, Norway, Switzerland, one each) from five different geographic areas (North America, Latin America, Australia, Japan and Europe) between 1 January 2016 and 31 December 2020, were reviewed. Institutions comprised three private practices and 23 university teaching hospitals. Private practices included Fethard Equine Hospital (Fethard, Ireland), Japan Racing Association Ritto Training Center (JRA Ritto, Japan), and Rood and Riddle Equine Hospital (RREH, USA). University teaching hospitals included The University of Adelaide (Adelaide), Auburn University (AU), University of Prince Edward Island (UPEI), Universidad Austral de Chile (AUCh), University of Copenhagen (Copenhagen), University of Helsinki (Helsinki), Iowa State University (ISU), Kansas State University (KSU), University of Lyon (Lyon),

TABLE 1 The proportion of horses admitted for acute diarrhea to 26 different institutions worldwide and their associated survival proportion.

	Admissions	Acute diarrhea		Survivors	
Institution	2016-2020	*n*	%	*n*	%
Adelaide	NA	24	NA	15	62%
Auburn	NA	47	NA	35	74%
UPEI	2637	12	0.46%	9	75%
UACh	NA	24	NA	14	58%
Copenhagen	6644	110	1.65%	74	67%
Fethard	NA	22	NA	16	72%
Helsinki	NA	156	NA	137	88%
Iowa	NA	30	NA	23	77%
JRA/Ritto	1039	35	3.37%	26	74%
KSU	7876	21	0.27%	12	57%
Lyon	6939	37	0.53%	28	76%
MdP	NA	32	NA	27	84%
Melbourne	6250	61	0.1%	39	64%
Murdoch	5756	20	0.35%	18	90%
The OSU	NA	56	NA	46	82%
Perugia	2269	15	0.66%	6	40%
RREH	NA	117	NA	92	79%
RVC	6080	40	0.66%	30	75%
UF	NA	38	NA	32	84%
UG	6977	191	2.7%	134	70%
UNAL	431	31	7.2%	28	90%
UNAM	1499	94	6.3%	76	80%
UQ	8930	36	0.4%	31	86%
UW	5340	44	0.82%	33	75%
WSU	4879	42	0.86%	26	62%
Zurich	11335	103	0.9%	86	83%

Abbreviations: Adelaide, The University of Adelaide; AU, Auburn University, UPEI, University of Prince Edward's Island, AUCh, Universidad Austral de Chile; Copenhagen University of Copenhagen; FETHARD, FETHARD equine hospital; Helsinki, University of Helsinki; ISU, Iowa State University; JRA Ritto, Japan Racing Association Ritto Training Center; KSU, Kansas State University; Lyon, University of Lyon; MdP, Marion duPont Scott Equine Medical Center; Melbourne, University of Melbourne; Murdoch, Murdoch University; The OSU, The Ohio State University; Perugia, University of Perugia; RREH, Rood and Riddle Equine Hospital; RVC, The Royal Veterinary College; UF, University of Florida; UG, University of Guelph; UNAL, Universidad Nacional de Colombia; UNAM, Universidad Nacional Autonoma de Mexico; UQ, University of Queensland; UW, University of Wisconsin-Madison; WSU, Washington State University; Zurich, University of Zurich.

Marion duPont Scott Equine Medical Center (MdP), University of Melbourne (Melbourne), Murdoch University (Murdoch), The Ohio State University (The OSU), University of Perugia (Perugia), The Royal Veterinary College (RVC), University of Florida (UF), University of Guelph (UG), Universidad Nacional de Colombia (UNAL), Universidad Nacional Autonoma de Mexico (UNAM), University of Queensland (UQ), University of Wisconsin-Madison (UW), Washington State University (WSU), University of Zurich (UZ). All institutions were in the temperate zones of the Southern and Northern hemispheres, except UNAL (Bogota, Colombia, 4°42′40″ North) and UNAM (Mexico City, Mexico 19°26′ North).

3.2 | The proportion of hospitalised horses with acute diarrhoea

A total of 1438 horses met the inclusion criteria. The number and proportion of horses admitted with acute diarrhoea, and the total number of horses admitted in each institution are presented in Table 1. The number of horses admitted to each geographic area was distributed as follows: 44% (630/1438) presented to North American institutions, 34% (483/1438) to European institutions, 10% to Latin American (149/1438), 10% to Australian institutions (141/1438) and 2% (35/1438) to an Asian institution. The proportion of diarrhoeic horses admitted to institutions varied from 0.1% to 7.2% (Table 1). These proportions were similar among all years of the study period.

The number of horses presenting with diarrhoea each year was as follows: 318 cases [22%] were admitted in 2016, 296 cases [21%] in 2017, 311 cases [21%] in 2018, 247 cases [17%] in 2019 and 266 cases [19%] in 2020. The number of horses admitted for diarrhoea to referral institutions was higher in 2016 than in 2019 and 2020 ($p < 0.01$). No other differences were identified. Horses from the temperate zones of the northern and southern hemispheres were presented during all four seasons autumn (335/1313, 26%), winter (358/1313, 27%), spring (281/1313, 21%) and summer (339/1313, 26%). However, the number of horses admitted for diarrhoea was lower in the spring than in the summer, autumn and winter ($p = 0.002$).

3.3 | Demographic information

The median age of the horses was 9 years (1 to 35 years). Data regarding sex was available for 1398 horses. Sex distribution was statistically different, with 53% (763) being males (675 geldings and 88 stallions) and 47% (635/1438) females ($p = 0.001$). The breed was available for 1427, and of 34 breeds represented, Thoroughbreds (283/1427; 20%), Quarter Horses (203/1427; 14%), ponies (140/1427; 10%) and Draught horses (113/1427; 8%) were the most prevalent.

3.4 | Presenting complaint

The main presenting complaints were diarrhoea (39%, 560/1438), colic (28%, 403/1438), colic and diarrhoea (11%, 165/1438), colic and fever (8%, 120/1438), fever (4.6%, 66/1438), altered demeanour (4.1%, 59/1438) and colic, fever and diarrhoea (2.1% 30/1438).

3.5 | History of antimicrobial drugs and NSAIDs administration

The referring veterinarian prescribed antimicrobial drugs to 25% (366/1428) of the horses, while NSAIDs were administered to 42% (607/1434) before admission. The data collection approach prevented us from differentiating if NSAIDs were administered for the current episode of gastrointestinal disease or previous disease. 120/1438 (8%) horses were treated with antimicrobial drugs before the episode of diarrhoea. Systems affected included the skin (29%, 35/120), musculoskeletal (27%, 32/120) and respiratory (24%, 29/120). In addition, 246/1438 (17%) were treated with antimicrobial drugs for the current episodes of diarrhoea.

3.6 | Clinicopathological findings

On admission, altered demeanour was observed in 56% (798/1416) of the horses, with 743 (52%) being obtunded, 13 (2%) stuporous and 42 (5%) comatose. Of the comatose horses, 29 (70%) of those horses died. Comatose horses were presented to European ($n = 38$), Asian ($n = 2$) and North America ($n = 2$) institutions. Median rectal temperature was 38.1°C (34–41°C), with 359/1376 (26%) horses having a temperature > 38.5°C and 49/1376 (3.5%) having a temperature < 36.5°C. Median HR was 56 bpm (28–140 bpm), with 1153/1423 (81%) horses having an HR > 40 bpm. Median RR was 20 rpm [range: 8–104 rpm] with 635/1335 [48%] having RR > 20 rpm. The following clinical alterations were evident on admission: diarrhoea in 884/1434 (77%), CRT > 2 s in 482/1311 (47%), toxic line in 233/1416 (16%), colic in 630/1402 (45%), signs of acute laminitis in 43/1436 (3%) and nasogastric reflux in 119/1312 (9%). In addition, two horses were reported to have chronic laminitis associated with an endocrinologic disease.

A total of 539/1413 horses [38%] had leukopenia (WBC < 5300 cells/μL), and 60 [4.2%] had leukocytosis (WBC > 14 800 cells/μL); 434/1104 [39%] had neutropenia (neutrophils < 2300 cells/μL) and 137/1104 [12%] had neutrophilia (neutrophils > 8500 cells/μL); 313/1167 [27%] horses had azotemia (creatinine > 168 μmol/L); 512/880 [58%] had hyperlactatemia (lactate > 2 mmol/L); 326/1366 [24%] had hypoproteinemia (TP/TS < 5.4 g/dL) and 107 [8%] had hyperproteinemia (TP/TS > 7.8 g/dL); 297/681 [44%] had ionised hypocalcemia (iCa < 1.4 mmol/L).

3.7 | Complications

In 80/1438 (6%), phlebitis/thrombophlebitis was reported, whereas neurological abnormalities, rectal prolapse and peritonitis were reported in 17/1438 (1.2%), 6/1438 (0.4%) and 5/1438 (0.4%), respectively.

3.8 | Aetiological agents and causes of diarrhoea

The comprehensive investigation of the causes of diarrhoea is described elsewhere.[15] An enteropathogen was identified in 16% (235/1438) of the horses. *Salmonella* spp. was detected in 81/633 (13%) horses via faecal culture or PCR in fresh or faeces after 24 h of enrichment. ECoV was detected in 37/422 (9%) horses, while *C. difficile* in 5% (27/578) of the horses. 120/1438 (8.3%) horses were treated with antimicrobial drugs for a different disease process before the development of diarrhoea and were considered to have AAD. Sixty-six (5%) of the 1438 horses with acute diarrhoea were diagnosed with sand enterocolitis.

3.9 | Laminitis

In total, 100/1438 (7%) horses developed laminitis associated with acute diarrhoea. Institutions with the highest number of horses developing laminitis included Lyon (25%, 9/36), Adelaide (17%, 4/24), KSU (15%, 3/20), RREH (15%, 18/117), UNAM (15%, 14/93), The OSU (11%, 6/54) and ISU (10%, 3/20). The proportion of horses that developed laminitis was lower in Europe (4%, 19/479) compared with North America (8%, 52/619), Australia (8%, 12/138) and Latin America (11%, 16/146) ($p < 0.05$). The age of horses that developed laminitis (median: 9 years, range: 1 to 33) was not different from those that did not (8 years, 1 to 35) ($p > 0.05$). The sex of horses that developed laminitis also was not different from those that did not (Table 2). The season of the presentation was available for 85 horses that developed laminitis. The proportion of horses that developed laminitis was higher in the summer (46%, 39/85) compared with winter (18%, 15/85), spring (18%, 15/85) and fall (19%, 16/85) ($p < 0.01$, for all comparisons) (Figure 1).

Table 2 compares clinical findings between horses that did and did not develop laminitis. Results of a multivariable logistic regression model used to evaluate the association between seasonality and clinicopathological variables and the development of laminitis are displayed in Table 3.

3.10 | Outcome

The overall survival for acute diarrhoea combining all institutions and years was 76% (1093/1438) (Table 1). Thirty-nine horses died, and 306 were euthanised. Reasons for euthanasia were available for 208/306 (68%), with 176/208 (89%) of the horses being euthanised because of poor prognosis and 22/345 (11%) due to economic constraints. Of the 176 horses euthanised for poor prognosis, 24 (14%) had laminitis. There was no difference in the survival proportion of horses admitted to Asia (74%, 26/35), Australia (73%, 103/141), Europe (78%, 377/483), Latin America (79%, 118/149) and North America (74%, 469/630) ($p = 0.47$). The survival proportion in Australian institutions varied from 62% to 90%. In Europe and North America, the survival proportion went from 40% to 88% and 57% to 84%, respectively. In Latin America, the survival proportion ranged between 58% and 90%.

3.11 | Factors associated with survival

Differences in clinical and laboratory variables between survivors and non-survivors are shown in Table 4. There were no differences in the

TABLE 2 Demographic characteristics and clinicopathologic findings of horses with acute diarrhoea that develop laminitis and those that did not develop laminitis.

Variable	Available data (non-lam | lam)	No-laminitis $n = [\%]$	Laminitis $n = [\%]$	p-Value
Sex	1287 | 91			0.389
Female		585 [45%]	38 [42%]	
Gelding		623 [48%]	44 [48%]	
Stallion		79 [6%]	9 [10%]	
Dehydration	1026 | 90			0.005
None		93 [9%]	2 [2%]	
Mild (5% to 7%)		478 [47%]	37 [41%]	
Moderate (8% to 10%)		324 [32%]	29 [32%]	
Severe (> 10%)		135 [13%]	22 [24%]	
Mentation				
Abnormal	1300 | 96	726 [56%]	56 [58%]	0.635
Toxic line	1300 | 99	194 [15%]	37 [37%]	<0.001
CRT	1010 | 301			<0.001
<2 s		707 [70%]	122 [40%]	
3 s		233 [23%]	100 [33%]	
4 s		48 [5%]	62 [21%]	
>4 s		22 [2%]	17 [6%]	
Reflux	1198 | 97	107 [9%]	10 [10%]	0.655
Diarrhoea	1315 | 100	812 [62%]	59 [59%]	0.587
Colic	1282 | 100	578 [45%]	43 [43%]	0.685
Age (years)	1316 | 100	9 [1 to 33]	8 [1 to 35]	0.369
Temperature (°C)	1262 | 97	38 [34.2 to 41]	38.2 [36 to 40.2]	0.007
Heart rate (bpm)	1303 | 100	54 [28 to 140]	68 [30 to 120]	<0.001
Respiration (rpm)	1221 | 97	20 [8 to 104]	24 [8 to 88]	0.003
PCV (%)	1250 | 97	42 [20 to 81]	48 [24 to 72]	<0.001
TP (g/dL)	1252 | 96	6.2 [2 to 11.2]	6.3 [3.2 to 10]	0.109
WBC (K/μL)	1112 | 88	5.9 [0.8 to 44]	6 [1.4 to 33.7]	0.876
Neutrophils (K/μL)	1009 | 82	3.2 [0 to 38.3]	3.65 [0.1 to 26.3]	0.999
Creatinine (μmol/L)	1074 | 79	133 [27 to 1096]	168 [53 to 796]	<0.001
L-lactate (mmol/L)	801 | 69	2.4 [0.3 to 26]	3.2 [0.6 to 15]	0.001
tCa (mmol/L)	438 | 37	2.7 [1.6 to 4.4]	2.7 [1.8 to 3.7]	0.69
iCa (mmol/L)	634 | 41	1.39 [0.5 to 2.47]	1.22 [0.65 to 2.38]	0.012

Note: Data presented as proportion or median and lower and higher range. p-Values were obtained using the Mann–Whitney test.
Abbreviations: CRT, capillary refill time; iCa, ionised calcium; lam, laminitis; non-lam, no laminitis; PCV, packed cell volume; tCa, total calcium; TP, total plasma proteins; WBC, total white blood cells.

survival proportion of horses presented in the different seasons worldwide ($p = 0.254$) or in North America ($p = 0.193$). However, the proportion of non-survival was higher in horses that developed laminitis (50%, 50/100) than in horses that did not (21%, 278/1317). In addition, horses with laminitis had greater odds of non-survival than those without laminitis (OR: 3.73, 95% CI: 2.47 to 5.65; $p < 0.001$).

The multivariable logistic regression model used to evaluate the association between demographic, clinical and laboratory variables and the outcome of non-survival showed that increases in PCV, L-lactate and creatinine and TPP concentrations at admission were associated with greater odds of non-survival. The presence of altered mentation and a toxic line in the oral mucus membranes on admission were also significantly associated with increased odds of non-survival (Table 5).

3.12 | Survival proportions of horses with SIRS

Complete information to calculate the SIRS score was available for 78% (1119/1438) of the horses. 800/1119 (66%) were classified as

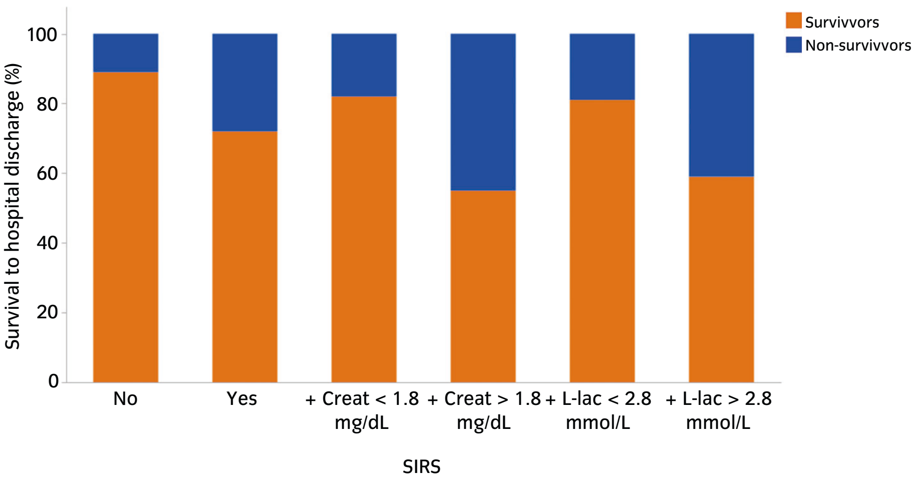

FIGURE 1 The survival proportions of horses with acute diarrhoea ($n = 1438$) with ($n = 800$) and without ($n = 319$) systemic inflammatory response syndrome (SIRS). The survival proportion of horses with SIRS and creatinine concentrations > 1.8 mg/dL ($n = 279$) and that of horses with SIRS and creatinine concentrations < 1.8 mg/dL ($n = 437$) is displayed. The survival proportion of horses with SIRS and L-lactate concentration > 2.8 mmol/L ($n = 298$) and that of horses with SIRS and L-lactate concentration < 2.8 mmol/L ($n = 296$) is also displayed.

TABLE 3 Multivariable mixed model evaluating the association between demographic and clinicopathological variables with the development of laminitis in horses with acute diarrhoea.

	Estimate	Lower 95% CI	Upper 95% CI	*p*-Value	OR	Lower 95% CI	Upper 95% CI
Random effects							
Institution	0.126	0.036	3.142	0.139	-	-	-
Fixed effects							
Intercept	−9.935	−14.085	−5.78	<0.0001			
Toxic line							
Yes	Referent						
No	−0.860	−1.333	−0.386	0.015	0.423	0.263	0.679
HR	0.118	0.062	0.175	<0.0001	-	-	-
PCV	0.132	0.051	0.212	0.001	-	-	-
HR × PCV	−0.001	−0.002	−0.0007	0.001	-	-	-

Note: OR for HR and PCV were not calculated due to involvement with compound effects. In total, 1325 horses with colitis were included in the analysis (96 horses with laminitis and 1229 without laminitis).
Abbreviations: 95% CI, 95% confidence interval; HR, heart rate; OR, odds ratio; PCV, packed cell volume.

meeting SIRS criteria, and 319/1119 (28%) did not. 372/800 (47%) had an alteration in 2 variables, 314/800 (39%) in 3 and 114/800 (14%) in 4 variables. The heart and respiratory rate and rectal temperature of horses with 2, 3 and 4 SIRS criteria differed significantly ($p < 0.05$ for all comparisons). The WBC was significantly lower in horses with 4 SIRS criteria than those with 2 or 3 SIRS criteria ($p < 0.05$). The survival proportion of horses with 2, 3 and 4 SIRS criteria was 74% (277/372), 70% (22/314) and 64% (41/114), respectively. The survival proportion differed between horses with 2 and 4 SIRS criteria ($p = 0.03$) but not between horses with 2 or 3 SIRS criteria ($p = 0.08$). The survival proportion of horses with and without SIRS was 72% (572/800) and 89% (283/319), respectively ($p < 0.001$). Overall, horses with SIRS had greater odds of dying or being euthanised than those without SIRS (OR: 3.11, 95% CI: 2.14 to 4.58; $p < 0.001$).

The multivariable logistic regression model revealed that L-lactate and creatinine concertation were associated with the outcome of non-survival, and the ROC curve analysis revealed that a creatinine concentration > 159 μmol/L and an L-lactate concentration > 2.9 mmol/L had the highest sensitivity and specificity to predict the outcome of non-survival (Table S1). The survival proportion of horses meeting SIRS criteria and creatinine concentrations > 159 μmol/L was 55% (154/279) compared with 81% (358/437) for those meeting SIRS criteria and creatinine concentrations < 159 μmol/L ($p < 0.001$). Horses meeting SIRS criteria and creatinine concentrations > 159 μmol/L had greater odds of nonsurvival than horses meeting SIRS criteria and creatinine concentrations < 159 μmol/L (OR: 3.78, 95% CI: 2.62 to 5.16; $p < 0.001$) (Figure 2 and Table S1).

The survival proportion of horses with meeting SIRS criteria that had an L-lactate concentration > 2.8 mmol/L was 59% (175/298) compared with 81% (240/296) in horses meeting SIRS criteria and L-lactate concentration < 2.8 mmol/L ($p < 0.001$). Horses meeting SIRS criteria and L-lactate > 2.8 mmol/L had greater odds of nonsurvival than horses meeting SIRS criteria and L-lactate < 2.8 mmol/L (OR: 3, 95% CI: 2.07 to 4.36; $p < 0.001$) (Figure 2 and Table S1).

TABLE 4 Demographic characteristics and clinicopathologic findings of surviving and non-surviving horses with acute diarrhoea.

Variable	Available data (surv | non-sur)	Survivors $n = 1093$ [76%]	Non-survivors $n = 345$ [24%]	p-Value
Sex	1064 | 334			0.161
Female		498 [47%]	137 [41%]	
Gelding		499 [47%]	176 [52%]	
Stallion		67 [6%]	21 [7%]	
Dehydration	941 | 214			<0.001
None		83 [9%]	14 [5%]	
Mild (5% to 7%)		447 [53%]	65 [22%]	
Moderate (8% to 10%)		248 [29%]	116 [39%]	
Severe (>10%)		163 [7%]	19 [34%]	
Mentation				
Abnormal	1080 | 336	540 [50%]	258 [76%]	<0.001
Toxic line	1049 | 327	129 [12%]	104 [30%]	
CRT	1010 | 301			<0.001
<2 s		707 [70%]	122 [40%]	
3 s		233 [23%]	100 [33%]	
4 s		48 [5%]	62 [21%]	
>4 s		22 [2%]	17 [6%]	
Reflux	1005 | 307	79 [8%]	40 [13%]	0.005
Diarrhoea	1091 | 343	671 [61%]	213 [62%]	0.186
Colic	1066 | 336	464 [43%]	166 [49%]	0.058
Laminitis[a]	1089 | 328	50 [5%]	50 [15%]	<0.001
Age (years)	1092 | 345	9 [1 to 33]	10 [1 to 35]	0.024
Temperature (°C)	1049 | 327	38.1 [35 to 41]	38.1 [34.2 to 41]	0.956
Heart rate (bpm)	1084 | 339	52 [28 to 140]	68 [28 to 124]	<0.001
Respiration (rpm)	1018 | 316	20 [8 to 100]	24 [8 to 104]	<0.001
PCV (%)	1049 | 316	40 [20 to 80]	52 [24 to 81]	<0.001
TP (g/dL)	1041 | 325	6.2 [2.6 to 11]	6 [2 to 11.2]	0.103
WBC (K/μL)	921 | 292	6.1 [0.8 to 44]	6 [1.4 to 28]	0.012
Neutrophils (K/μL)	839 | 265	3.5 [0 to 38.3]	2.7 [0 to 26.3]	0.005
Creatinine (μmol/L)	895 | 271	124 [26 to 796]	177 [53 to 1061]	<0.001
L-lactate (mmol/L)	639 | 241	2.1 [0.3 to 15]	3.7 [0.3 to 26]	<0.001
tCa (mmol/L)	369 | 114	2.7 [1.6 to 4.7]	2.6 [1.6 to 3.9]	0.04
iCa (mmol/L)	503 | 178	1.4 [0.5 to 2.5]	1.3 [0.65 to 2.38]	<0.001

Note: Data presented as proportion or median and lower and higher range. *p*-Values were obtained using the Mann–Whitney test.

Abbreviations: CRT, capillary refill time; iCa, ionised calcium; non-surv, non-survivors; PCV, packed cell volume; surv, survivors; tCa, total calcium; TP, total proteins; WBC, total white blood cells.

[a]Laminitis at any time of hospitalisation.

4 | DISCUSSION

This retrospective multicentre investigation is the most extensive study describing horses with acute diarrhoea and the first comparing clinical, laboratory and epidemiologic findings across different geographic regions. Previous studies have focussed on cases from either one institution,[5,6,8,11] one geographic location[4,16] or one country.[2,17] In line with previous reports,[2,4,11,17] horses with acute diarrhoea comprised a low to moderate percentage of the total caseload ranging between 0.1% and 7.2%, with the highest rates reported in a university from Colombia and one from Mexico. However, for several institutions, total annual case numbers were unavailable, making it difficult to draw further conclusions from this finding. No substantial seasonal variations were apparent, although statistically, fewer horses with acute diarrhoea were admitted in the spring compared with other seasons. Previous studies indicated the highest case numbers in the summer in North America[2,18] and in winter in some European countries.[19] Geographic location and season can influence the presence of common equine enteric pathogens, with increased detection of *Salmonella* spp. in the summer and fall in the South of the USA and higher detection of *N. risticii* in the fall in the Midwest of the USA.[4,11,20,21] In contrast, acute larval cyathostomins, an important cause of acute

TABLE 5 Multivariable mixed model evaluating the association between demographic and clinicopathological variables with the mortality of horses with acute diarrhoea.

	Estimate	Lower 95% CI	Upper 95% CI	p-Value	OR	Lower 95% CI	Upper 95% CI
Intercept	−3.517	−4.724	−2.348	<0.0001			
Mentation							
Bright	Referent						
Altered demeanour	0.233	0.036	0.435	0.021	1.767	1.168	2.672
Toxic line							
No	Referent						
Yes	0.267	0.048	0.482	0.015	1.750	1.131	2.708
PCV	0.032	0.015	0.049	0.0002	1.032	1.014	1.050
L-lactate	0.102	0.045	0.162	0.0006	1.107	1.045	1.176
Creatinine	0.511	0.337	0.701	<0.0001	-	-	-
TP	−0.098	−0.235	0.037	0.156	-	-	-
TP (Quad)	0.095	0.025	0.167	0.008	-	-	-
Creatinine × TP	−0.147	−0.229	−0.064	0.0003	-	-	-

Note: OR for total protein and creatinine were not calculated due to involvement with compound effects. In total, 817 horses with colitis were included in the analysis (625 survivors and 192 non-survivors).
Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; PCV, packed cell volume; Quad, quadratic term; TP, total protein.

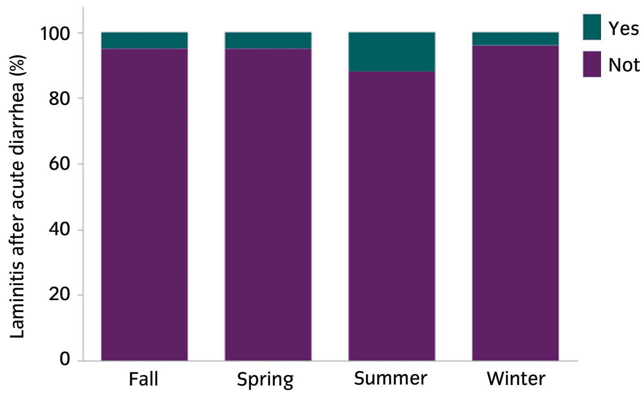

FIGURE 2 The proportion of horses admitted to institutions from the Northern and Southern hemispheres with acute diarrhoea ($n = 1293$) that developed laminitis ($n = 100$) during the different seasons.

diarrhoea in many European countries,[22,23] usually develop in late winter to early spring and could explain the numerically high percentage of cases seen in winter.[22,24,25]

The age and breed distribution reported here was comparable to previous reports and is likely representative of the general population of the contributing institutions. However, this was not explicitly assessed.[2,3,26–29] In addition, a numerically higher proportion of males than females has been described in individual studies,[3,7] but this is again probably more reflective of the hospital populations rather than a true sex predilection.

In this study, the presenting complaints and clinicopathological findings were similar to previous investigations, corresponding to the primary disease process and secondary systemic inflammation, cardiovascular compromise and electrolyte derangements.[5,16,30]

Complications, excluding laminitis, were reported in 8% of horses, with thrombophlebitis being the most common adverse event. Thrombophlebitis was documented in 6% of cases, similar to previous reports in horses with colic and colitis.[31–33] Horses with colitis have a higher risk of developing thrombophlebitis because they are exposed to multiple risk factors, including fever, systemic inflammation, hypoproteinaemia, large intestinal disease and possibly salmonellosis.[5,33–35] Due to the retrospective nature of this study, it is possible that the prevalence of catheter-related complications was higher, as mild or subclinical presentations of catheter-related complications might not have been reported.

Laminitis is a well-known and often debilitating complication in horses with acute colitis, and the reported incidence varies between 2.4% and 36%.[2–4,6,11] The prevalence in this study was comparatively low at 7% but varied widely between institutions ranging from 0% to 25%. Risk factors include specific aetiological pathogens, with horses with ECoV rarely developing laminitis compared with horses with neorickettsiosis which had the highest laminitis rate.[2,11,20,36,37] Findings consistent with more severe disease and systemic compromise, such as higher heart rates, band neutrophils, haemoconcentration, lower plasma protein and acid–base disturbances, have also been recognised as risk factors.[2,6,11] This is also reflected in the present study where similar variables were identified, including more severe dehydration, presence of a toxic line, higher rectal temperature, HR, RR, PCV, creatinine, and L-lactate concentrations, and lower iCa concentration in horses that developed laminitis. In addition, horses with SIRS and those admitted during the summer were at an increased risk of developing laminitis.

Interestingly, laminitis developed overall less commonly in Europe compared with the other geographic regions, even though one European hospital had the numerically highest prevalence. Reasons for this are not immediately apparent as disease severity was similar across centres in different geographic locations. Specific pathogens, such as *Neorickettsia risticii*, have been associated with a higher risk of laminitis which could have contributed to the observed variation. *Neorickettsia risticii* is predominately present in some areas of the USA but has also been reported in Canada, southern Brazil and Uruguay.[20,38,39] While this might explain differences between North America and Europe, it would not account for the differences in laminitis between Europe and the other geographic regions where *N. risticii* is less common. Furthermore, another study only identified differences in the prevalence of laminitis between horses with *N. risticii* and ECoV infection, but not other pathogens.[11] Treatment approaches used in the different geographic areas could have impacted the rates of laminitis development; however, due to the retrospective nature, the associations between therapies and the development of laminitis could not be evaluated. Changes in microbial communities of the gastrointestinal tract are associated with the development of laminitis.[40,41] Thus, differences in microbiota could explain, in part, the differences in laminitis between Europe and other geographic locations. Although geographic regions can affect the microbiota,[42] investigations into regional microbiota differences are confounded by a wide range of types of hay or pasture and athletic occupations influencing management strategies in certain regions.[43–45] In addition, differences in the microbiota from horses with colitis that did and did not develop laminitis are minor,[46] and whether or not, and to what degree bacterial by-products derived from different intestinal microbial populations contribute to lamellar separation remains to be determined.[41,46]

Overall, 76% of horses survived to discharge, similar across all geographic regions. Most horses were euthanised due to a poor prognosis, and only 11% were due to economic considerations. However, the variation in survival proportions between different institutions ranged from 40% to 90% short-term survival. Reasons for this could not be extracted from the data but might reflect referral practices, the economic climate in different regions, the emotional and financial value of the horses admitted and client expectations. Factors associated with non-survival essentially indicated disease severity and subsequent cardiovascular compromise, as demonstrated in several other studies.[2,5,6] Increased PCV, L-lactate and creatinine concentrations, and altered mentation and a toxic line on the oral mucus membranes on admission were all significantly linked to non-survival. As previously shown, SIRS was also associated with non-survival, and survival decreased with an increasing number of SIRS criteria being present.[9] This is unsurprising as many of the variables closely associated with non-survival are used to determine SIRS status. The association between SIRS status, increased creatinine concentrations, and hyperlactatemia was further explored. Both are common abnormal findings in horses with acute diarrhoea and represent organ injury or failure and cardiovascular deficiencies. An increase in creatinine concentration > 1.8 mg/dL decreased the percentage of survivors to 55%. This finding resembles a smaller multicentre study investigating equine colitis.[6] Hypercreatininemia likely represents a measure of disease severity and hypovolemia at presentation, and horses predominately succumb to the primary disease process rather than renal failure playing a direct part in mortality. A return to normal creatinine concentration within 72 h is associated with a better prognosis than persistently increased concentrations[47] and assessing repeated values throughout hospitalisation would have been interesting in the described cases to differentiate the effects of the primary disease process from the impact of acute kidney injury. In contrast, no association between hypercreatininemia and survival or SIRS was established in a different investigation.[47] However, in that study, only 13% of the included horses were hypovolemic, and 25% showed evidence of SIRS,[47] corroborating the assumption that the latter factors are more important in determining survival than creatinine concentrations per se. Similar to a previous study,[9] an association was established between horses with SIRS and L-lactate concentrations in this situation were probably predominately indicative of hypovolemia, aerobic glycolytic flux stimulated by catecholamine release and increasing disease severity,[30,48] which explains the association with non-survival. The clinicopathological variables needed to classify a horse with SIRS and blood L-lactate or creatinine concentrations are simple, inexpensive to measure and widely used and could aid clinicians in identifying and monitoring critically ill horses with colitis at high risk of dying. It can also aid in standardising case selection for prospective randomised clinical trials. Horses that developed laminitis were less likely to survive, but it is difficult to ascertain whether the development of laminitis was interpreted as a worse prognosis (poor welfare and poor prognosis for intended usage) and therefore made euthanasia more likely or whether the severity of the laminitis contributed to the need for euthanasia.[6,11]

The main limitation of the present study is its retrospective nature and the varying amount of information collected by the 26 participating institutions. Data collection and sample processing were not standardised within or across institutions, and the categorisation of clinical signs was not possible, which could have resulted in information bias. This limitation resulted in missing data for several predictor factors, but the reason for missing data were unrelated to the outcome of survival (e.g., creatinine and L-lactate concentrations were not determined in any of the horses admitted to certain institutions). Thus, missing data was considered to be completely at random, and therefore, the analysis was conducted based on complete cases.[12] Multiple imputation has been proposed as an approach to deal with missing data.[49] However, these analyses also have multiple limitations that could result in erroneous conclusions if not carefully considered.[12,50] Several variables were only gathered on admission, which can be problematic when assessing their influence on non-survival. Trends over time are more valuable than a single analysis on admission, particularly for L-lactate and creatinine concentrations. In addition, some assessments, such as mucous membrane colour, the presence of a toxic line and capillary refill time, are subjective and might not have been assessed uniformly across all institutions and all clinicians. This study included only horses with acute diarrhoea presented to referral institutions could bias the study toward sicker animals. Therefore, caution must be exercised while extrapolating the findings to different populations. Nevertheless, the study is the largest to date on acute equine diarrhoea. It is reassuring that several findings from smaller studies were confirmed in a larger population, and some new aspects were uncovered.

In conclusion, clinicopathological findings in horses with acute diarrhoea and their association with survival are similar across geographic regions and similar to results from previous studies. Survival of horses with acute diarrhoea is similar across geographic areas and institutions. However, laminitis secondary to acute diarrhoea is more frequent in North America than in other geographic regions, and further investigations are necessary to identify underlying reasons for this finding.

AUTHOR CONTRIBUTIONS

Diego E. Gomez, David L. Renaud and Ramiro E. Toribio contributed to the study design, data collection, analysis and interpretation and manuscript preparation. Bettina Dunkel, Luis G. Arroyo, Angelika Schoster, Jamie J. Kopper and David Byrne contributed to the data collection, and interpretation and manuscript preparation. Anna Mykkanen, William F. Gilsenan, Tina H. Pihl, Gabriela Lopez-Navarro, Brett S. Tennent-Brown, Laura D. Hostnik, Mariano Mora-Pereira, Fernando Marques, Jenifer R. Gold, Sally L. DeNotta, Isabelle Desjardins, Allison J. Stewart, Taisuke Kuroda, Emily Schaefer, Olimpo J. Oliver-Espinosa, Gustavo Ferlini Agne, Benjamin Uberti, Pablo Veiras, Katherine M. Delph Miller, Rodolfo Gialletti and Emily John contributed to data collection and manuscript preparation. All authors approved the final version of the manuscript. Diego E. Gomez had full access to all the study data and takes responsibility for the integrity of the data of the accuracy of the data analysis.

ACKNOWLEDGEMENTS

We acknowledge the contribution of all research technicians, graduate students and clinical staff of the participating institutions that collaborated in collecting the data. The authors also acknowledge William Sears for his assistance with the statistical analysis.

FUNDING INFORMATION

Not applicable.

CONFLICT OF INTEREST STATEMENT

No competing interests have been declared.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/evj.14032.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request: Open sharing exemption granted by editor for this descriptive retrospective clinical report.

ETHICAL ANIMAL RESEARCH

Research ethics committee oversight not required by this journal: retrospective study of clinical records.

INFORMED CONSENT

Explicit owner consent for animals' inclusion in the study was not stated.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gomez DE, Dunkel B, Renaud DL, Arroyo LG, Schoster A, Kopper JJ, et al. Survival rates and factors associated with survival and laminitis of horses with acute diarrhoea admitted to referral institutions. Equine Vet J. 2023. https://doi.org/10.1111/evj.14032