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Prognostic factors for 1-week survival in dogs diagnosed with meningoencephalitis of unknown aetiology

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Highlights

- This retrospective records study investigated 116 dogs diagnosed with meningoencephalitis of unknown aetiology (MUA).
- Thirty of 114 (26%) of dogs died within 1 week of diagnosis of MUA.
- Negative prognostic factors were decreased mentation and seizures at presentation.
- An increased neutrophil percentage in CSF was also a negative prognostic factor.

Abstract

Although long-term outcomes of meningoencephalitis of unknown aetiology (MUA) in dogs have been evaluated, little is known about short-term survival and initial response to therapy. The aim of this study was to evaluate possible prognostic factors for 7-day survival after diagnosis of MUA in dogs. Medical records were reviewed for dogs diagnosed with MUA between 2006 and 2015. Previously described inclusion criteria were used, as well as 7-day survival data for all dogs. A poor outcome was defined as death within 1 week.

Of 116 dogs that met inclusion criteria, 30 (26%) died within 7 days of diagnosis. Assessed variables included age, sex, bodyweight, duration of clinical signs

and treatment prior to diagnosis, venous blood glucose and lactate levels, white blood cell count on complete blood count, total nucleated cell count / total protein concentration / white blood cell differentiation on cerebrospinal fluid (CSF) analysis, presence of seizures and cluster seizures, mentation at presentation, neuroanatomical localisation, imaging findings and treatment after diagnosis. Multivariate analysis identified three variables significantly associated with poor outcome; decreased mentation at presentation, presence of seizures, and increased percentage of neutrophils on CSF analysis. Despite initiation of appropriate treatment, more than a quarter of dogs died within one week of diagnosis of MUA, emphasising the need for evaluation of short-term prognostic factors. Information from this study could aid clinical staff to provide owners of affected dogs with prognostic information.

Keywords: GME; Inflammatory CNS Disease; MRI; MUO; Necrotising encephalitis

Introduction

Meningoencephalitis of unknown aetiology (MUA) describes all clinically diagnosed cases of granulomatous meningoencephalitis (GME), necrotising meningoencephalitis (NME) and necrotising leucoencephalitis (NLE) that lack histopathological confirmation (Coates and Jeffery, 2014). A clinical diagnosis can be achieved based on a combination of neurological examination results, magnetic resonance imaging (MRI) findings and cerebrospinal fluid (CSF) abnormalities (Coates and Jeffery, 2014). The exact aetiology and pathophysiology of MUA are currently unknown, but the cornerstone of medical treatment is immunosuppressive therapy. Several treatment protocols using different immunomodulating drugs, resulting in different long-term survival times have been reported (Munana and

Luttgen, 1998; Jung et al., 2007; Coates et al., 2007; Granger et al., 2010; Flegel et al., 2011; Beckmann et al., 2015; Barnoon et al., 2016).

Although several studies have focused on long-term survival, little is known about early survival and initial response to therapy of dogs diagnosed with MUA. The primary aim of this study was therefore to evaluate early survival and initial response to immunosuppressive therapy in those dogs. A secondary aim was to investigate possible prognostic factors for 7-day survival after diagnosis of MUA. It was hypothesised that a substantial portion of dogs with MUA would succumb in the first week after diagnosis despite appropriate treatment and monitoring. It was further hypothesised that specific characteristics of the clinical presentation, neurological examination, clinical pathology abnormalities, imaging findings and type of treatment would be associated with 7-day survival in dogs with a presumptive diagnosis of MUA.

Materials and methods

Case selection

The electronic medical database of the Small Animal Referral Hospital, Royal Veterinary College, University of London, was searched between January 2006 and April 2015 for dogs diagnosed with MUA. Dogs were included based on the criteria used by Granger et al. (2010), if they had: (1) complete medical records available; (2) a complete neurological examination performed leading to a focal or multifocal intracranial neuroanatomical localization; (3) inflammatory CSF analysis; (4) MR imaging of the brain demonstrating single, multiple or diffuse intra-axial hyperintense lesions on T2W images; and (5) if 7-day follow-up information was available. Dogs

with histopathological confirmation of MUA only needed to fulfill inclusion criteria (1) and (5). In this study, the term MUA was used for all dogs included in the study, including those with histopathological confirmation of GME, NME or NLE.

Dogs were excluded if: (1) clinical records or imaging studies were incomplete or not available for review; (2) dogs were diagnosed with meningomyelitis without clinical signs of intracranial involvement; (3) no pleocytosis was found on CSF analysis, with the exception of dogs with signs of raised intracranial pressure (ICP) on imaging studies, in which case CSF collection was not performed; and (4) if positive test results were found on serology or PCR examination for canine distemper virus (CDV), *Toxoplasma gondii* or *Neospora caninum.*

Information retrieved from the medical records included breed, gender, age at diagnosis, sex, bodyweight, neurological examination results and neuroanatomical localisation, duration of clinical signs and treatment prior to diagnosis, presence of concurrent disease, results of complete blood count (CBC) and biochemistry profile, results of CSF analysis including total nucleated cell count (TNCC), white blood cell differentiation and total protein (TP) concentration, lactate and glucose concentration on venous blood gas analysis, treatment received and 7-day survival time.

Dogs were considered small or medium breed if bodyweight was < 15kg, and large breed if bodyweight was ≥ 15kg. Mentation was classified as bright alert responsive (BAR), quiet alert responsive (QAR), obtundation, stupor or coma, representing decreasing mental status. Possible neuroanatomical localisations included forebrain, brainstem or cerebellum. Dogs with vestibular signs attributable to

a brainstem-associated lesion were diagnosed with central vestibular signs. If two or more CNS regions appeared to be affected on neurological examination, a multifocal neuroanatomical localization was made, whereas in dogs with only one region affected a focal neuroanatomical localization was made. MRI was performed under general anaesthesia with a 1.5T magnet (Intera, Philips Medical Systems). All images were reviewed by a board certified neurologist (SDD) using Osirix Dicom viewer (Osirix Foundation, V.5.5.2). The reviewer was blinded to results of the neurological examination, outcome after 7 days and histopathological findings. Sequences could vary, but studies included a minimum of T2-weighted (T2W; repetition time (ms); TR/echo time (ms); TE, 3000/120), T1-weighted (T1W; TR/TE, 400/8) and fluid attenuating inversion recovery (FLAIR) images of the entire brain in a sagittal, transverse and dorsal plane. The T1W images were acquired before and after IV administration of paramagnetic contrast medium (0.1 mg/kg, gadoterate meglumine, Dotarem, Guerbet). Variables recorded were lesion localisation and distribution, presence of parenchymal or meningeal contrast enhancement and presence of mass effect (brain herniation, midline shift, flattening of gyri/sulci). For CSF analysis, site of collection (cisternal or lumbar), TNCC, TP and cytological differentiation were recorded. A TNCC < 5 cells/mm^3 was considered normal. Protein concentration was considered normal for a cisternal collection if < 0.25 g/L and for a lumbar collection if < 0.4 g/L (Dewey et al., 2016).

Treatment and follow-up

For all dogs, the specific treatment protocol was recorded (corticosteroids with or without cytosine arabinoside). During hospitalisation, all dogs underwent at least one daily general physical examination and a complete neurological examination by a

board-certified neurologist or a neurology resident. Neurological examination results and response to treatment (improvement, deterioration, or static) were systematically recorded on the kennel sheets. Follow-up information for the first 7 days after diagnosis was collected from medical records. If dogs were discharged within the first 7 days, medical records were searched for the presence of a re-examination or owner communication to confirm the dog was alive. Dogs were excluded from the study if this information was not available. A successful outcome was defined as survival for at least 7 days after diagnosis of MUA, while an unsuccessful outcome was defined as death in the first 7 days after diagnosis. For dogs that died in the first week after diagnosis, information on whether dogs were euthanased at the owner's request after diagnosis without treatment, they failed to recover from general anesthesia after MRI, or they died or were euthanased due to progression of disease after recovery from general anesthesia was recorded. Dogs that did not survive general anaesthesia or were euthanased at the owner's request after diagnosis without treatment were not included for further analysis.

Statistical analysis

Outcome was defined as dead or alive 7 days after diagnosis. Data analysis was performed using a statistical software package (Prism, Graphpad Software). A Mann-Whitney *U* test was used to compare age, weight, duration of clinical signs prior to diagnosis, venous blood glucose and lactate levels, white blood cell (total, neutrophil and lymphocyte) count on CBC, TNCC/TP/neutrophil percentage in CSF, between dogs that were dead or alive 1 week after diagnosis. A Fisher's exact test was used to compare differences in sex, treatment prior to diagnosis, presence of seizures and cluster seizures, mentation (BAR, QAR, obtundation, stupor, coma),

158 neuroanatomical localisation (multifocal, forebrain, brainstem, central vestibular),
159 treatment after diagnosis (steroids, cytosine arabinoside, mannitol) and imaging
160 findings (lesion localisation, meningeal or parenchymal contrast enhancement, mass
161 effect, brain herniation, flattening gyri/sulci, rostral or caudal transtentorial herniation,
162 foramen magnum herniation) between dogs that were dead or alive 1 week after
163 diagnosis.
164
165 A binary response mixed model was carried out using SPSS (Statistical
166 Package for the Social Sciences v. 21.0.1, SPSS). The binary response variable was
167 whether the dog was dead or alive 7 days after diagnosis. Factors found to be
168 significant at the univariate level were taken forward for multivariate analysis.
169 Bodyweight, duration of clinical signs, lactate concentration on venous blood gas
170 analysis, TNCC on CSF analysis and percentage of neutrophils in CSF were modeled
171 as continuous fixed effects. Mentation was modeled as a categorical fixed effect, and
172 the presence of seizures, cluster seizures and cytosine arabinoside administration were
173 modeled as binomial fixed effects. Breed was included as a random effect, with cross
174 breeds coded plainly as 'cross breed' due to unknown parentage. This random effect
175 took into account the genetic non-independence of multiple members of the same
176 breed in the study population, and possible demographic and environmental factors.
177 All models were checked for multicollinearity, identified from inflated standard errors
178 in the models, and thus avoided. Model fit was assessed using the deviance and
179 Akaike's information criterion. Numeric variables were expressed as median and
180 interquartile range. Values of $P<0.05$ were considered significant. Receiver operating
181 characteristic (ROC) analysis was performed to examine the performance of the
182 significant continuous variables on multivariate analysis as an indicator of prognosis,

by determining the power of the test by measuring the area under the curve (AUC). A perfect test has an AUC value of 1.0; an AUC of 0.5 means the test performs no better than chance.

Results

Signalment

One hundred and sixteen dogs met the inclusion criteria and were included in the study. Eighty-seven dogs (75%) were small or medium breed and 29 dogs (25%) were large breed. Median age at presentation was 52.5 months (4 – 146 months) and median bodyweight was 9.2 kg (1.65 – 94 kg). Fifty dogs (43%) were female, of which 30 were neutered, compared to 66 males (57%), of which 40 were neutered. Median duration of clinical signs before diagnosis was 7 days (range 1 – 180 days). Twenty dogs (17%) were treated with anti-inflammatory doses of glucocorticoids (doses ranging from 0.5 – 1 mg/kg administered every 12 – 24 h) prior to diagnosis, with a median duration of 3.5 days (range 1 – 90 days).

Neurological examination

Mentation was classified as BAR in 30 dogs (26%), QAR in 21 dogs (18%), obtundation in 59 dogs (51%) and stupor in six dogs (5%). No dogs presented comatose. Twenty-nine dogs (25%) presented with seizures, of which 20 dogs (69%) presented with cluster seizures and two dogs (31%) with status epilepticus. Sixty-six dogs (57%) presented with multifocal neurological signs, 50 dogs (43%) with focal neurological signs. Of the latter, 39 dogs (78%) presented with focal forebrain signs, eight dogs (16%) with focal brainstem signs, two dogs (4%) with focal cerebellar signs, and one dog (2%) with central vestibular signs.

Diagnostic findings

Results of CBC and biochemistry profile were available in 97 dogs (84%). Leucocytosis was present in 13 dogs (13%) and lymphopenia in 32 dogs (33%). Serology and/or PCR analysis for *Toxoplasma gondii*, *Neospora caninum* and canine distemper virus were available and negative in 82 dogs (71%). Lactate and glucose concentrations on venous blood gas analysis were available in 49 dogs (42%), revealing an increased lactate and/or glucose concentration in nine (18%) and 12 (24%) dogs, respectively. CSF analysis was not performed in 20 dogs (17%); it revealed no abnormalities in three dogs (3%); and a pleocytosis in the remaining 93 dogs (80%). In the three dogs with normal TNCCs, complete necropsy revealed GME (n=1), NME (n=1) or NLE (n=1). For the dogs with a pleocytosis (n=93), median TNCC was 80 WBC/mm^3 (6-2560 WBC/mm^3). For the dogs that died in the first week after diagnosis, median percentage of lymphocytes, neutrophils and monocytes/macrophages was 54%, 5% and 24%, respectively, compared to dogs that survived the first week after diagnosis, where percentages were 66%, 1% and 23%, respectively. Pretreatment with glucocorticoids did not significantly influence the TNCC on CSF analysis (P=0.9116).

Magnetic resonance imaging revealed a focal lesion in 31 dogs (27%), a multifocal lesion in 77 dogs (66%) and a diffuse lesion in eight dogs (7%). Mass effect was seen in 66 dogs (57%), consisting of brain herniation (n=44), midline shift (n=38) and/or flattening of gyri or sulci (n=51).

Treatment and outcome

All but two dogs were alive after MR imaging. Spontaneous breathing did not return in one dog (1%) after anaesthesia; treatment was initiated with dexamethasone but the dog was euthanased after 1 h. This dog was excluded from further analysis. One dog (1%) was not administered further treatment and was euthanased during general anaesthesia at the owner's request because of severe neurological signs. The remaining 114 dogs (98%) were treated with glucocorticoids. Detailed treatment data were available in 104 cases. Treatment consisted mainly of a single IV dose of dexamethasone (0.3 – 0.6 mg/kg) within hours of diagnosis, followed by oral prednisolone therapy (1-2 mg/kg every 12-24 h; *n*=79), or oral prednisolone therapy (1-2 mg/kg every 12-24 h, initiated within hours of diagnosis; *n*=25). Eighty-eight of 114 dogs (85%) received additional treatment with cytosine arabinoside, given as SC injections (50 mg/m^2 SC every 12 h for 2 consecutive days) in 69 dogs (78%) and as an IV constant rate infusion (CRI; 200 mg/m^2 over 8 h; *n*=19; 22%). Twenty-seven dogs (23%) required mannitol (0.5 - 1 g/kg IV over 15-20 mins) administration during hospitalisation for clinical signs suggestive of raised ICP. This was administered immediately after intracranial MRI in nine dogs (33%) and during hospitalisation in the remaining 18 dogs (67%), at a median time after diagnosis of 1 h (range, 1 – 48 h).

Of the 114 dogs in which treatment was initiated, 84 (74%) survived and 30 dogs (26%) died or were euthanased during the first 7 days after diagnosis. These dogs died (*n*=10) or were euthanased (*n*=20) because of deteriorating neurological signs. The median survival time (MST) of all deceased dogs was 1 day. Overall, histopathological confirmation (necropsy) was available in 14 dogs, revealing a diagnosis of GME (*n*=9), NME (*n*=4) or NLE (*n*=1). Dogs that demonstrated

neurological improvement did so within a median time of 24 h after diagnosis (range, 12-72 h) and clinical improvement within this time period was significantly associated with 7-day survival (P<0.0001).

Factors associated with survival

Univariate analysis revealed that higher bodyweight (P=0.027), shorter duration of clinical signs prior to diagnosis (P=0.042), decreased mentation at presentation (P=0.048), the presence of seizures (P=0.002) or cluster seizures (P=0.005), increased lactate concentration on venous blood gas analysis (P=0.026), higher TNCC on CSF analysis (P=0.031), higher percentage of neutrophils in CSF (P=0.0224), administration of IV dexamethasone (P=0.0019), and no administration of cytosine arabinoside (P=0.012), were all associated with a poor outcome. The administration of a cytosine arabinoside CRI was significantly associated (P<0.0001) with a poor outcome compared to the administration of SC cytosine arabinoside. None of the other evaluated clinical, clinical pathology, or imaging variables were significantly associated with outcome in this model (Table 1).

A binary response mixed model was performed on factors found to be significant at the univariate level. Three variables were significantly associated with poor outcome in the final model: percentage of neutrophils in CSF, decreased mentation at presentation, and a history of seizures (Table 2). Dogs with a higher percentage of neutrophils were at an increased risk of death at 1 week (mean ± standard error dead, 14.88 ± 4.01; alive, 6.31 ± 1.40). Dogs with decreased mentation at presentation were at increased risk of death within 1 week (% dead at 1 week BAR, 20% vs. stupor, 66.7%). Dogs presented as BAR had an 18.33 increased odds of

being alive at 1 week compared to those presented in a stuporous state. Finally, dogs with a history of seizures were at an increased risk of death at 1 week (dead at 1 week no seizures, 19.5% vs. seizures, 51.7%). Dogs without seizures had 4.20 increased odds of being alive at 1 week compared to those with seizures. ROC-analysis revealed that none of the significant continuous variables was able to reliably differentiate between good and poor short-term outcome in dogs with MUA (Fig. 1).

Discussion

This study evaluated the prevalence and potential risk factors for 1-week survival in dogs diagnosed with MUA. Although it was hypothesised that a proportion of dogs would not survive the first week after obtaining a diagnosis of MUA, a high proportion (26%) of dogs died within this specific time frame despite the initiation of appropriate treatment and careful monitoring. Therefore, the inclusion of this group of dogs when considering the overall prognosis of dogs with MUA is important.

It has been reported previously that approximately 15% of dogs diagnosed with GME died before being treated (Granger et al., 2010), compared to only 1/116 dogs (0.9%) in the present study, where the owner decided to euthanase the dog without attempting to treat. A recent study reported that 56% of dogs diagnosed and treated for MUA died or were euthanased with a median survival time of 2 days (Lowrie et al., 2013), which is over twice the frequency reported here.

In a recent study by Sharma and Holowaychuk (2015), increased venous lactate concentrations were a risk factor for non-survival to hospital discharge in dogs with head trauma. Additionally, hyperglycaemia has been associated with severity of

injury in cases of head trauma in dogs and cats, but not with outcome (Syring et al., 2001). In the present study, blood glucose and lactate levels were measured on admission or before MR imaging on standard venous blood gas analysis. No significant difference was found in blood glucose levels between dogs that did or did not survive the first week after diagnosis. In the univariate analysis, lactate concentrations were significantly increased in dogs with a poor outcome, but this result was not confirmed in the multivariate analysis. As both measurements were only available for review in approximately 20% of cases, further prospective studies are required before accurate conclusions can be drawn.

This study identified some potential risk factors for death in the first 7 days after diagnosis of MUA, including seizures and/or decreased mentation at presentation, as has been reported previously (Bateman and Parent, 1999; Coates et al., 2007). Although it is possible that these dogs represent a group of animals with a more severe clinical phenotype, we cannot exclude the possibility that the necessity of administering anti-epileptic drugs in these dogs was associated with increased sedation and therefore contributed to a further decline of their neurological function. In contrast to results of a recent study (Lowrie et al., 2013), higher neutrophil percentage on CSF analysis was significantly associated with increased risk of death in the first week after a diagnosis of MUA. However, our ROC-curve did not generate a reliable threshold value with combined high sensitivity and specificity to predict survival, so the exact neutrophil percentage should not be considered a useful tool for assessing prognosis in individual animals with MUA.

Previous studies have reported that adding another immunosuppressive agent or radiation therapy to the standard glucocorticoid treatment protocol improved survival of dogs with MUA (Munana and Luttgen, 1998; Jung et al., 2007; Coates et al., 2007; Granger et al., 2010; Flegel et al., 2011; Beckmann et al., 2015; Barnoon et al., 2016) but this was not confirmed in the present study. Surprisingly, treatment with SC cytosine arabinoside and oral prednisolone were both significantly associated with better short-term outcomes. This finding is unlikely to be reliable, as clinicians might have administered IV dexamethasone and an additional CRI of cytosine arabinoside only to dogs with more severe neurological signs. Additionally, a previous study (Crook et al., 2013) indicated more favorable pharmacokinetic properties of IV CRI of cytosine arabinoside compared to SC injections. Neither of these findings could be confirmed in the multivariate analysis performed in our study.

This study is limited by its retrospective design. Inclusion criteria were based on previously reported studies, but were not restrictive. In our study, dogs were excluded if TNCC on CSF analysis and/or intracranial MRI were within normal limits. Infectious disease testing was not required for inclusion and the treatment protocol was not standardised. Medical management was also tailored to individual needs and therefore some dogs might have received additional medication, such as anti-epileptic drugs and mannitol. Additionally, dogs received different treatment protocols prior to admission and diagnosis. Our inclusion criteria might have been biased towards more severely affected dogs because only dogs with CSF pleocytosis, dogs with abnormal intracranial imaging and/or dogs with clinical signs of raised ICP in the absence of CSF analysis were included. Definitive post-mortem diagnosis was available in almost half of the dogs (14/30; 47%) that died within 1 week after

hospital diagnosis. This might also suggest a bias towards the inclusion of more severely affected cases, as dogs that died or were euthanased in a hospital environment might have been more likely to undergo post-mortem examination.

Conclusions

Twenty-six percent of dogs diagnosed with MUA in this study died within 1 week after diagnosis, emphasising the need to evaluate of short-term prognostic factors. The presence of decreased mentation at time of presentation, seizures, and increased neutrophil percentage in the CSF were significantly associated with death within 7 days after diagnosis. The results of this study could be important when considering the overall prognosis of dogs with MUA and managing expectations of owners and hospital staff.

Conflict of interest

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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474 **Figure legend**

475

476 Fig. 1. Receiver operating characteristic (ROC) curve for neutrophil percentage in
477 cerebrospinal fluid. The area under the curve was 0.63, indicating that this continuous
478 variable has no clinical use in differentiating between good and poor outcome within
479 7 days after diagnosis. Consequently, no reliable threshold values with combined high
480 sensitivity and specificity could be identified to differentiate between both dogs with a
481 good and poor outcome.

482

483 **Table 1.** Results after univariate analysis. Values are numbers with respective
484 percentages or median values with respective interquartile ranges. Dogs (*n*=2) that did
485 not recover from the general anesthesia for MR imaging, were not included in the
486 analysis considering treatment.

Variable	Death ≤7 days (*n*=32)	Alive after 7 days (*n*=82)	*P*
Signalment			
Age (months)	55 (7 - 35)	50.5 (4 - 146)	0.987
Male	21 (66%)	45 (54%)	0.521
Female	11 (34%)	39 (46%)	0.521
Bodyweight (kg)	10.25 (3 – 94)	8.9 (1.65 – 54.9)	0.027 [a]
Duration of clinical signs prior to diagnosis (days)	6 (1 – 60)	8 (1 – 180)	0.042 [a]
Treatment with glucocorticosteroids prior to diagnosis (days)	1.5 (1 – 9)	3 (1 – 48)	0.061
Clinical signs			
Seizures	15 (47%)	14 (17%)	0.002 [a]
Cluster seizures	11 (34%)	9 (11%)	0.005 [a]
Neuroanatomical localisation			
Forebrain	24 (75%)	56 (67%)	0.502
Brainstem	21 (66%)	50 (60%)	0.671
Central vestibular	8 (25%)	23 (27%)	1.000
Abnormal mentation	7 (22%)	23 (27%)	0.362
Stuporous	4 (13%)	2 (2%)	0.048 [a]
Complete blood count			

Variable	Death ≤7 days (*n*=32)	Alive after 7 days (*n*=82)	*P*
White blood cells (.10^9/l)	13.10 (3.54 – 25.1)	9.97 (4.6 – 32.8)	0.103
Neutrophils (.10^9/l)	10.16 (2.4 – 23.9)	7.2 (3 – 28.3)	0.267
Lymphocytes (.10^9/l)	1.1 (0.1 – 3.5)	1.3 (0.17 – 3.6)	0.177
Lymphopenia	11 (34%)	21 (25%)	0.217
Venous blood gas			
Lactate (mmol/l)	2.1 (0.5 – 5.5)	1.4 (0.4 – 5,6)	0.026 [a]
Glucose (mmol/l)	6.3 (4 – 7.9)	5.69 (3.2 – 11.1)	0.100
CSF analysis			
TNCC (WBC/mm^3)	364 (1 – 2220)	66 (5 - 2560)	0.031 [a]
Total protein (g/l)	0.79 (0.1 – 5.56)	0.46 (0.11 – 8.5)	0.410
Not performed because signs of raised ICP	7 (22%)	13 (15%)	0.289
Lymphocyte percentage	54 (2 – 97)	66 (1 – 98)	0.087
Neutrophil percentage	5 (0 – 64)	1 (0 – 61)	0.022 [a]
Monocyte/macrophage percentage	24 (3 – 87)	23 (0 – 92)	0.981
MRI findings			
Focal lesion	7 (22%)	24 (29%)	0.635
Multifocal lesion	22 (69%)	55 (65%)	0.635
Diffuse lesion	3 (9%)	5 (6%)	0.386
Forebrain localisation	26 (81%)	63 (75%)	0.327
Brainstem localisation	16 (50%)	45 (54%)	0.445
Cerebellum localisation	4 (13%)	17 (20%)	0.248
Mass effect	16 (50%)	50 (60%)	0.405
Brain herniation	8 (25%)	36 (43%)	0.058
Caudal transtentorial herniation	7 (22%)	36 (43%)	0.053
Foramen magnum herniation	8 (25%)	22 (26%)	0.549
Midline shift	11 (34%)	27 (32%)	0.492
Flattening gyri/sulci	15 (47%)	36 (43%)	0.427
Contrast enhancement			
Meningeal contrast enhancement	24 (75%)	54 (64%)	0.191
Parenchymal contrast enhancement	20 (63%)	60 (71%)	0.239
Treatment			
Dexamethasone	27 (84%)	52 (62%)	0.002 [a]
Prednisolone	1 (6%)	24 (28%)	0.002 [a]
Cytosine arabinoside	19 (60%)	69 (82%)	0.012 [a]
Cytosine arabinoside CRI	12 (20%)	7 (10%)	< 0.001 [a]
Cytosine arabinoside SC	9 (47%)	60 (87%)	< 0.001 [a]
Mannitol	8 (25%)	19 (23%)	0.806
Improvement after treatment	4 (13%)	82 (97%)	<0.001 [a]
Time from diagnosis to	2 (1 – 48)	2 (1 – 72)	0.153

Variable	Death ≤7 days (*n*=32)	Alive after 7 days (*n*=82)	*P*
treatment with corticosteroids (h)			

CSF, cerebrospinal fluid; TNCC, total nucleated cell count; WBC, white blood cells; ICP, intracranial pressure; CRI, constant rate infusion

[a] $P<0.05$

Table 2. Results of binary response mixed model analysis of key predictors on the risk of death after 1 week (reference category: dead at 1 week).

Variable	Sub category	SE (coefficient)	OR (95% CI OR)	*t*	*P*
Neutrophils	-	0.96	0.093-0.99	-2.21	0.030 [a]
Mentation	BAR	18.33	1.39-241.33	2.24	0.027 [a]
	QAR	4.77	0.41-55.00	1.27	0.208
	Obtundation	6.40	0.58-69.72	1.55	0.126
	Stupor	Reference category			
Seizures	No	4.20	1.08-16.37	2.10	0.039 [a]
	Yes	Reference category			

OR, odds ratio; CI, confidence interval; SE, standard error; BAR, bright alert responsive; QAR, quiet alert responsive.

[a] $P<0.05$