

STANDARD ARTICLE

Incidence and risk factors for recurrence of endocrinopathic laminitis in horses

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Abstract

Background: Endocrinopathic laminitis is common in horses and ponies, but the recurrence rate of the disease is poorly defined.

Objectives: To determine the incidence of, and risk factors for, the recurrence of endocrinopathic laminitis.

Animals: Privately owned horses and ponies with acute laminitis (n = 317, of which 276 cases with endocrinopathic laminitis were followed up to study completion).

Methods: This prospective cohort study collected data on veterinary-diagnosed cases of acute laminitis for 2 years. Each case was classified on acceptance to the study as endocrinopathic or non-endocrinopathic using data collected in a questionnaire completed by the animal's veterinarian. Follow-up data were collected at regular intervals to determine whether the laminitis recurred in the 2-year period after diagnosis.

Results: The recurrence rate for endocrinopathic laminitis was 34.1%. The risk of recurrence during the 2-year study period increased with basal, fasted serum insulin concentration ($P \leq .05$), with the probability of recurrence increasing markedly as the insulin concentration increased beyond the normal range (0–20 $\mu\text{IU/mL}$) to over the threshold for normal (up to approximately 45 $\mu\text{IU/mL}$). Being previously diagnosed with laminitis (before the study; $P = .05$) was also a risk factor for recurrent laminitis. Cases with a higher Obel grade of laminitis were likely ($P = .05$) to recur sooner.

Conclusions and clinical importance: Knowing that hyperinsulinemia and being previously diagnosed with laminitis are significant risk factors for recurrence will enable clinicians to proactively address these factors, thereby potentially reducing the risk of recurrence of laminitis.

KEYWORDS

ACTH, equine metabolic syndrome, horse, hyperinsulinemia, insulin dysregulation, pituitary pars intermedia dysfunction

Abbreviations: BCS, body condition score; CNS, cresty neck score; EMS, equine metabolic syndrome; ID, insulin dysregulation; NSC, nonstructural carbohydrate; OGT, oral glucose test; OST, oral sugar test; PPID, pituitary pars intermedia dysfunction.

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1 | INTRODUCTION

Laminitis can be a clinical outcome of endocrine disease, sepsis, or unrelenting unilateral weight bearing (supporting limb laminitis), and despite its prevalence remains without a targeted treatment that can achieve lamellar repair.¹ Endocrinopathic laminitis occurs in association with equine metabolic syndrome (EMS) and pituitary pars intermedia dysfunction (PPID). The critical factor in cases of endocrinopathic laminitis appears to be insulin dysregulation (ID), which results from a complex, often multifactorial disruption to the normal interactions between glucose and insulin. The diagnosis and management of ID can be challenging,² and failure to recognize and control the underlying endocrinopathy means that laminitis might recur and become chronic.³ Furthermore, the management of ID currently relies on ongoing strategies to mitigate hyperinsulinemia, such as dietary restriction, weight loss, and exercise, the success of which is dependent on owner compliance.⁴

There is insufficient epidemiological data on endocrinopathic laminitis.⁵⁻⁷ Currently, due to a lack of dedicated studies, the rate of recurrence of endocrinopathic laminitis is poorly defined. Estimates vary between 30% and 70%, and it is unknown whether the risk factors for the initial disease onset remain the same for recurrent disease.⁷⁻⁹ Recurrent episodes of laminitis not only increase animal morbidity, and potentially lead to death, but are distressing and expensive for horse owners.¹ A better understanding of the likelihood of, and risk factors for, laminitis recurrence is desirable, as it would aid in the prevention of subsequent episodes of disease. However, the risk factors related to the recurrence of endocrinopathic laminitis have not yet been prospectively investigated.

Our study sought to evaluate the recurrence rate of laminitis in a cohort of horses and ponies, and more specifically to focus on the recurrence rate of the endocrinopathic form of laminitis. The explicit aims were: (1) to determine the incidence of recurrence of endocrinopathic laminitis and (2) to investigate risk factors that predispose horses to recurrence of endocrinopathic laminitis.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a multinational (USA, UK/Europe, Australia/NZ; Supp item 1) prospective cohort study of privately owned horses and ponies diagnosed with an acute case of laminitis (of any cause, known or otherwise) by a veterinarian. Animals were recruited to the study using multiple channels, including advertising campaigns, media releases, mail-outs, posters, promotion at veterinary meetings, conferences and industry roadshows, and word-of-mouth. Potential participants were then directed to a study web site, which provided all details pertinent to involvement, including how to access free laboratory tests. Cases were accepted within 4 weeks of their laminitis episode over a 2-year period,¹⁰ and each case was followed up for 2 years after inclusion. The veterinarian completed a detailed questionnaire about the animal,

and owners provided consent for their animal to be included in the study. Veterinarians reported on animal factors, including signalment, history, Obel grade of lameness¹¹ and clinical signs of the disease, including the presence or absence of digital pulses, a positive response to hoof testers, founder rings or hoof deformity or both, as well as geographic factors (location and season), and any treatments and management strategies.¹⁰ The animals might have had previous episodes of laminitis and could be of any signalment (except donkeys). Owner data were not collected and the animal data were de-identified on entry to the study before analysis.

Each case was followed up with the submitting veterinarian at 6 months, 12-18 months, and 24 months after recruitment of the equid into the study. The veterinarian was asked to complete and return a follow-up questionnaire by email. The questions related to whether the animal had a recurrence of laminitis, whether the episode was considered to be a separate recurrence (ie, complete resolution of clinical signs prior to recurrence) or a continuation of chronic disease (ie, mild or intermittent clinical signs of laminitis had persisted since the initial diagnosis), and whether they considered the cause to be the same as for the previous episode. A final question asked whether management changes had been implemented by the owner (recommended by the veterinarian or otherwise) since the initial bout of laminitis. The email also included a free text option to enable pertinent details to be included (Supp item 2). The follow-up questionnaire was simpler and faster to complete than the initial questionnaire in order to encourage maximal participation in the follow-up process by the submitting veterinarian.

To aid with case classification, blood samples were collected from each animal at the time that they entered the study and were placed into plain and EDTA tubes (glass or plastic) and sent to 1 of 3 commercial laboratories (VetPath Laboratories, Epsom WA, Australia; Animal Health Laboratories, Cornell, New York; and Liphook Equine Hospital Laboratory, Hampshire, UK) for serum insulin and plasma ACTH analyses. The analysis of ACTH at all laboratories was performed using a chemiluminescent assay (Immulite, Siemens Healthcare).¹² The ACTH concentration was interpreted according to location and season-specific reference ranges. Insulin was analyzed at VetPath and Liphook using a chemiluminescent assay (Immulite, Siemens Healthcare) and using a radioimmunoassay (Siemens Healthcare) at Cornell. These assays have been evaluated previously,^{13,14} and because of discrepancies between the insulin assays, the data obtained from Cornell (4% of samples) were only used for case classification, and were not included in the insulin analyses.

2.2 | Case classification

The data for each case were examined to determine the likely cause of the laminitis. Given that endocrinopathic laminitis is the most common form of the disease; each case of laminitis was designated to be either endocrinopathic or non-endocrinopathic in origin. The criteria used for classification of the cases have been reported previously.¹⁰ Briefly, these were elevated resting serum insulin concentration (>20 μ U/mL), elevated plasma ACTH concentration (considered to

have PPID if >35 pg/mL or $>$ seasonally adjusted, location-specific reference ranges during autumn^{12,15}), body condition score (BCS) $\geq 6/9$,¹⁶ cresty neck score (CNS) $\geq 2/5$,¹⁷ other evidence of regional adiposity, history of recent access to pasture, sudden increase in nonstructural carbohydrate (NSC) content of the diet (in the absence of diarrhea or colic), breed at-risk of EMS,¹⁸ being an easy-keeper, divergent growth rings in 1 or more hoof wall, a familial history of laminitis, and a dysregulated post-prandial serum insulin response to an oral glucose test (OGT¹⁹) or an oral sugar test (OST²⁰). If 2 or more of the criteria were met, or 1 criterion in the absence of an obvious non-endocrine cause for laminitis, the case was classified as endocrinopathic in origin. The presence of an endocrine disease and a history of recent exposure to pasture was previously evaluated in each animal,¹⁰ with cases deemed to have PPID, EMS or pasture-associated laminitis, or a combination of factors.

2.3 | Data analyses

Power analyses ($\alpha = 0.05$, power = 0.8, assumed relative risk of 2) using conservative estimates of the rate of laminitis recurrence (15%) and attrition rate (20%) stipulated a minimum cohort size of 284. The data are presented as either a proportion (%) or median [interquartile range]. Significance was accepted at $P \leq .05$. The calculation of cumulative incidence rate for laminitis recurrence accounted for all incidences of recurrence, including repeat episodes in an individual, that occurred across all horse years at risk for the cohort of 267 animals, and incorporated individual animal attrition (due to euthanasia).

Exploratory analyses of risk factors for recurrence were undertaken by calculating odds ratios (95% confidence interval [CI]). For continuous variables, we also inspected plots of the empirical log-odds against each variable. If the relationship was linear, the variable was modeled using logistic regression without modification, whereas variables with nonlinear relationships were transformed or included as a hyperbolic term (eg, insulin) to enable logistic regression. Two binary logistic regression models were initially used to estimate the probability of laminitis recurrence based on combined risk factors grouped as either non-modifiable (eg, animal/case) or modifiable (eg, management), prior to the development of a combined, final model. Risk factors for inclusion in the final model were selected via stepwise regression based on the Akaike information criterion, which rewards model fit but penalizes model complexity.²¹ The fit of the data for the models was deemed acceptable based on Hosmer and Lemeshow "goodness-of-fit" tests.²² The accuracy of the final model for predicting laminitis recurrence was determined by calculating the area under the curve of the receiver operator characteristic curve based on results from a leave-1-out cross validation analysis. Single incidences of missing values were ignored. Where multiple missing values were apparent for 1 animal, the case was deleted from the data set. Thus, the n value reported for any given statistical outcome might not necessarily equal the expected total.

As there was variability in the time taken by each veterinarian to respond to the follow-up request, the time to follow-up was placed into 1 of 3 categories: ≤ 6 months, 7-18 months, or 19-24 months. This

and other categorical variables were examined with the chi-squared test or a Kruskal-Wallis ANOVA on ranks with Dunn's post-hoc test. Variables examined further in population subsets were analyzed with logistic regression as described above. The data were analyzed using R v.3.3 (The R Foundation) or SigmaPlot v.13 (Systat software, San Jose, California).

3 | RESULTS

3.1 | Case recruitment

A total of 317 cases were recruited to the study, comprising male and female horses and ponies belonging to 19 different breeds, predominantly Shetland, Australian, and Welsh ponies and Quarter horses (stock type) and Warmbloods (hunter type).¹⁰ A high proportion of cases (301) were considered to have laminitis of endocrinopathic origin. The endocrinopathic causes for laminitis that were identified included EMS ($n = 248$), PPID ($n = 113$), and pasture-associated laminitis ($n = 95$). Of the 301 animals, 134 (45%) had more than 1 of these factors.¹⁰

For the cases of non-endocrinopathic laminitis, a clear cause of the laminitis could not be identified in 12 of the horses/ponies. Three of these non-identified cases were suspected of having endocrinopathic laminitis, and were treated as such by the submitting veterinarian, but did not meet the study criteria. One case of supporting limb laminitis was recruited and 3 cases developed laminitis after a sepsis-related event. For the cases that recurred, no animal in the endocrinopathic laminitis group was recorded as having a non-endocrinopathic cause for their laminitis at recurrence. For animals with non-endocrinopathic laminitis, recurrent disease might have been endocrinopathic in some cases; but due to the small number of animals in this group, they were not included in any analyses.

3.2 | Laminitis recurrence rate

For the whole cohort, which included both endocrinopathic and non-endocrinopathic laminitis cases, 280 cases (88%) were followed up for the 2-year period. For the cases of endocrinopathic laminitis, a total of 267/301 (89%) cases were followed up to completion with a laminitis recurrence rate of 34.1% within 2 years. In cases where laminitis recurred ($n = 91$), 65.2% had 1 recurrence in the 2-year follow-up period, whereas 34.8% of cases had 2 or more episodes of laminitis. Furthermore, 45.2% ($n = 42$) of the cases of recurrence of laminitis occurred within 6 months of the initial diagnosis. For all cases followed up, the cumulative incidence rate for recurrence events was 29 laminitis events for every 100 horse years at risk.

Of the 37 cases that were unable to be followed up, 19 occurred as a result of a failure of the submitting veterinarian/farrier to respond to repeated requests for follow-up information. The remaining 18 cases either died, or were euthanized, from causes other than laminitis recurrence, during the follow-up period ($n = 10$) or the owner was no longer able to be contacted ($n = 8$).

3.3 | Risk factors for the recurrence of endocrinopathic laminitis

3.3.1 | Animal factors

Risk factors for recurrence were examined in the cohort of animals with laminitis that was endocrinopathic in origin. The variables of age, breed (grouped according to type), sex, type (horse or pony), height, BCS, and CNS, were not predictive of disease recurrence (Table 1). The presence of EMS, PPID, both EMS and PPID, or a history of pasture-associated laminitis was also not associated with an increased risk of disease recurrence (Table 1).

Based on exploratory analyses, the basal serum insulin concentration did not differ ($P = .08$; Table 1) between the recurrent and non-recurrent groups. However, when the probability of laminitis recurrence was visually evaluated in relation to resting insulin concentration, a hyperbolic relationship was evident (Figure 1A). Accordingly, both insulin and insulin^2 were considered and included in the final regression model, where the probability of recurrence increased with resting insulin concentration, showing both a linear effect ($P = .04$) and a quadratic effect ($P = .05$). When the insulin data were grouped as quantiles and plotted against the probability of recurrence of laminitis (in these groups), it was apparent that the probability of recurrence increased markedly as the basal, fasted insulin concentration increased beyond the normal range (0–20 $\mu\text{IU/mL}$) to over the threshold for normal (up to $\sim 45 \mu\text{IU/mL}$). By comparison, when the insulin concentration increased above 50 $\mu\text{IU/mL}$, the rate of increase in the probability of laminitis recurring was less marked (Figure 1A).

Animals with a previous history of laminitis experienced a greater ($P = .05$) rate of laminitis recurrence than did animals with no prior laminitis history (Table 1). However, neither the severity of disease (Obel grades 3 and 4 compared to Obel grades 1 and 2) nor having all 4 feet affected was a significant predictor of laminitis recurrence.

3.3.2 | Seasonal factors

As an association was identified between the probability of recurrence and the season when the initial case occurred during exploratory analyses (increased odds of recurrence in summer, compared to spring; $P = .04$), these data were examined further. In order to correct for latitude, these data were reanalyzed with just the southern hemisphere data ($n = 242$). When examining a plot of the probability of recurrence and the month and season of the initial case of laminitis for this subset, cases that occurred in spring had the lowest probability of recurring (Figure 1B).

3.3.3 | Management factors

Whole cohort

Both the accommodation and diet of the animals were investigated for an association with the likelihood of laminitis recurrence. However, there was no increase in risk for recurrence when animals were allowed access to pasture for >3 hours/day, nor if they were fed

concentrates (Table 2). Dietary restriction and dietary modification were management strategies frequently recommended by veterinarians (61.8% (165/267) and 74.2% (198/267) of cases that were followed up, respectively). However, neither the recommendation of dietary modification, nor dietary restriction, had an impact on the likelihood of recurrence of laminitis (Table 2). In an effort to determine whether dietary restriction was able to be successfully implemented, we quantified the number of cases where dietary restriction was considered by the veterinarian to have been maintained. Of the cases where dietary restriction was initially recommended, 88.5% (146/165) were determined to have been successfully maintained. However, the maintenance of dietary restriction did not reduce the risk of recurrence of laminitis (Table 2). Similarly, recommendations of weight loss (46.1% [123/267] of cases), exercise (23.6% [63/267] of cases), or both had no impact on the likelihood of recurrence (Table 2).

Many animals were treated with non-steroidal anti-inflammatory drugs (NSAIDs; 75.7%; 202/267) or by a farrier (76.0%; 203/267), or received both treatments, but neither of these disease management strategies had an impact on the rate of recurrence of laminitis (Table 2).

Population subsets

Dietary restriction and exercise might not be appropriate or recommended in animals with PPID. Therefore, the effect of recommending dietary restriction on the incidence of recurrence was investigated separately in the animals without PPID. However, neither dietary restriction (OR = 0.6 [0.27–1.3]; $P = .21$) nor exercise (OR = 1.97 [0.79–4.92]; $P = .15$) were effective at preventing laminitis in these animals.

The effect of pergolide treatment in cases that had been diagnosed with PPID and that had been successfully followed up for 2 years was examined ($n = 98$). Treatment with pergolide did not affect the frequency of recurrence of laminitis (OR = 0.88 [0.37–2.08]; $P = .77$). In cases with PPID that were not treated with pergolide, the ACTH concentration did not differ ($P = .15$) between cases that recurred ($n = 18$; 65.7 [46.8–155] pg/mL) and those that did not ($n = 32$; 49.5 [39.5–113] pg/mL). Lastly, in animals treated with pergolide, the insulin concentrations did not differ ($P = .41$) for animals whose laminitis recurred ($n = 17$; 51.6 [6–119] $\mu\text{IU/mL}$), compared to those whose did not ($n = 33$; 24 [3–45] $\mu\text{IU/mL}$).

3.4 | The time to recurrence for endocrinopathic laminitis

In order to determine what might have influenced how quickly a case recurred several variables were compared among the early (6 month), mid (7 to 18 months), and late (19 to 24 months) recurring groups. A significant factor for the speed of recurrence was the Obel grade of lameness,¹¹ where a greater proportion of cases with a higher Obel grade were more likely ($P = .05$) to recur within 6 months, than later in the study (Table 3). No other significant risk factors for recurrence within 6 months were identified.

TABLE 1 Animal risk factors investigated for an association with the recurrence of laminitis in 267 horses and ponies diagnosed with endocrinopathic laminitis

Factors	Recurrence (n = 91) n (%) or median [IQR]	No recurrence (n = 176) ^a n (%) or median [IQR]	Odds ratio [95% CI]	P value
Age (years)	15 [12-19]	15 [10.3-20]	0.98 [0.94-1.03]	.96
Breed groups				
Hunter	15 (16.5)	24 (13.6)	1.0	
Stock	21 (23.1)	46 (26.1)	0.73 [0.31-1.15]	.45
Shetland	17 (18.7)	32 (18.2)	0.85 [0.41-1.33]	.72
Australian pony	10 (11.0)	25 (14.2)	0.67 [0.17-1.17]	.42
Welsh pony	12 (13.2)	19 (10.8)	1.01 [0.62-1.66]	.98
Other	16 (17.5)	30 (17.1)	0.92 [0.46-1.46]	.86
Type				
Pony	53 (58.2)	110 (64.3)	1.0	
Horse	38 (41.7)	61 (35.7)	0.77 [0.46-1.3]	.33
Sex				
Male	51 (56.0)	83 (48.5)	1.0	
Female	40 (44.0)	88 (51.5)	1.35 [0.81-2.25]	.25
Height (cm)	142 [114-152]	142 [122-152]	0.99 [0.98-1.01]	.89
BCS (1-9)				
(≤5/9)	29 (31.9)	55 (32.2)	1.0	
(≥6/9)	62 (68.1)	116 (67.8)	1.01 [0.59-1.75]	.96
CNS (0-5)				
(≤2/5)	45 (49.5)	81 (47.4)	1.0	
(≥3/5)	46 (50.5)	90 (52.6)	0.92 [0.55-1.53]	.75
Serum insulin (μIU/mL)	25 [8-73]	19 [5-53]	0.99 [0.99-1.0]	.08
EMS				
No	16 (17.6)	32 (18.7)	1.0	
Yes	75 (82.4)	139 (81.3)	1.08 [0.56-2.09]	.82
PPID				
No	55 (60.4)	109 (63.7)	1.0	
Yes	36 (39.6)	62 (36.3)	1.15 [0.68-1.94]	.60
EMS + PPID				
No	66 (72.5)	129 (75.4)	1.0	
Yes	25 (27.5)	42 (24.6)	1.16 [0.65-2.07]	.61
P-A				
No	62 (68.1)	119 (69.6)	1.0	
Yes	26 (28.6)	52 (30.4)	0.96 [0.55-1.68]	.88
Season				
Spring	25 (27.5)	69 (39.2)	1.0	
Summer	30 (33.0)	42 (23.9)	1.99 [1.42-2.78]	.04
Autumn	19 (20.9)	37 (21.0)	1.48 [1.02-2.13]	.29
Winter	17 (18.6)	28 (15.9)	1.71 [1.16-1.86]	.17
Obel grade				
≤2/4	76.9 (70/91)	82.4 (145/176)	1.0	
≥3/4	23.1 (21/91)	17.6 (31/176)	1.4 [0.75-2.62]	.29
Number of feet				
<4	52 (57.1)	101 (59.1)	1.0	
All 4	39 (42.9)	70 (40.9)	1.08 [0.65-1.81]	.76

(Continues)

TABLE 1 (Continued)

Factors	Recurrence (n = 91) n (%) or median [IQR]	No recurrence (n = 176) ^a n (%) or median [IQR]	Odds ratio [95% CI]	P value
Previous Diagnosis				
No	23 (25.3)	58 (33.9)	1.0	
Yes	60 (65.9)	85 (49.7)	1.78 [0.99-3.19]	.05
Do not know	8 (8.8)	28 (16.4)	-	-

Continuous variables are presented as median [IQR] and binomial categorical variables as n (percentage).

Abbreviations: BCS, body condition score; CNS, cresty neck score; EMS, equine metabolic syndrome; P-A, pasture-associated laminitis; PPID, pituitary pars intermedia dysfunction.

^aSample size might vary due to missing data points.

TABLE 2 Management risk factors investigated for an association with the recurrence of laminitis in 267 horses and ponies diagnosed with endocrinopathic laminitis

Variable	Recurrence (n = 91) ^a n (%)	No recurrence (n = 176) ^a n (%)	Odds ratio [95% CI]	P value
Accommodation				
Inside	7 (8)	4 (2.3)	1.0	
Outside	80 (92)	171 (97.7)	0.31 [0.27-1.04]	.08
Diet				
Pasture	9 (9.9)	25 (14.2)	1.0	
Pasture/forage	46 (50.5)	73 (41.5)	1.0	.27
Pasture/forage/grain	31 (34.1)	61 (34.7)	1.61 [1.04-2.48]	.61
Forage/grain	2 (2.2)	15 (8.5)	1.25 [0.80-1.96]	.16
Other	3 (3.3)	2 (1.1)	0.30 [0.12-0.70]	-
>3 h grazing				
No	18 (20)	37 (21.8)	1.0	
Yes	72 (80)	133 (78.2)	1.11 [0.59-2.09]	.74
DM				
No	25 (27.5)	44 (25.1)	1.0	
Yes	66 (72.5)	131 (74.9)	0.89 [0.50-1.57]	.92
DR				
No	39 (42.9)	63 (36)	1.0	
Yes	52 (57.1)	112 (64)	0.75 [0.45-1.26]	.28
DR maintained				
No	39 (42.9)	82 (46.9)	1.0	
Yes	52 (57.1)	93 (53.1)	1.18 [0.71-1.96]	.78
Weight loss				
No	51 (56)	92 (52.6)	1.0	
Yes	40 (44)	83 (47.4)	0.87 [0.52-1.45]	.47
Exercise				
No	68 (74.7)	135 (77.1)	1.0	
Yes	23 (25.3)	40 (22.9)	1.14 [0.63-2.06]	.76
Farrier				
No	19 (20.9)	44 (25.1)	1.0	
Yes	72 (79.1)	131 (74.9)	1.27 [0.69-2.34]	.44
NSAIDS				
No	23 (25.3)	42 (24)	1.0	
Yes	68 (74.7)	133 (76)	0.93 [0.52-1.67]	.82

Abbreviations: DM; dietary modification; DR, dietary restriction, NSAIDs, nonsteroidal anti-inflammatory drugs.

^aSample size might differ between variables due to missing values.

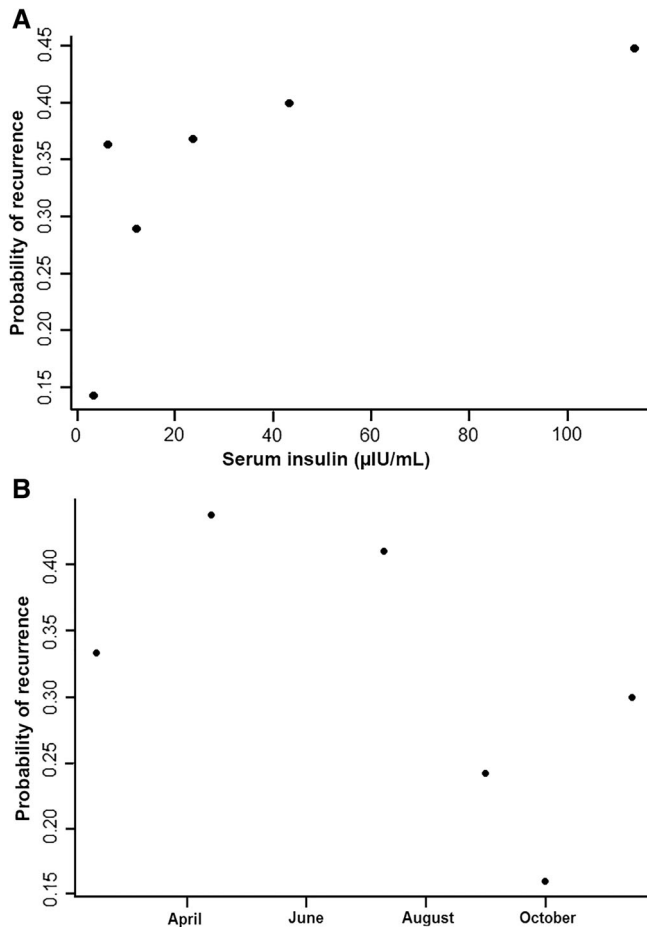


FIGURE 1 The probability of recurrence of endocrinopathic laminitis in horses and ponies. A, The relationship between the probability of the recurrence of laminitis and basal (resting) serum insulin concentration ($\mu\text{IU/mL}$; quantiles) was hyperbolic ($P = .05$; $n = 267$). B, The probability of the recurrence of laminitis was lowest in horses/ponies that experienced an initial episode of laminitis in the spring months (data from animals in the Southern hemisphere [$n = 242$])

3.5 | Predicting the recurrence of endocrinopathic laminitis

The final regression model developed for this study had suboptimal power for predicting the likelihood of recurrence in an individual animal (Supp item 3). The leave-1-out cross-validation results for the

TABLE 3 Association of Obel grade of laminitis with likelihood of laminitis recurring within 6 months of diagnosis in ponies and horses with recurrent endocrinopathic laminitis ($n = 91$)

Proportion	Recurred in ≤ 6 m ($n = 41$)	Recurred in 7-18 m ($n = 13$)	Recurred in 19-24 m ($n = 37$)
Obel grade			
1	14.9% ($n = 13$)	9.2% ($n = 8$)	18.4% ($n = 16$)
2	12.6% ($n = 11$)	4.6% ($n = 4$)	16.1% ($n = 15$)
3	17.2% ($n = 15$)	0% ($n = 0$)	5.7% ($n = 5$)
4	1.1% ($n = 1$)	0% ($n = 0$)	0% ($n = 0$)

model showed that if the model were to be used in the future as a tool for predicting the recurrence of laminitis the model could correctly predict whether or not laminitis would recur in a new individual 53% of the time.

4 | DISCUSSION

Our epidemiological understanding of laminitis is limited, which hinders the success of preventative strategies for the disease.²³ Knowing the likelihood of recurrence for endocrinopathic laminitis may improve the success of disease management and prevention. Furthermore, a better understanding of disease risk factors is necessary to enable the targeted development and use of effective treatment and prevention strategies. Our study has provided further insight by specifically reporting the rate of recurrence for endocrinopathic laminitis from a prospective study of 34.1%, and identifying some risk factors for recurrence, such as hyperinsulinemia and having had a previous episode of laminitis.

Prospective (longitudinal) cohort studies of laminitis are uncommon, but 2 recently completed prospective studies of disease incidence confirmed the importance of endocrinopathies⁵ and hyperinsulinemia⁷ in laminitis occurrence. It is important to note that the current study was not designed to evaluate the incidence of endocrinopathic laminitis. The high proportion of cases of endocrinopathic laminitis recruited to the study, when compared to the other inciting causes, is most likely related to the fact that the study offered endocrine blood tests as part of the study. Attrition rates for surveys can be high, and the excellent retention rate for the participants in this study was attributed to the regularity of contact between the investigators and the participants.

The recurrence rate of 34.1% for endocrinopathic laminitis in the current study is strikingly similar to a previous report that 33.7% of horses/ponies in a defined population diagnosed with pasture-associated laminitis experienced repeated episodes of the disease.⁶ However, it is considerably lower than the recurrence rate of 70% reported in a retrospective data mining study of veterinary records over a longer time-frame.⁸ Prospective studies that follow up animals for a longer period of time would help to determine how or if the recurrence rate increases in the longer term. However, the finding from the current study that endocrinopathic laminitis is likely to recur in approximately one third of animals within 2 years of diagnosis is important, and suggests that new therapeutic strategies to manage the disease are needed urgently. Until effective therapeutic strategies specific to this form of the disease become available,²⁴ the use of management and preventative strategies is exceptionally important to address the high risk of recurrent disease.

There is an increasing body of evidence that hyperinsulinaemia is directly correlated with laminitis risk,^{25,26} and the results of the present study are consistent with this premise. The small odds ratio for the relationship between recurrence risk and insulin concentration can be explained by the fact that the variability in insulin was large (almost 900 $\mu\text{IU/mL}$) and the odds ratio represents the change in odds per $\mu\text{IU/mL}$ of insulin, without consideration of where in the range of insulin concentrations an increase might occur. Thus, it is important to consider the linear and hyperbolic (quadratic) relationships between

insulin concentration and the probability of laminitis recurrence, which indicated that the greatest change in risk occurred lower in the range of concentrations, up to 50 $\mu\text{U}/\text{mL}$. However, resting or fasted hyperinsulinemia can be a poor predictor of ID,^{18,27} and the lack of a stronger association between resting (basal) insulin concentration and recurrence probability was not surprising. Resting insulin concentrations were measured in this study in an effort to reduce workload and minimize complexity for participants. However, in the 5 years since the design and implementation of this study the inaccuracy of resting insulin concentration for the diagnosis of ID has been recognized and it is no longer recommended, and its use was a limitation of the study. Therefore, it is important for clinicians to note that whereas a high resting insulin concentration suggests an increased likelihood of disease recurrence, a normal resting serum insulin concentration is unlikely to be useful in predicting recurrent disease. In this case, a dynamic test of the enteroinsular axis, such as the OGT or OST, would be recommended to determine the degree of ID more accurately. As such, determination of the metabolic status of the animal, including their basal and post-prandial insulin concentration, should be an integral part of disease management.

Another risk factor for the recurrence of laminitis identified in this study was a previous history of laminitis. The odds of recurrence were 56% less for animals with no history of the disease. Given that the insulin concentration of the participants was not different for animals with a history of laminitis, compared to those with no previous laminitis,¹⁰ at the time of their inclusion into the study (index case of laminitis) the increased risk of recurrence might be more likely to be related to structural and mechanical changes within the lamellar structure. Pre-existing lamellar lesions in chronic disease²⁸ presumably weaken the lamellar interface, predisposing it to repeated failure. This highlights the importance of addressing laminitis in a timely manner, with the implementation of strategies aimed at reducing lamellar damage, such as through farriery and cryotherapy,^{29,30} paramount. It also highlights the need for a targeted treatment for laminitis, that aims to prevent lamellar deterioration and promote repair.

A relationship between season and the incidence of laminitis has been described previously, with most studies indicating that spring and summer are associated with the greatest risk of disease.^{5,6} Also, the greatest proportion of cases in the current cohort of animals occurred in spring.¹⁰ However, the current study found that cases occurring in spring had the lowest probability of experiencing a recurrent episode of the disease. In fact, cases that occurred in summer and autumn were at the highest risk of recurring. The reason for this finding is unknown, but if replicated in future studies, it might potentially provide valuable insight into the pathophysiology of the condition. There might simply have been a temporal association, with autumn cases recurring in spring, given that nearly half of the recurrences occurred within 6 months of the initial episode. However, plasma ACTH concentrations are higher in autumn,^{31,32} and a role for this hormone in disease recurrence (and indeed occurrence) should be investigated. There are also a number of other neuroendocrine peptides that fluctuate seasonally,³³ and further investigation of the hypothalamic-pituitary-adrenal axis might shed light on this interesting observation. However, environmental factors might

also have been important here, with the fact that the study was conducted over only 2 years potentially playing a role. Conditions for the accumulation of pasture NSC content, such as increased light and lower ambient temperatures, are optimal in spring and autumn.³⁴ During the study timeframe, conditions that promoted sugar accumulation in the grass might have caused laminitis of greater severity in autumn (which was more likely to recur), or could simply have affected when laminitis cases occurred, irrespective of the timing of the initial bout of laminitis. Future epidemiologic studies of laminitis would ideally collect data on sunlight, rainfall, and pasture type quality and quantity, but this was beyond the means of this study.

Other variables, including BCS, CNS, sex, age, and type/height were all unable to be identified as significant risk factors for laminitis recurrence. Both BCS and CNS are risk factors for developing laminitis.^{5,35} However, the likelihood of detecting a difference in adiposity in the group that recurred, compared to those that did not, was confounded by the fact that many animals already had a BCS above ideal (5/9) upon entry to the study. These data indicate that it might be difficult for a clinician to determine which of their cases is more likely to suffer recurrent episodes of disease, compared to 1 another, based solely on phenotypic data. In addition, the lack of an association with age, sex, or breed provides no guidance with respect to using signalment to predict recurrence, although a systematic review found increased odds of laminitis for some pony breeds, including Shetland and Welsh ponies.³⁶ Regardless, judicious ongoing monitoring of all cases of endocrinopathic laminitis is recommended, as are sustained efforts to manage the underlying endocrinopathy. With respect to the management of PPID, pergolide did not reduce the odds of laminitis recurring. Whereas studies have shown an improvement in laminitis in some animals following the instigation of pergolide therapy, laminitis might still occur or recur in pergolide-treated animals,³⁷ and more data on this topic are required. Currently, the relationship between ACTH and insulin and their respective, or cumulative, roles in laminitis pathophysiology are inadequately understood. In our study, only a subset of animals were determined to have PPID, and some of these animals might also have been insulin-dysregulated. In addition, the details of pergolide administration, such as dose and formulation, were not recorded. Thus, a larger prospective study that specifically examines the effect of pergolide on the recurrence of laminitis would be beneficial.

With respect to how quickly laminitis might recur, nearly half of the cases that experienced recurrent disease did so within 6 months of diagnosis. In addition, early recurrence was more likely for cases that experienced more severe lameness (as graded on the Obel scale). This outcome might be related to the severity of lamellar lesions, with more severe disease associated with increased lamellar damage,³ and therefore an increased risk for the disease to flare up subsequently, as well as an increased time taken for the damage to repair.³⁸ However, the need to group responses by receipt time was a limitation of this study. As completed follow-ups were not always returned by the veterinarians promptly, the date of the actual recurrence might not have been accurately aligned with the timing of their response (animal recheck dates were not always provided by the veterinarians). Furthermore, it would have been desirable to be able to separate the

7- to 18-month category into 2 6-month periods, but unfortunately the response time was more unreliable through the middle period of the survey, so we erred on selecting the broader timespan. Overall, the finding that animals with more marked disease might recur sooner after diagnosis supports that these animals need to be monitored carefully for the first 6 months after each episode of laminitis.

Laminitis is an acute disease, with the early subclinical phase usually undetectable.³⁹ Furthermore, horse owners might not be particularly skilled at identifying the disease.^{3,40} Another recent study examining this same cohort of animals also found that owners frequently did not call the veterinarian until later in the clinical time course of the disease.¹⁰ Thus, the disease might be reasonably advanced before veterinary help is sought. Being able to predict the likelihood of recurrence based on the risk factors present in each individual case would therefore be useful for the management, and ideally prevention, of recurrent disease. As such, we attempted to design a mathematical (regression) model using data from the current study that was able to predict the likelihood of disease recurrence in individual animals.

In conclusion, our study has found that approximately one-third of horses/ponies in this population diagnosed with endocrinopathic laminitis had a recurrence of the disease within 2 years of diagnosis. Given that the predictive power of the statistical model for disease recurrence was suboptimal, it remains reasonably difficult for practitioners to reliably predict which animals might experience recurrent disease. However, the findings that hyperinsulinemia and having been previously diagnosed with laminitis are significant risk factors for disease recurrence will enable clinicians to proactively address these factors, thereby potentially reducing the recurrence risk. Lastly, for animals with more severe disease, recurrence is more likely to happen within 6 months of diagnosis. However, vigilant monitoring of all animals that have had a previous diagnosis of endocrinopathic laminitis is encouraged.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study was approved by the Human and Animal Ethics Committees of Queensland University of Technology (1 600 000 936, 1 300 000 744).

HUMAN ETHICS APPROVAL DECLARATION

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SUPPORTING INFORMATION

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

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