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Survival in dogs with meningoencephalomyelitis of unknown etiology with and without lesions detected by magnetic resonance imaging

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Abstract

Background: The prognosis of individual dogs with meningoencephalomyelitis of unknown etiology (MUE) remains difficult to predict. MUE cases with no lesions detected by magnetic resonance imaging (MRI) occur, but it is unknown whether this finding is associated with prognosis.

Hypothesis: MUE cases without detectable lesions on MRI have a better outcome than cases with detectable lesions.

Animals: Study included 73 client-owned dogs with MUE presenting to Purdue University Veterinary Hospital from 2010 to 2020.

Methods: Retrospective study. Dogs with a clinical diagnosis of MUE were identified by medical record search. MRI reports were reviewed for presence or absence of lesions consistent with MUE. Clinical findings at presentation, treatment, disease-specific survival, and outcomes including rates of remission and relapse were compared between cases with normal MRI or abnormal MRI.

Results: Overall, 54 dogs (74%) were classified as abnormal MRI, and 19 dogs (26%) were classified as normal MRI cases. Death caused by MUE occurred in 1/19 (5%) normal MRI dogs and 18/54 (33%) abnormal MRI dogs ($P = .016$). Median survival was >107 months in both groups, but survival was significantly longer in the normal MRI group ($P = .019$). On multivariate analysis, abnormal MRI was significantly related to death (hazard ratio, 7.71; 95% confidence interval 1.03-58.00, $P = .0470$), whereas significant relationships with death were not identified for either the use of secondary immunosuppressive medications or cerebrospinal fluid nucleated cell count.

Conclusions: MUE dogs with no detectable lesions on MRI have reduced disease-related death compared with dogs with abnormal MRI. The presence or absence of MRI lesions in MUE dogs is prognostically relevant.

KEYWORDS
brain, canine, encephalitis, GME, meningitis, necrotizing encephalitis

Abbreviations: CSF, cerebrospinal fluid; GME, granulomatous meningoencephalitis; MRI, magnetic resonance imaging; MUE, meningoencephalomyelitis of unknown etiology; NME, necrotizing meningoencephalitis; TNCC, total nucleated cell count; T2W, T2-weighted; T1W, T1-weighted.

1 | INTRODUCTION

Meningoencephalomyelitis of unknown etiology (MUE) is a common disease in dogs. The prognosis for dogs with MUE is highly variable, with life-threatening neurologic deterioration in some but prolonged remission in others.[1,2] Few prognostic indicators exist to predict outcome. The presence of mass effect on magnetic resonance imaging (MRI), is associated with early (<3 month) death, suggesting a possible relationship between MRI findings and outcome.[3]

Normal MRI is observed routinely in human patients with noninfectious encephalitis.[4-8] Abnormal MRI is not required to diagnose 1 of the group of diseases referred to as autoimmune encephalitis.[4] This is particularly the case for leucine-rich glioma-inactivated 1 (LGI1) antibody-associated encephalitis and anti-N-methyl-D-aspartate receptor encephalitis, for which only about half of patients have abnormal MRI.[6-8] Similarly, normal MRI is repeatedly reported in dogs with MUE,[1,2,9-13] but the outcome and survival of this subset of dogs is not reported. Other reported prognostic factors for MUE include cerebrospinal fluid (CSF) total nucleated cell count (TNCC), mentation change, body weight, and seizures.[11,14-16]

The primary goal of the current study was to determine whether any difference in survival exists between MUE dogs with and without MRI lesions. The secondary goal of our study was to investigate various other outcome measures, in addition to survival. We hypothesized that in dogs diagnosed with MUE, normal MRI cases would have improved survival and other outcome measures compared with abnormal MRI cases.

2 | METHODS

2.1 | Case selection

Medical records from Purdue University Veterinary Hospital's database from 2010 to 2020 were searched for client-owned dogs. To be included in the study, dogs had to have a clinical diagnosis of MUE, and meet all of the following criteria[9]:

1. Age between 6 months and 10 years at diagnosis.
2. Brain or spine MRI performed.
3. Cerebrospinal fluid TNCC >5 cells/μL.
4. Infectious diseases tests performed.
5. Minimum follow-up (until the date of death or euthanasia, or for at least 3 months past the date of MUE diagnosis).

We additionally included dogs with MRI and a histologic diagnosis of granulomatous meningoencephalitis (GME), necrotizing meningoencephalitis (NME), or necrotizing leukoencephalitis, regardless of whether they met all the criteria above. We then excluded dogs diagnosed with any of the following:

1. Infectious meningoencephalitis/meningomyelitis.
2. Eosinophilic meningoencephalitis, corticosteroid responsive tremor syndrome or steroid-responsive meningitis arteritis.

2.2 | Clinical data collection

Clinical information obtained from the medical records of each dog included: signalment, presence/absence of seizures (at presentation for MRI), neurolocalization, spinal cord-only neurolocalization (myelitis-only), MRI findings, CSF TNCC, histopathologic findings (when available), corticosteroid dose in the 1st month of treatment, adjunctive treatment (used at any time during treatment), whether remission was achieved (neurologic status remaining improved or normal after discontinuing corticosteroids; some cases were still receiving adjunctive medications on the date corticosteroids were discontinued), whether relapse occurred (recurrence of neurologic clinical signs, further characterized as occurring before or after discontinuing corticosteroids), date of last contact, date of death if applicable, and whether death occurred because of MUE (including death caused by MUE treatment complications). For 39 dogs, the date and cause of death were retrieved from the Purdue medical record. For 34 cases, follow-up information was obtained via phone call to the primary veterinarian's office and reviewing their medical records. Details recorded included the date of the last appointment, if the dog was dead, the date of death, the cause of death or euthanasia, and details of all medications (current or at the time of death). Additional questions were asked as necessary, to ascertain whether the cause of death was caused by MUE (including MUE treatment complications), or unrelated to MUE. When necessary, the owner was then contacted to confirm whether a dog was still alive, and if not, their date and cause of death.

All MRI studies were performed using a 1.5 Tesla magnet (GE Signa LXI, GE Medical Systems, Milwaukee, Wisconsin) and images were retrieved using an image analysis workstation. Images were contemporaneously reviewed by a board-certified neurologist and a board-certified radiologist who were aware of the dog's clinical status.

Abnormal MRI was defined as T2-hyperintense or contrast-enhancing lesions or both, in the brain, spinal cord, and/or meninges, consistent with noninfectious inflammatory disease. Normal MRI was defined as the absence of such lesions. For the purposes of our study, concurrent lesions unrelated to MUE (e.g., caudal occipital malformation syndrome) were not considered when classifying MRI status.

A neurology resident reviewed the MRI report of each dog to obtain the following MRI data: site imaged (brain, spine, or both); sequences performed; abnormal or normal MRI; and the presence of the following signs of mass effect: midline shift, loss of sulci, or transforaminal herniation.[3,11] The number of these features of mass effect present (0, 1, 2, or 3) was then tabulated for each MRI.

2.3 | Outcome measures

All dogs were allocated to the normal MRI group or the abnormal MRI group. The primary outcome measure was disease-specific survival, measured from the date of the 1st MRI until date of death caused by MUE.

The secondary outcome measures were death rate because of MUE (percentage of each group dying because of MUE), remission rate, disease-free interval (months), relapse while taking corticosteroids (early relapse), relapse after discontinuation of corticosteroids (late relapse; including dogs who relapsed after discontinuing corticosteroids but before discontinuing secondary medications), death in hospital, and death within the first 3 months.

2.4 | Data analysis and statistical methods

Disease-specific survival time was defined as the total time from the date of MRI until the time of death specifically caused by MUE. Dogs were censored on the date they died from non-MUE causes, and on the date of last follow-up for dogs who were still alive. Disease-specific survival was compared between groups (normal MRI and abnormal MRI) using a log rank test and displayed using Kaplan-Meier curves.

To determine the effects of discrepant therapeutic protocols on outcomes, the highest prednisone dose received within the 1st month of diagnosis was recorded for all dogs as either lower dosage (<1.5 mg/kg per day) or higher dosage (≥1.5 mg/kg per day). Dogs receiving dexamethasone had the dose converted to prednisone-equivalent (dose divided by 7). Other variables were also compared with investigate factors between the normal MRI and abnormal MRI groups. Numerical variables of median follow-up time, CSF TNCC, body weight, and age were compared between the 2 groups using Wilcoxon rank sum tests. Proportional data of mass effect on MRI, death rate caused by MUE, death in hospital, and death in first 3 months were compared using Fisher's exact tests because of low expected frequencies. The percentage of dogs with mentation change, myelitis-only (spinal cord-only neurolocalization), seizures at presentation, and use of secondary immunosuppressive medications were compared using Pearson chi-squared tests.

Variables significantly associated with outcomes after univariable analyses were placed into multivariable Cox proportional hazard regression analyses with Breslow method for ties. A P value ≤.05 was considered statistically significant for all analyses.

3 | RESULTS

3.1 | Study sample

A total of 314 dogs with meningoencephalomyelitis were identified within the study period (Figure 1). After excluding dogs who did not meet all inclusion and exclusion criteria, a total of 73 dogs with MUE remained. This included 19 normal MRI dogs and 54 abnormal MRI dogs. Table 1 compares clinical characteristics of the normal and abnormal MRI groups and Table 2 compares secondary outcome measures between the 2 groups.

There were 30 male (19 neutered) and 43 female (38 neutered) dogs. This included 12 mixed breeds, 10 Maltese, 7 Chihuahuas, 6 shih tzus, 4 Yorkshire terriers, 2 each of pugs, French bulldogs, Havanese, miniature schnauzers, Pomeranians, Boston terriers, and Airedale terriers, and 1 each of 20 other breeds.

3.2 | Clinical data

A definitive diagnosis based on histopathology was obtained in 7 dogs (6 GME and 1 NME). All 7 had abnormal MRI. For 1 of these dogs, CSF analysis was not available.

MRI studies performed on the brain only (43 cases), spine only (12 cases), or both (18 cases) were available for review. For brain MRI, multiplanar T2-weighted (T2W), T1-weighted (T1W), and postcontrast T1W images of the entire brain were obtained in all cases. Transverse T2W fluid attenuation inversion recovery, T2*-weighted gradient echo, and diffusion weighted images were variably performed. All spine studies included multiplanar T2W, T1W, and postcontrast T1W images, except for 2 cases that lacked postcontrast images. T2W short tau inversion recovery and half Fourier acquisition single-shot turbo spin-echo images were variably performed.

The duration of follow-up was ≤3 months for 14/73 (19%) dogs, 4 to 12 months for 12/73 (16%) dogs and >12 months for 47/73 (64%) dogs. The median follow-up was 9 months (range, 1-105) in normal MRI cases and 12 months (range, 0-65) in abnormal MRI cases ($P = .64$).

3.3 | Primary outcome measure: survival

Disease-specific survival time significantly differed between the normal MRI group and the abnormal MRI group ($P = .02$). Median survival was not reached in either group in the Kaplan-Meier survival analysis (Figure 2) and was >107 months in both groups.

3.4 | Secondary outcome measures

Death caused by MUE occurred in 1/19 (5%) dogs with normal MRI and 18/54 (33%) dogs with abnormal MRI, which was significantly different ($P = .02$; Table 2).

There were no significant differences between the normal MRI and abnormal MRI groups in the percentage of dogs experiencing remission, disease-free interval, early relapse (while still receiving prednisone), or late relapse (after discontinuing prednisone). Remission (remaining neurologically improved to normal despite discontinuing steroids) was achieved in 68% (13/19) of the normal MRI group after a median of 25 months and in 53% (29/54) of the abnormal MRI group after a median of 19 months. No dogs with normal MRI died in hospital, whereas 11% of dogs with abnormal MRI died during hospitalization (1 within 24 hours and another 5 before discharge). This difference was also not significant ($P = .33$). The total number of dogs dying within 3 months of diagnosis was 1 dog (5%) in the normal MRI group and 7 dogs (13%) in the abnormal MRI group ($P = .67$). Of these

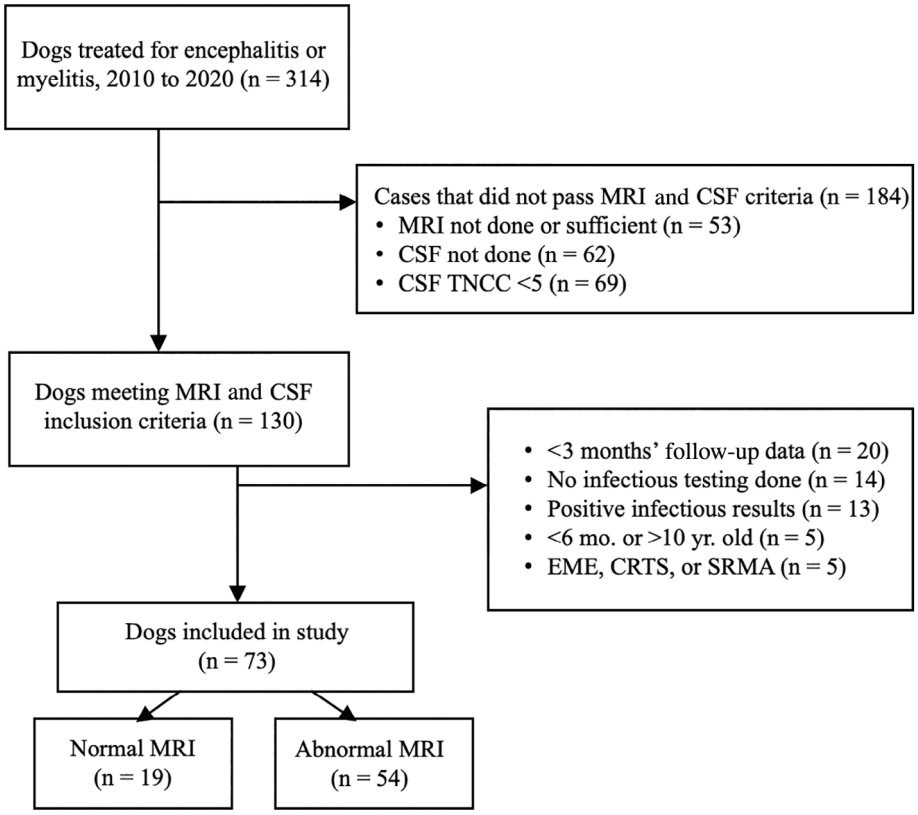

FIGURE 1 Case selection for inclusion in the current study. Flow chart demonstrating criteria for inclusion of 73 dogs in the study. CRTS, corticosteroid-responsive tremor syndrome; CSF, cerebrospinal fluid; EME, eosinophilic meningoencephalitis; MRI, magnetic resonance imaging; SRMA, steroid responsive meningitis-arteritis; TNCC, total nucleated cell count.

TABLE 1 Univariate analyses for potential confounding variables between normal MRI and abnormal MRI groups, in dogs diagnosed with meningoencephalomyelitis of unknown etiology.

Variable	Normal MRI (n = 19)	Abnormal MRI (n = 54)	*P* value
Demographic characteristics			
Sex			.12
Male neutered (intact)	4 (6)	15 (5)	
Female neutered (intact)	8 (1)	30 (4)	
Age (years)	4.2 (0.5-10.6)	4.2 (1.0-10.0)	.70
Median (range)			
Body weight (kg)	5.6 (1.2-47.6)	7.0 (1.4-33.4)	.35
Median (range)			
Clinical presentation			
Mentation change	4 (21%)	16 (30%)	.47
Seizures at presentation	5 (26%)	13 (24%)	.84
Myelitis-only	5 (26%)	13 (24%)	.84
Diagnostics			
CSF TNCC (cells/μL) median (range)	24 (6-1405)	98 (4-7650)	**.04**
Mass effect on MRI			.16
Present	0 (0%)	11 (20%)	
1 feature	0 (0%)	9 (17%)	
2 features	0 (0%)	2 (4%)	
3 features	0 (0%)	0 (0%)	

Note: Data are presented as count (percentage) of cases unless otherwise specified. Cases were included if TNCC >5, or if necropsy confirmed granulomatous meningoencephalitis or necrotizing encephalitis. *P* values ≤ 0.05 were considered significant.
Abbreviations: CSF TNCC, cerebrospinal fluid total nucleated cell count; MRI, magnetic resonance imaging.

TABLE 2 Secondary outcome measures in dogs with normal and abnormal MRI.

Outcome measure	Normal MRI (n = 19)	Abnormal MRI (n = 54)	*P* value
Remission			
Remission achieved	13 (68%)	29 (53%)	.26
Subsequent disease-free interval (months)	25	19	.38
Relapse			
Early relapse	5 (26%)	13 (24%)	.84
Late relapse	2 (11%)	11 (20%)	.49
Death			
Death in hospital	0 (0%)	6 (11%)	.33
Death in first 3 months	1 (5%)	7 (13%)	.67
Death caused by disease	1 (5%)	18 (33%)	**.02**

Note: The outcome of dogs with meningoencephalitis of unknown etiology with normal and abnormal magnetic resonance imaging (MRI) is presented as count (percentage) of cases. Early relapse, relapse while still receiving prednisone. Late relapse, relapse after discontinuing prednisone. Remission was achieved if a dog discontinued prednisone and remained neurologically improved to normal. *P* values ≤ 0.05 were considered significant.

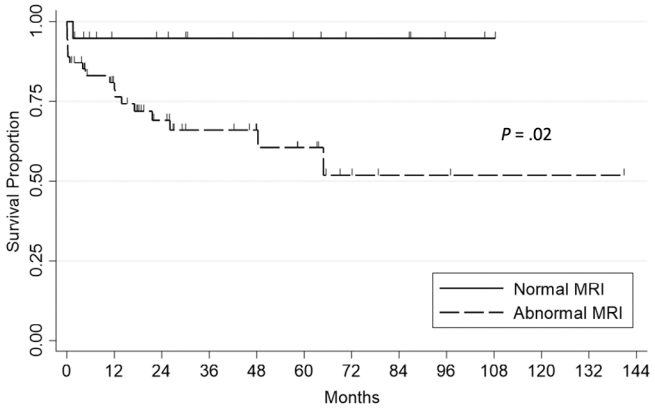

FIGURE 2 Disease-specific survival. Kaplan-Meier analysis of 73 dogs with meningoencephalitis of unknown etiology, comparing cases with normal magnetic resonance imaging (MRI) (n = 19) and abnormal MRI (n = 54). Each vertical tick mark represents a censored dog that was either lost to follow-up or deceased because of causes unrelated to meningoencephalomyelitis of unknown etiology. Median survival because of disease was not reached in either group. Survival time because of disease differed by group (*P* = .02, log rank test).

8 deaths, 6 dogs died, and 2 were euthanized because of failure to respond to treatment.

3.5 | Confounding factors between normal MRI and abnormal MRI groups

Between the normal MRI and abnormal MRI groups of dogs, there was no significant difference in sex distribution, age, body weight, or the percentage of dogs with each of mentation change, seizures at presentation, or myelitis-only (Table 1). There was also no significant difference in the percentage of dogs receiving ≥1.5 mg/kg/day of prednisone (Table 3).

There was a significant difference in CSF TNCC. Abnormal MRI dogs had a higher median TNCC (98 cells/μL, range, 4-7650) than normal MRI dogs (24 cells/μL, range, 6-1405; *P* = .04).

Mass effect was present in 11 dogs in the abnormal MRI group, comprised of 9 dogs with 1 feature of mass effect, 2 dogs with 2 features of mass effect, and no dogs with all 3 features of mass effect (Table 1). In line with the study design, there were no cases with mass effect in the normal MRI group. This difference in mass effect between the 2 groups was not significant (*P* = .16). Survival of all dogs grouped by mass effect was not significantly different (Figure 3).

3.6 | Influence of immunosuppressive treatment

All dogs received corticosteroids, at a dosage of <1.5 mg/kg/day of prednisone (n = 28) or ≥1.5 mg/kg/day (n = 45) in the 1st month of treatment. Some dogs received additional immunosuppressive medications (Table 3). Compared with lower dose prednisone, higher dose prednisone was not statistically significantly related to any outcome measure, including death caused by MUE, achievement of disease remission, occurrence of relapse before or after discontinuing prednisone, or disease-free interval (*P* > .35, for each analysis).

Dogs with an abnormal MRI were significantly more likely to receive 1 or more secondary immunosuppressive drugs (*P* = .01).

3.7 | Multivariate analyses

In univariate analyses (above), there were significant differences between the normal MRI and abnormal MRI groups in the percentage of dogs dying because of MUE, the median CSF TNCC, and the use of secondary immunosuppressive medications.

In Cox proportional hazard models, the abnormal MRI group was significantly related to death caused by disease (hazard ratio, 7.71;

TABLE 3 Use of immunosuppressive medications in dogs with normal and abnormal MRI.

Treatment	Normal MRI (n = 19)	Abnormal MRI (n = 54)	*P* value
Prednisone ≥1.5 mg/kg/day	12/19 (63%)	33/54 (61%)	.88
Secondary immunosuppressive (n = 31)	3/19 (16%)	28/54 (52%)	**.01**
Number of dogs receiving:			
Cytosine arabinoside	1	14	
Mycophenolate	1	11	
Cyclosporine	1	9	
Procarbazine		3	
CCNU		2	
Leflunomide		1	
Chlorambucil		1	

Note: Treatment of dogs with meningoencephalomyelitis of unknown etiology is presented as the count (percentage) of cases. Some dogs in the abnormal magnetic resonance imaging (MRI) group received more than 1 secondary medication. *P* values ≤ 0.05 were considered significant.

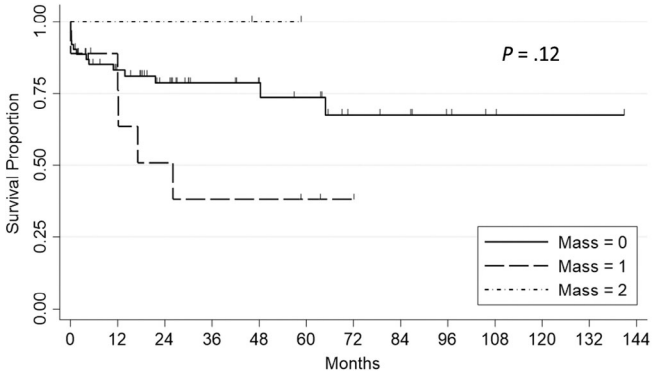

FIGURE 3 Survival in dogs with and without magnetic resonance imaging (MRI) features of mass effect. Survival in 73 dogs with meningoencephalitis of unknown etiology, with 0, 1, or 2 features of mass effect on MRI. Features of mass effect evaluated were midline shift, loss of sulci, and transforaminal herniation. There were only 2 dogs with 2 features of mass effect. Survival was not significantly different between groups ($P = .12$, log rank test). Mass = 2, 2 features of mass effect present. Mass = 1, 1 features of mass effect present. Mass = 0, no features of mass effect present.

95% confidence interval, 1.03-58.00, $P = 0.047$), whereas the use of secondary immunosuppressive medications ($P = .60$) and CSF TNCC ($P = .67$) were not significant.

4 | DISCUSSION

The most important finding of our study was that dogs in the abnormal MRI group had significantly more deaths compared with the normal MRI group, in univariate and multivariate analyses. In univariate analyses, both the CSF TNCC and the percentage of dogs receiving secondary immunosuppressive medications were significantly higher in the abnormal MRI group. Both of these factors were assessed because they are prognostic indicators in some studies.[9,11,14] However, in our sample, multivariate analyses confirmed the significant association between abnormal MRI and death, discounting a significant relationship between both CSF TNCC and secondary medications with death.

4.1 | Survival data

There were significant differences in survival between normal MRI and abnormal MRI dogs with MUE. Both the primary outcome measure (survival time) and 1 of the secondary outcome measures (percentage of cases dying) were significantly worse in the abnormal MRI group. Multivariate analyses confirmed the significance of abnormal MRI, discounting both CSF TNCC and the use of secondary immunosuppressive medications. Taken together, these relationships suggest abnormal MRI truly carries a worse prognosis. The large hazard ratio of abnormal MRI for death (7.71; 95% confidence interval, 1.03-58.00) suggested that the relationship is clinically important as well as statistically significant. The prognosis of dogs with MUE having normal MRI findings has not yet been well described, and our findings suggest that these dogs have better survival.

The finding of improved survival in normal MRI dogs could be used early in the disease course to predict the prognosis of individual dogs. Negative prognostic factors for MUE include mentation change, seizures at presentation, and body weight,[15,16] as well as MRI features of mass effect.[3] We accounted for each of these confounding factors, finding no significance difference in their prevalence between the normal and abnormal MRI groups. We also accounted for another negative prognostic indicator, increased TNCC[11,14] (see below).

The overall outcome in our sample (normal and abnormal MRI dogs) was similar to findings in other samples for outcome measures such as relapse rate.[14,17-19] However, the rate of death in the first 3 months, remission rate, median survival time, 5-year survival rate, and the rate of death caused by MUE appeared improved compared

TABLE 4 Outcome comparison between current and previous studies.

Outcome measure	Current study	Previous findings	References
MST (days)	>3240	>1095	Stee et al, 2020[20]
>1-year survival rate	48/73 (66%)	Between 57% and 74%	Pausova et al, 2021,[21] Kaczmarska et al, 2020,[22] Goncalves et al, 2022,[23,a] Lowrie et al, 2016[24]
>5-year survival rate	16/73 (22%)	19/182 (10%)	Pausova et al, 2021[21]
Remission achieved	42/73 (58%)	9/45 (20%)	Portero et al, 2019[12,b]
Relapse rate	31/73 (42%)	Between 23% and 51%	Brady et al,[18] Wong et al,[19] Kaczmarska et al, 2020,[22] Pausova et al, 2021,[21] Song et al,[14] Goncalves et al, 2023,[25] Stee et al, 2020[20]
Death in first 3 months	8/73 (11%)	Between 22% and 56%	Stee et al, 2020,[20] Lowrie et al, 2016,[24] Lowrie et al, 2013[3]
Total deaths caused by MUE	19/73 (26%)	Between 40% and 55%	Brady et al, 2020,[18] Kaczmarska et al, 2020,[22] Portero et al, 2019[12]

Note: Comparison of outcomes in dogs with meningoencephalitis of unknown etiology. All of these studies had abnormal MRI findings as an inclusion criterion, except Portero et al.[11] Remission achieved, neurologic status remaining improved or normal after discontinuing corticosteroids.
Abbreviations: MRI, magnetic resonance imaging; MST, median survival time; MUE, meningoencephalitis of unknown etiology.
[a]65.3% of all dogs with inflammatory CNS disease alive at 1 year; no difference in short or long-term survival between infectious and noninfectious causes.
[b]9/45 dogs had a normal neurologic examination while remaining treatment-free for 1 year or longer.

with previous reports (Table 4). Given that the rates of MUE-related death in our study were significantly lower in the normal MRI dogs compared with abnormal MRI dogs, it is plausible that the inclusion of normal MRI dogs is an important reason for the improved outcome compared with previous studies. In fact, the presence of focal or multifocal MRI lesions has been a criterion for inclusion in most previous studies of MUE. When conducting future MUE studies that include normal MRI dogs, it will therefore be important to account for the potential for normal MRI to exert an independent effect on the outcome of the study sample.

Even when considering only the abnormal MRI group in our current study, the proportions of deaths in the first 3 months and total proportion of deaths caused by MUE (13% and 33%, respectively) were somewhat lower than that of previous studies (22%-56% and 40%-55%; Tables 2 and 4). Possible explanations for this finding might include the relatively longer follow-up time provided, differences in disease severity or patient samples between institutions, differences in treatment protocols, and differences in decisions made by pet owners. In addition, the number of dogs in both the current study and previous studies are fewer than ideal, which can be a reason for apparent differences in outcome.

Our primary and secondary outcomes of dogs with MUE should be assessed carefully for several reasons. First, survival data can be prone to average values that are poorly representative of the population as a whole, particularly when sample sizes are small or the number of outliers is high. Second, discrepancies in study period duration make it difficult to compare results between studies, and follow-up that is prematurely ended could result in underestimation of survival times. Lastly, the requirement of CSF values for the clinical diagnosis of MUE risks excluding the most severely affected dogs from the dataset. This is the case in our study as well as most other studies of MUE, because dogs with signs of increased intracranial pressure on MRI have a high risk of brain herniation and death during CSF collection.[15-17]

4.2 | Inclusion of normal MRI cases in studies of dogs with MUE

There have been multiple MUE case series that included some dogs with normal MRI.[1,9-13] Abnormal CSF analysis or lesions on T2W images or both have been used as inclusion criteria, rather than requiring abnormal MRI for every case.[12] Up to 7% of MUE dogs show no T2W abnormalities, with 31% showing no abnormal contrast-enhancement.[1,9] Review articles state that it can be acceptable to include normal MRI cases in MUE studies.[1] It is largely accepted that some MUE dogs will have a normal MRI; it is rare for any diagnostic test to be 100% sensitive, and this certainly applies to MRI of MUE.[9] In human medicine, it is well-accepted that MRI can be normal in the group of diseases referred to as autoimmune encephalitis.[4] The diagnostic criteria for the autoimmune encephalitis require only 1 of the following: new focal central nervous system (CNS) findings, new-onset seizures, CSF pleocytosis, and MRI suggestive of encephalitis.[4] Many such diseases are confirmed by autoantibody confirmation. In LGI1 antibody-associated encephalitis, MRI is usually normal.[5] Pretreatment MRI was abnormal in only 43% of cases.[6] ^{18}F-FDG positron emission tomography-computed tomography, which appears to be a more sensitive form of imaging, was abnormal in every case. Similarly, for anti-N-methyl-D-aspartate receptor encephalitis, MRI was abnormal in only 56% or 57% of patients.[7,8]

4.3 | Confounding factors between normal MRI and abnormal MRI groups

Other than MRI findings, the only significant difference between the normal MRI and abnormal MRI groups at the time of presentation was a higher median CSF TNCC in the latter. We considered it important to compare TNCC between the 2 groups because previous studies on the relationship between CSF TNCC and survival yielded conflicting results.[11,14-17] Although a higher CSF TNCC was correlated to shorter

survival in 2 studies, the strength of the influence was weak.[11,14] In 1 of these, the relative hazard ratio of TNCC in predicting mortality was only 1.004.[14] Furthermore, 3 other studies failed to demonstrate an association between CSF TNCC and survival time.[15-17] Ours is the 2nd study to find a higher TNCC in the subgroup with more pronounced MRI findings.[11] It is possible that both TNCC and MRI abnormalities increase in severity as the disease progresses, but putting together all the studies to date, MRI lesions appear to be more useful in predicting prognosis.

4.4 | Influence of immunosuppressive treatment

The percentage of dogs in the current study that died because of MUE did not significantly differ between dogs receiving lower dosage (<1.5 mg/kg/day) and immunosuppressive (≥1.5 mg/kg/day) doses of prednisone. Similarly, there was no significant difference in the achievement of disease remission, early relapse (relapse while taking steroids), or late relapse (relapse when not taking steroids).

Treatment of MUE with glucocorticoids at initial doses less than 2 mg/kg/day is reported sparsely,[26] and studies comparing glucocorticoid doses are lacking. Given that prednisone dose in the current study did not significantly impact the primary or secondary outcome measures in dogs with MUE, and considering the adverse effects associated with high doses of glucocorticoids, further studies to evaluate anti-inflammatory dose glucocorticoids for the treatment of MUE are indicated.

In the present study, abnormal MRI dogs were significantly more likely to receive a secondary immunosuppressive treatment than normal MRI dogs (52% vs 16%, $P = 0.047$). In retrospective studies, it is possible that more severe cases can receive more aggressive treatment, resulting in a loss of apparent significance of the impact of treatment choices. As such, it is possible that the differences in treatment protocols between groups could be exerting its own effect on outcome. Considering that several studies suggest improved outcomes in dogs treated with polytreatment,[14,17-19,27-29] available literature does not provide any evidence that dogs receiving glucocorticoid monotreatment have improved survival over polytreatment-treated dogs. Therefore, in our study it is likely that the normal MRI group truly had a better outcome, and despite the abnormal MRI group receiving putatively more aggressive treatment.

In general, conflicting data exist regarding the efficacy of treatment outcomes with monotreatment versus polytreatment, and median survival varies profoundly between studies.[14,17,27-29]

4.5 | Relationship between mass effect and survival

In 1 study, mass effect was associated with 1 specific measure of survival (survival to 3 months).[3] We therefore analyzed whether the prevalence of mass effect was different between the 2 groups (normal MRI and abnormal MRI) to account for any confounding effect, finding no significant difference. There was also no significant relationship between mass effect and survival, but by requiring CSF collection, we might have excluded the worst mass effect cases. One possible interpretation of our findings combined with the previous study[3] is that there is a spectrum of decreasing survival from cases with no MRI lesions, to MRI lesions, to MRI lesions including mass effect.

4.6 | Limitations

There are several limitations to our study. Follow-up data was obtained for some cases by contacting owners, which relies upon owner recall. This is less precise than data obtained from medical records. The retrospective nature and lack of standardized treatment protocol between dogs means that outside variables (e.g., medications used, owner finances) could influence outcomes. Being a retrospective study, we were not able to investigate the mechanisms through which MRI changes might influence survival.

By requiring abnormal CSF results for inclusion, we likely excluded some dogs with clinical or imaging signs of brain herniation where the clinician chose not to attempt CSF collection. Because mass effect reduces 3-month survival,[3] this might have skewed our study to include less severe cases not fully representative of all MUE cases encountered in practice. However, requiring CSF pleocytosis is typical in MUE studies[3,10,15-17,19,27-30] and is recommended as a routine inclusion criterion.[1,2,9,13,26,31] In addition, because our study was specifically investigating MUE cases with normal MRI, requiring abnormal CSF was deemed important to heighten the likelihood of a correct diagnosis of MUE.

In the past 2 decades, it has become routine to use antemortem diagnostic tests (MRI, CSF, etc.) as inclusion criteria in MUE studies, and to not require histology. Only one tenth of our cases were histologically confirmed. There has been concern that the survival time of those cases that undergo necropsy vastly underestimates the prognosis of a typical MUE case. MUE studies must be interpreted in light of which dogs are included/excluded, which varies from study to study. As is now routine in studies reliant upon antemortem diagnosis, it is certainly possible that some of our cases were misdiagnosed. There is a known diagnostic challenge, differentiating between MUE and diseases with a worse prognosis (eg, glioma) and diseases with a better prognosis (e.g., cerebrovascular accident).[32-39] Although we required pleocytosis, TNCC >5 is routinely seen in neoplasia, cerebrovascular accident and other diseases. There is no ideal TNCC value to discriminate between inflammatory and noninflammatory diseases. Regardless of the TNCC cutoff value chosen, there is always some likelihood of inadvertently excluding MUE cases while including noninflammatory cases. Although multiple other studies have included MUE or GME cases with normal MRI,[9,10,12] including such cases could increase the misdiagnosis rate. Infectious disease testing was not standardized in this retrospective study, and in addition misdiagnosis because of false negative results is possible. The prolonged survival of most cases in the face of immunosuppressive treatment, and the histologic diagnosis of GME or NME in all necropsied dogs, suggests that the

inadvertent inclusion of infectious or neoplastic diseases was mitigated. Given the prolonged survival, unintended inclusion of benign diseases such as cerebrovascular accident is conceivable. It is difficult to postulate whether this could have preferentially affected the normal MRI group or the abnormal MRI group.

In addition, it is possible the dogs with clinical signs and MRI abnormalities limited to the spinal cord could have a different disease entity to those with encephalitis. The occurrence of spinal-only meningoencephalomyelitis of unknown etiology has been previously described and is postulated, but not proven, to overlap with the histopathologic subtypes of meningoencephalitis of unknown etiology.[36-39] As it remains ambiguous whether immune-mediated meningoencephalitis, encephalomyelitis, and myelitis should be considered a spectrum of 1 disease process or different clinical entities, the findings of our study should be interpreted considering this caveat.

Finally, there is an inherent dramatic variability in the outcome of MUE cases, and in small studies, one must be cautious ascribing apparent survival differences between groups to factors such as diagnostic findings or treatment, when random variation in the disease itself appears to be a major factor.

5 | CONCLUDING COMMENTS

Our results demonstrate that dogs diagnosed with MUE with normal MRI have reduced disease-related death compared with dogs with abnormal MRI, confirming our hypothesis. There was no significant difference in the other measures of outcome (e.g., death during first 3 months); however, consideration of other outcome measures has yielded useful information in previous studies, and we might have not had enough cases to detect true differences.

Based on our findings, the presence or absence of MRI lesions in MUE dogs is prognostically relevant and suggests a potential role for MRI as a biomarker of disease severity.

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CONFLICT OF INTEREST DECLARATION

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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.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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