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STANDARD ARTICLE

Survival associated with cerebrospinal fluid analysis in downer adult dairy cows: A retrospective study (2006-2014)

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Background: Threshold values for total nucleated cell count (TNCC) and protein concentration in cerebrospinal fluid (CSF) of downer dairy cows suggestive of a spinal cord lesion were recently published.

Objectives: Determine short- and long-term survival of downer cows that underwent CSF analysis using the reported threshold values. Evaluate the prognostic value of these threshold values to predict short- and long-term survival.

Animals: Two hundred and fourteen downer adult dairy cows that underwent CSF analysis during hospitalization at the Centre Hospitalier Universitaire Vétérinaire (CHUV) of the Université de Montréal.

Methods: Retrospective study. Medical records of downer adult dairy cows presented to the hospital between January 2006 and October 2014 for which CSF analysis results were available were studied. Short-term (discharge from hospital) and long-term (completion of lactation) survival were determined and compared in accordance with CSF TNCC and protein concentration, using a Chi-square test.

Results: Cows with CSF TNCC and/or protein concentration above the threshold values had a significantly lower short-term survival rate ($P = .02$). The odds of nonsurvival of cows with one or both CSF values above the threshold values was 2.16 times higher than the odds for cows with values under the threshold values. CSF TNCC >4.5 cells/μL had sensitivity and specificity of 17.3% (95% CI: 10.7%-25.7%) and 92.3% (95% CI: 85.4%-96.6%), respectively, for predicting short-term nonsurvival. CSF protein concentration >0.39 g/L had sensitivity and specificity of 20.9% (95% CI: 13.7%-29.7%) and 91.4% (95% CI: 84.2%-96.0%), respectively.

Conclusions: CSF analysis above threshold values used in this study is associated with increased odds of short-term nonsurvival.

KEYWORDS

outcome, nonambulatory, ruminant, spinal cord

1 | INTRODUCTION

Recumbency is a common medical problem in cattle and can be difficult to manage on the farm. Diagnosis and treatment are challenging.

Among the possible causes of recumbency, lesions of the spinal cord are probably the most difficult to investigate in adult cattle. Given that determining a definitive antemortem diagnosis is challenging, establishing a prognosis for these animals is difficult. Available ancillary tests for lesion localization are limited. Moreover, recumbency and patient size limit the use of some procedures, such as medical imaging.[1] Cerebrospinal fluid (CSF) analysis, a technique that is simple and safe in cattle,[2] is a valuable tool. However, normal references values

Abbreviations: CHUV, Centre Hospitalier Universitaire Vétérinaire; CI, confidence interval; CSF, cerebrospinal fluid; EDTA, ethylenediaminetetraacetic acid; RBCC, red blood cell count; ROC, receiver operating characteristic; TNCC, total nucleated cell count

for CSF analysis in cattle vary among studies.[3–6] In a previous study, it was shown that CSF analysis is a good diagnostic tool for identification of spinal cord lesions in downer dairy cows.[7] A CSF total nucleated cell count (TNCC) >4.5 cells/μL and/or a protein concentration >0.39 g/L yielded a specificity of 100% for the presence of a spinal cord lesion in downer dairy cows. However, the survival for animals with CSF analysis results above these threshold values was not known because only those cows that underwent a full postmortem exam were used in that study.

The first objective of this study was to retrospectively evaluate the short- and long-term survival of downer adult dairy cows presented to the CHUV of the Faculté de médecine vétérinaire de l'Université de Montréal and who underwent CSF analysis, based on CSF TNCC and protein concentration values using the previously suggested threshold values. We hypothesized that cows with CSF TNCC >4.5 cells/μL and/or a protein concentration >0.39 g/L would have a less favorable short- and long-term survival than cows with CSF TNCC and protein concentration below these values. The secondary objective was to evaluate the accuracy of both CSF threshold values in predicting outcome in downer cows. Finally, the third objective was to present descriptive statistics regarding the study population.

2 | MATERIALS AND METHODS

The medical records of downer dairy cows for which a CSF analysis was performed between January 2006 and October 2014 were obtained from the medical archives of the Farm Animal Veterinary Teaching Hospital of the CHUV at the Université de Montréal. Inclusion criteria were recumbency (cows that were referred for recumbency or that became recumbent during their hospitalization), female, dairy breeds, and a minimum age of 2 years, or heifer that had already calved once. Cows diagnosed with coxofemoral luxation at presentation were excluded from the study. All CSF samples were aseptically collected at the lumbosacral intervertebral space and placed in an EDTA ethylenediaminetetraacetic acid vacutainer for clinicopathologic analysis. Excess EDTA in the vacutainer was removed by shaking the tube upside down. CSF analysis was performed by a board certified clinical pathologist and only patients with CSF analysis that reported both TNCC and protein concentration were included in the study.

The following information was obtained from the medical record of each cow: age, breed, number of days in lactation, duration of hospitalization, CSF TNCC, protein concentration and red blood cell count (RBCC), and outcome (discharge from hospital, natural death, or euthanasia). Short-term survival was based on discharge from the hospital versus death/euthanasia. For the long-term survival, the Canadian Dairy Network database was consulted using the Agri-Traçabilité Québec number (Web site: https://www.cdn.ca/), for cows that survived and were discharged from the hospital. Long-term survival was considered favorable if the cow had completed at least one lactation after discharge from the hospital; otherwise it was considered unfavorable.

Cows were divided into 2 groups based on their CSF analysis results. The first group included cows with both TNCC and protein

concentration under the threshold values previously described (TNCC ≤4.5 cells/μL and protein concentration ≤0.39 g/L). The second group included cows with one or both parameters above the threshold values (TNCC >4.5 cells/μL and/or protein concentration >0.39 g/L). The latter group was further divided into 3 subgroups according to the following scenarios: only CSF TNCC above the threshold value (group 2a), only CSF protein concentration above the threshold value (group 2b), and both CSF TNCC and protein concentration above the threshold values (group 2c).

For statistical analysis, because data were not normally distributed, the median and range were calculated. Results between the survival group and the nonsurvival group were compared using a Mann–Whitney–Wilcoxon test. For the short- and long-term survival based on the TNCC value and total protein concentration, the logistic regression model was used (Chi-square test) with the outcome variables being survivors versus nonsurvivors for short-term survival, and completion of at least one lactation versus failure to complete one lactation after returning to the farm for long-term survival. When P was <.05, the result was considered statistically significant. Odds ratios for nonsurvival were calculated for each CSF parameter. Statistical analysis was performed using the commercially available GraphPad Prism 6 Software (GraphPad Prism Statistical Software, version 6, GraphPad Software Inc, San Diego, California). The sensitivity and specificity of CSF protein concentration and TNCC for prediction of short-term (survival) and long-term survival (lactation completed) were determined. Using GraphPad Prism 6 Software, receiver operating characteristic (ROC) curves were generated and sensitivity and specificity for different cutoff values (with 95% confidence intervals [CI]) were determined.

3 | RESULTS

Out of the 7773 cattle that were treated at the Farm Animal Veterinary Teaching Hospital between January 1, 2006, and October 31, 2014, 799 (10.3%) were downer cows. Among those cows, a CSF analysis was performed on 247 of them (30.9%) and 224 cows met the inclusion criteria. Ten cases were further excluded because they had been diagnosed with coxofemoral luxation.

Of the 214 cows included in the study, the vast majority (97.2%) were Holstein cows. A total of 104 cows (48.6%) were discharged from the hospital and 110 cows (51.4%) died or were euthanized while hospitalized. This survival rate was not significantly different from the overall survival rate of downer adult dairy cows that were presented during that same time period and on which no CSF analysis was performed (54.2%, n = 585; P = .16) (unpublished data). The median age of the cows included in the study was 5.7 years (range 2.0-14.5, n = 212). The median age of the cows that survived (5 years; range 2-11) was significantly lower than the median age of the cows that died/were euthanized (5.5 years; range 2-14) (P = .013). There were 172 lactating cows, 36 nonlactating cows, and 6 cows for which the information was missing. Among lactating cows, the median days in milk was 8 days (range 1-500). The median days in milk did not differ between the group of cows that survived (6 days; range 1-500) and did not survive (11 days; range 1-379) (P = 0.24).

The median duration of hospitalisation for all cows was 7 days (range 1-48 days, n = 214). The median duration of hospitalization of cows that survived (11 days; range 2-36) was significantly higher than that of cows that did not survive (5 days; range 1-48) (P < .0001).

Of the 214 cows in the study, 167 (78%) were classified in group 1 (CSF with TNCC ≤4.5 cells/µL and protein concentration ≤0.39 g/L), and 47 cows (22%) were classified in group 2 (TNCC >4.5 cells/µL and/or protein concentration >0.39 g/L). Among the second group, 15 cows were classified in group 2a (TNCC >4.5 cells/µL and protein concentration ≤0.39 g/L), 20 cows were classified in group 2b (TNCC ≤4.5 cells/µL and protein concentration >0.39 g/L), and 12 cows were classified in group 2c (TNCC >4.5 cells/µL and protein concentration >0.39 g/L).

CSF analysis results are summarized in Table 1. A significant difference was only observed in CSF protein concentration between cows that survived and cows that did not survive during the period of hospitalization. The nonsurvivor cows had significantly higher median CSF protein concentration (0.29 g/L; range 0.04-6.42) than cows that survived (0.26 g/L; range 0.13-1.49) (P = .02).

Cows with CSF TNCC ≤4.5 cells/µL had a significantly higher short-term survival rate (51%) than cows with CSF TNCC >4.5 cells/µL (30%) (P = .03). Cows with CSF protein concentration ≤0.39 g/L had also a significantly higher short-term survival rate (52%) than cows with CFS protein concentration >0.39 g/L (28%) (P = .01). Finally, the overall short-term survival rate (34%) was significantly lower if cows had either one or both parameters above threshold values (group 2: TNCC >4.5 cells/µL and/or protein concentration >0.39 g/L), than if both parameters were under the threshold values (53%) (P = .02). Having one or both CSF parameters above threshold values was associated with short-term nonsurvival (Table 2). Cows with either CSF TNCC or protein concentration above the threshold values had more than 2 times the odds of nonsurvival than cows with CSF TNCC and protein concentration under the threshold values.

For long-term survival (Figure 1), from the 104 cows that survived and were discharged from the hospital, 88 had CSF TNCC and protein concentration below the threshold values (group 1), and 16 cows had CSF TNCC and/or protein concentration above the threshold values (group 2). The long-term survival rates were not significantly different between groups 1 and 2 (61% versus 75%, respectively; P = .37). However, the power of the analysis of long-term survival was low (22%) because of the small number of animals.

ROC curves of CSF TNCC and protein concentration for prediction of short-term nonsurvival were generated (Figures 2 and 3). For

TABLE 1 Cerebrospinal fluid analysis findings of downer adult dairy cows

CSF parameter	Survivors (n = 104)	Nonsurvivors (n = 110)	P value
TNCC (cells/µl)	1.1 (0-117)	1.1 (0-31.35)	.11
Protein concentration (g/L)	0.26 (0.13-1.49)	0.29 (0.04-6.42)	.02*
RBCC (cells/µl)	4.4 (0-8960)	8.25 (0-18290)	.20

Abbreviations: CSF, cerebrospinal fluid; RBCC, red blood cell count; TNCC, total nucleated cell count. Downer cows were characterized as survivors or nonsurvivors. Data are presented as median (range). A Mann–Whitney–Wilcoxon test was used.. *Statistically significant (P ≤ .05).

**TABLE 2** Association between cerebrospinal fluid analysis findings and short-term nonsurvival (death/euthanasia)

CSF parameter	Odds ratio	95% confidence interval
TNCC > 4.5 cells/µl	2.51	1.045-6.008
Protein concentration > 0.39 g/L	2.79	1.22-6.36
TNCC > 4.5 cells/µl and/or protein concentration > 0.39 g/L	2.16	1.098-4.24

Abbreviations: CSF, cerebrospinal fluid; TNCC, total nucleated cell count.

CSF TNCC, using a cutoff value of 4.5 cells/uL, the sensitivity and specificity were 17.3% (95% CI: 10.7%-26.7%) and 92.3%, (95% CI: 85.4%-96.6%), respectively. For CSF protein concentration, using a cutoff value of 0.39 g/L, the sensitivity and specificity were 20.9% (95% CI: 13.7%-29.7%) and 91.4% (95% CI: 84.2%-96.0%) respectively. In order to increase specificity, higher threshold values would be required: CSF TNCC >10.23 cells/uL and protein concentration >0.61 g/L yielded a specificity of 98.1% of nonsurvival.

4 | DISCUSSION

The results of our study show that the previously published threshold values of CSF TNCC and protein concentration are helpful in establishing short-term survival in downer adult dairy cows. In fact, the odds of fatality (either natural death or euthanasia) in cows with TNCC and/or protein concentration above the threshold values was more than 2 times greater than the odds of the group of cows with both CSF parameters under the threshold values. Our conclusions are in agreement with previous studies that found that spinal cord lesions, regardless of their nature, are usually associated with a poor prognosis in cattle.[8,9]
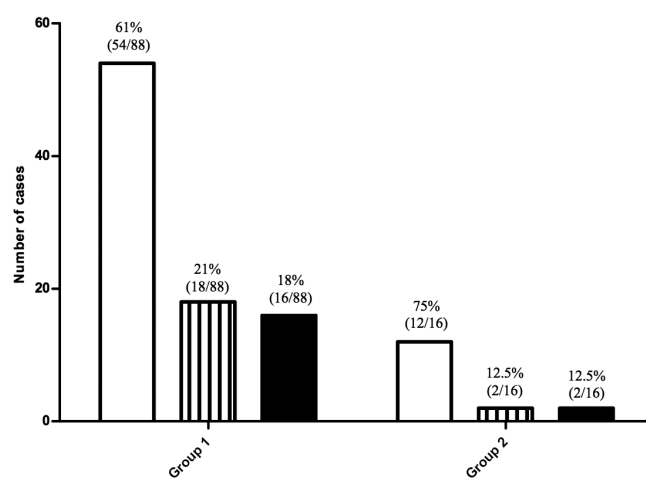
FIGURE 1 Long-term survival (completion of at least one lactation) based on cerebrospinal fluid (CSF) analysis results of the 104 downer dairy cows that survived and were discharged from the hospital. Group 1: cows with CSF total nucleated cell count (TNCC) and protein concentration under the threshold values. Group 2: cows with CSF TNCC and/or protein concentration above the threshold values. White: at least one lactation completed; lines: failure to complete one lactation; black: information was not available. Chi-square test. P = .37
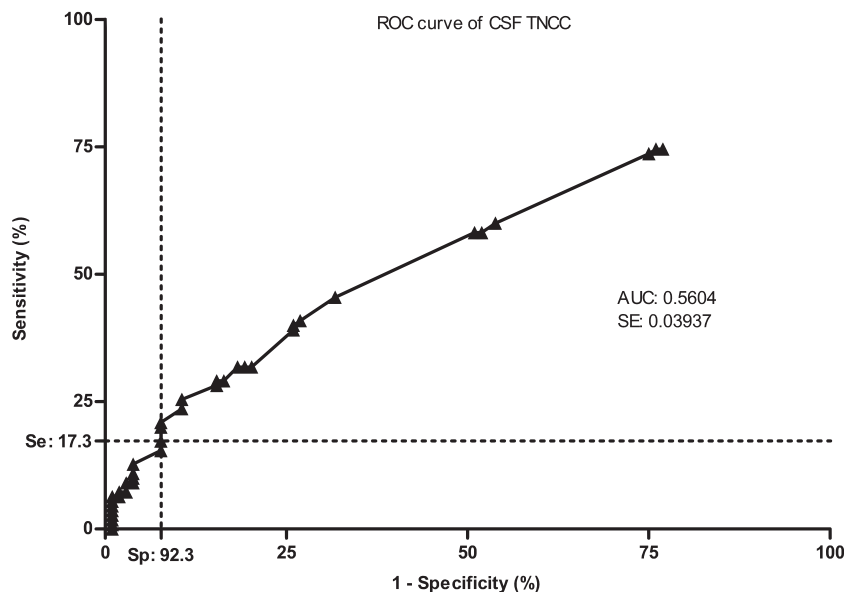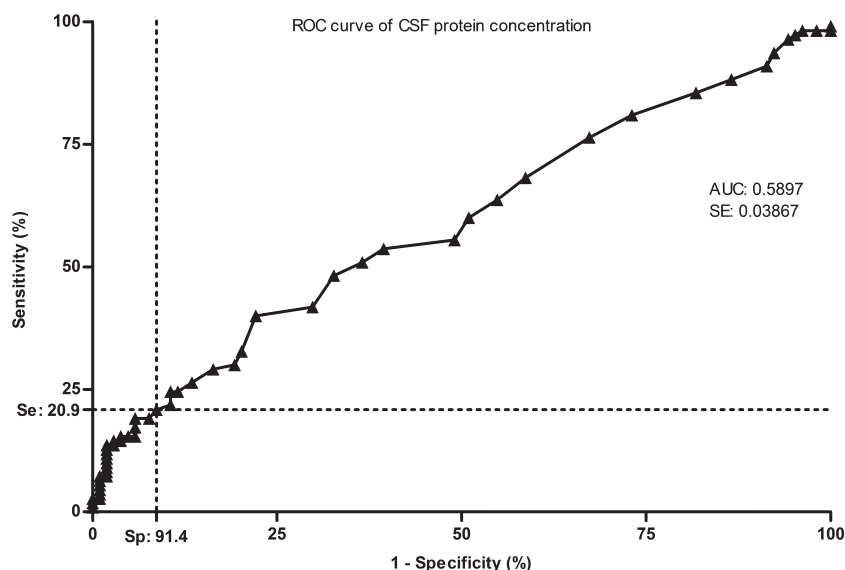
FIGURE 2 Receiver operating characteristic (ROC) curve data of cerebrospinal fluid (CSF) total nucleated cell count (TNCC) in recumbent dairy cows that did or did not survive. The sensitivity and specificity of CSF TNCC for the prediction of nonsurvival was determined by ROC curve analysis. ROC curves were generated, and sensitivity and specificity for different cutoff values (with 95% confidence interval [CI]) were determined. Dotted lines represent the sensitivity and specificity for the CSF TNCC cutoff value of >4.5 cells/μl. AUC, area under the curve; SE, standard error

Long-term survival could not be determined using CSF analysis results in the present study. Our findings indicate that downer adult dairy cows that have CSF analysis results above the threshold values (compatible with a spinal cord lesion) and that are discharged from the hospital can have a favorable long-term outcome. These results suggest that damage caused by spinal lesions may be reversible in some cows. One possible example is a spinal cord contusion. Such a lesion would most likely cause CSF changes,[3,10] despite full recovery being possible. Long-term survival in our study population appears to be better than previously reported data, in which recumbency was associated with a higher rate of culling, with more than 50% of downer cows that failed to complete one lactation.[11] One possible explanation for this difference is that our study was performed in a hospital setting, where downer cows were given supportive care that is not available on the farm, for example, flotation tank treatment.

Finally, even though no difference in long-term survival was observed between the two groups of cows, the power of analysis of long-term survival was low, because of the low number of surviving

FIGURE 3 Receiver operating characteristic (ROC) curve data of cerebrospinal fluid (CSF) protein concentration in recumbent dairy cows that did or did not survive. The sensitivity and specificity of CSF protein concentration for prediction of nonsurvival was determined by ROC curve analysis. ROC curves were generated, and sensitivity and specificity for different cutoff values (with 95% confidence interval [CI]) were determined. Dotted lines represent the sensitivity and specificity for the CSF protein concentration cutoff value of >0.39 g/L. AUC, area under the curve; SE, standard error

cows with at least one CSF value above threshold for which long-term prognosis information was available. A higher number of cows discharged from the hospital with CSF TNCC and/or protein concentration above the threshold values would be needed to increase the power of the study and to best estimate the long-term survival.

To the best of our knowledge, studies that describe an association between CSF analysis results and outcome in farm animals are rare. In a study on cattle diagnosed with listeriosis, when univariable analysis was used, elevated CSF TNCC was associated with a lower survival rate. However, it was not a significant factor in the multivariable analysis, as only recumbency, clinical signs of excitement, and a weak or absent menace response were identified as factors negatively associated with survival.[12] In sheep with listeriosis, even though CSF protein concentration tends to be lower in individuals that recovered from the disease, it was an unreliable prognostic indicator of survival.[13] Similarly, CSF TNCC, protein concentration, and RBCC failed to predict outcome in horses suffering from herpesvirus myeloencephalopathy.[14] In small animals, the prognostic value of CSF analysis has been studied by several investigators.[15-20] In dogs, most of the studies were focused on cases of intervertebral disk herniation.[15-19] It was shown that TNCC,[15,16] protein concentration,[16] predominant CSF cell type,[15-17] myelin basic protein concentration,[18,19] and creatine kinase activity [19] can be used to predict surgical success and overall outcome. One study concluded that an increase in CSF TNCC was not associated with a worse prognosis in dogs with intervertebral disk herniation.[19] CSF TNCC and protein concentration also could not be used to predict outcome in cases of meningoencephalitis of unknown origin in dogs.[20]

In the present study, nonsurviving downer cows were older than the cows that survived. Several criteria are involved in the decision for euthanasia in dairy cows. Age may be one of those criteria, as owners may be less prone to pursue treatment for older cows. Survival did not differ according to the stage of lactation and the majority of the cows included were in the postpartum period. It is reasonable to assume that factors other than spinal cord lesions, such as metabolic or neurological factors, may have contributed to recumbency in some of the cows included in the study. As comorbidities were not investigated, we cannot determinate if such factors were present at the farm and/or during hospitalization and could have influenced the short-term survival. It is possible that such factors could have worsened the clinical condition of some of the cows, leading to a decrease in the survival rate. Our ROC analyses suggest that CSF TNCC and protein concentration are not perfect in predicting short-term nonsurvival, which is not surprising because other factors are likely contributing to the animal's state and overall prognosis (muscular enzymes, CBC or biochemistry changes, and number of days recumbent). A multivariable analysis that takes into account such factors may help to identify other prognostic indicators.

Cows that survived had longer hospitalization times than cows that did not survive. Although this fact is not surprising, it would be interesting to determine what factors contributed to a shorter hospital stay in nonsurvivors, such as severity of clinical signs, lack of clinical improvement despite treatment, the prognosis given to the owner, and CSF analysis results.

The median CSF protein concentration was higher in the group of cows that did not survive, compared to the group that survived. However, the median value of the nonsurvivor group remains below the proposed threshold value of 0.39 g/L.

There is in the literature some debate about the fact that EDTA could falsely elevate the protein concentration in the CSF. We think that as all our CSF analyses were performed with the same approach, the results of our study remain valid. However, the threshold value for protein concentration could be slightly different in a different hospital where additive free tubes are used to analyze the CSF. In our clinic, although the EDTA tube is used, the excess EDTA is removed by removing the top and shaking the tube upside down before adding the CSF in the tube.

The characteristics of the cows included in the study may not be representative of all cows for which a CSF analysis is generally performed, as only downer dairy cows were included and the study was performed in a referral veterinary hospital. Some of these patients were highly valuable dairy cows, which often influences how aggressively owners pursue treatment before electing euthanasia. The overall survival rate seems to be higher in our study than previously reported.[21-25] However, the study population and design make comparison between studies virtually impossible. Furthermore, the retrospective nature of this study makes it difficult to establish the primary cause of death/euthanasia for each case. CSF analysis results could have influenced the decision to euthanize a cow and this was not possible to ascertain from the medical files. Retrospective studies regarding survival are potentially biased because the impact of the discussion between the client and the clinician cannot be studied and taken into consideration. As an example, the CSF analysis results may have influenced the clinician during his discussion regarding the prognosis with the client. It seems reasonable to presume that elevated values would lower the clinician's perception of prognosis and that this would likely be communicated to the client. Inevitably, this would lower the short-term survival for the down cows with CSF analysis results higher than the threshold values. Finally, CSF cell differential and morphology were not included in the analysis. It would be interesting to see if the prognostic value of CSF analysis could be increased if these factors are taken into account.

A wide variety of conditions can cause recumbency in dairy cattle.[26,27] Moreover, secondary muscle and nerve damage can develop after only a few hours of recumbency, which may cause clinically important complications.[28,29] Those facts highlight the multifactorial etiology of recumbency in cattle, as well as the multiple possible prognostic indicators. Several prognostic indicators for survival have been identified in downer cows: duration of recumbency,[21,28,30] quality of care provided,[27,30,31] severity and nature of secondary damage,[22,29] and serum muscle enzyme activities.[23,32] Even though the objective of the present study was to determine the prognosis of downer dairy cows based on CSF analysis results only, it would be interesting to use multivariable analysis to explore other factors and how they impact the overall survival rate.

There were several limitations to our study, mainly pertaining to its retrospective nature. Multiple coinciding factors may have influenced the short-term survival rate but were not studied because of study design and, in some cases, an absence from the medical record.

The reason for euthanasia was often not recorded and, as such, the impact of the CSF analysis result on the prognosis given to the client and his subsequent decision could not be evaluated. The justification and choice to perform CSF analysis could have biased the short-term survival rate, as CSF analysis may have been performed more often on cows with a poor response to the Aquacow treatment. However, we did not find a significant difference between short-term survival rate of downer cows that have had a CSF analysis and survival rate of downer cows for which a CSF analysis was not performed during the same period. Short-term survival rate in our study is presumably higher than in a field setting because the study was performed with the benefits of a hospital environment. Moreover, some cows were highly valuable and, as a result, clients could justify a longer, more expensive period of treatment that would be more likely to result in improvement and, ultimately, survival. Other factors that may have influenced the short-term survival rate were not studied, given that a multivariable study was not performed. Also, the low number of cows with CSF analysis results above the threshold values that survived and were discharged from the hospital made the power of the analysis low for the long-term survival.

In conclusion, the findings of the present study indicate that CSF TNCC >4.5 cells/μL and protein concentration >0.39 g/L are associated with a poorer short-term survival in downer adult dairy cows. CSF analysis can be used to help investigate the cause of recumbency, as well as help determine the short-term survival. For some cases, full recovery may be possible despite CSF findings suggestive of a spinal cord lesion.

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

Authors declare no IACUC or other approval was needed.

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