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Usefulness of neurological assessment scales in prognosis of meningoencephalitis of unknown origin in Yorkshire Terriers

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Abstract

Background Attempts to determine the prognostic factors that affect the survival time of canine patients with meningoencephalitis of unknown origin (MUO) have produced highly variable results. Scaled complex ratings to predict general outcomes are required. Scaled rating was recently proven to help predicting prognosis in general MUO population of dogs. However, Yorkshire Terriers (YST) are predisposed to necrotizing meningoencephalitis, especially necrotizing leukoencephalitis, which more frequently manifests itself with forebrain lesions and may exhibit a distinct disease course compared to granulomatous meningoencephalitis. This study aimed to determine the usefulness of neurological assessment scales in the prognosis of YST with MUO. The study population comprised 127 YST which met inclusion criteria for a highly probable diagnosis of MUO. This multicentre, cohort study was designed as a retrospective review of medical records. Based on documented neurological examinations, animals were scored on three scales: the Modified Glasgow Coma Scale, Neuro Disability Scale 1 (Smith et al.), and Neuro Disability Scale 2 (Gonçalves et al.). The association between the scores and survival time was investigated over three periods of time – 7 days, 100, and 365 days (1 year) after onset of clinical signs.

Results All scales were significantly associated ($p < 0.001$) with MUO-specific survival and death of MUO within the first 7 days and had high prognostic accuracy in terms of short-term prognosis. None of the scales was significantly associated with the probability of survival after 100 or 365 days. Dogs with unilateral lesions on magnetic resonance images (MRI) had approximately 12- and threefold higher odds of surviving up to 100 and 365 days, respectively, than dogs with bilateral lesions on MRI. Dogs heavier than 3.2 kg at presentation had approximately sixfold higher odds of survival up to day 365.

Conclusions The study provides strong evidence for a high short-term prognostic accuracy of the three neurological assessment scales in YST with MUO – the scales seem to be very useful in predicting death within the first week of the onset of MUO. However, the scales do not appear to have prognostic value in the longer time frame. However, the presence of unilateral MRI changes and dog's body weight may assist with medium- and long-term prognosis.

Keywords Canine, Brain inflammatory diseases, Modified Glasgow coma scale, MUO, Neurodisability scale

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Background

Meningoencephalitis of unknown origin (MUO) serves as a hypernym for a group of inflammatory diseases of the central nervous system (CNS) that share common features and are suspected to be of autoimmune origin [1]. The actual incidence remains unknown, but it is estimated that MUO in dogs accounts for 5%–25% of all CNS disorders and approximately a half of non-infectious inflammatory cases [2–4]. Necrotizing encephalitis (NE) affecting Yorkshire Terriers (YST) was first reported in 1993 [5]. As only 25% of all MUO cases occur in large-breed dogs, and bearing in mind the ever-growing popularity of toy-breeds, MUO is an increasingly commonly diagnosed neurological disease [6, 7]. Despite numerous studies investigating the most effective treatment, it remains a clinical challenge with no established gold-standard treatment protocol [7].

When left untreated, the natural course of MUO is considered fatal [8]. However, outcomes vary greatly, both across and within studies, despite treatment. In recent literature (post-2009), median survival times range from 26 to 1,834 days. [7, 9, 10]. Notably, only one study specifically distinguished between NE and granulomatous meningoencephalitis (GME), reporting median survival times of 329 days for NE and 457 days for GME, respectively [11].

In previous years, numerous attempts have been made to determine the prognostic factors affecting the survival time of dogs with MUO. Factors such as MRI lesion distribution and severity, cerebrospinal fluid (CSF) analysis features, neurological signs, incidence of seizures, time to presentation, sex, age, and treatment protocols have been investigated and the results are highly inconsistent [1, 12, 13] thus contributing to the difficulties in prognostication. Recent findings suggest that certain MRI features, such as lower T2 lesion load, are associated with longer survival, while higher T1 post-contrast lesion load is linked to relapse [14]. In terms of biochemical markers, elevated blood and CSF lactate concentrations have been correlated with lower survival rates, with high CSF lactate levels also linked to more severe signs, indicating neuronal damage [15].

While some reproducible findings exist regarding short-term outcomes — such as the correlation between obtundation at presentation and a poorer prognosis [12, 16] — in most studies prognostic thresholds have not been determined. The current state of knowledge is even less advanced in terms of the long-term prognosis. [1] Therefore, due to variability of findings, coupled with the absence of standardised prognostic tools, it is challenging to translate these findings into practical guidance for clinical decision-making, and a need for establishment of robust clinical scores for evaluation of treatment has been suggested [7]. In response to those needs, a novel prognostic tool was developed – a Neuro Disability Scale [17]. Several other established scales have been used to describe the neurological status of dogs, however their usefulness in MUO-specific prognostication have not been compared so far.

In humans, the Glasgow Coma Scale (GCS) is designed to objectively describe the extent of impaired consciousness in patients after trauma [18]. The GCS can be applied not only in post-traumatic cases but also in neuroinflammatory diseases [19, 20]. A modified Glasgow Coma Scale (MGCS) was proposed by Shores for use in veterinary medicine [21], and its usefulness has been subsequently confirmed in a large group of animals [22, 23]; however, correlation with the prognosis of dogs with inflammatory diseases has not yet been investigated. The Neuro Disability Scale designed by Smith et al. [24] (NDS1), intended as a scoring system for patients with MUO to provide an objective assessment of their clinical status, allocates arbitrary scores to three categories of clinical deficits, and has been successfully applied to initial neurological condition assessment and treatment monitoring [25, 26]. Yet, it has not been evaluated for prognostication. The Neuro Disability Scale designed by Gonçalves et al. [17] (NDS2) attempts at a more complex assessment of the neurological state of patients with MUO in terms of prognosis. It is calculated by attributing a numerical rating of dysfunction in seven categories. Initially its use as a treatment progress monitoring tool was proposed by its authors. Later, usefulness of NDS2 in the long-term (6 months) MUO-specific prognostication was confirmed in a canine population of various breeds [27]. Unlike previous studies, our study focuses on breed-specific prognostication. It evaluates three different scales to explore their potential utility for prognostication and determine the one of the highest prognostic accuracy.

YST represent a particularly unique subgroup of MUO patients since they are predisposed to necrotizing encephalitis (NE) especially necrotizing leukoencephalitis (NLE) [28]. This breed-specific susceptibility makes YST an important focus for investigating potential prognostic tools or differences in disease outcomes. Furthermore, the predisposition of YST to NE also influences the localization of lesions, as the majority of these patients present with forebrain localization compared to dogs with GME [29]. This is particularly significant because forebrain involvement has been previously associated with worse prognoses in MUO patients [13], likely contributing to the poorer outcomes observed in necrotizing encephalopathies compared to GME [11].

Diagnosing specific MUO subtypes, such as NLE, definitively requires a brain biopsy or postmortem examination which is considered the gold standard [30].

However, the brain biopsy is rarely performed in clinical settings due to its invasive nature and high costs. By focusing on a single breed, such as YST, which is highly predisposed to NE, we aimed to establish a more homogeneous study group. Currently, no genetic test is available to identify or address the predisposition to NE in YST, making it difficult to implement strategies for disease elimination within the breed. This fact further underscores the necessity of studies aimed at improving our understanding and management of this condition in YST. Moreover, YST were overrepresented in our clinical population during the study period, reflecting both their popularity as a breed in our region and their apparent predisposition to MUO. This overrepresentation provided a robust sample size for analysis while reducing the potential diagnostic bias that could arise from including breeds with varying levels of predisposition to MUO.

The present study aimed to determine (1) whether MGCS, NDS1, or NDS2 scores at admission were associated with the survival time of YST with MUO and (2) whether they played a role in providing the short-term (7 days), middle-term (100 days), or long-term prognosis (365 days).

Results

Study population

The study population consisted of 127 YSTs – 61 males (48.0%) and 66 females (52.0%), aged 6 months to 11 years, with a median (IQR) of 4 (2–4) years. The dogs weighed between 1.0 and 7.0 kg with a median (IQR) of 2.5 (2.0–3.5) kg. Age did not differ significantly between sexes, but males were significantly heavier (median 3.0 kg, IQR 2.3–3.7 kg) than females (median 2.3 kg, IQR 1.8–3.1 kg) ($p = 0.003$).

As shown by MRI, the lesions were nearly equally focal, including only one of three regions (forebrain, brainstem or cerebellum) of the brain (71/126 dogs; 56.4%) and multifocal, including at least two regions of the brain (55/126 dogs; 43.6%), and usually present in both sides of the brain (90/126 dogs; 71.4%). Most multifocal lesions were bilateral as well (44/55 dogs; 80.0%) (Table S2).

CSF analysis was performed in 92/127 dogs (72.4%) and mononuclear pleocytosis was detected in 81/92 dogs (88.0%, 95% CI: 79.8%–93.2%). Brain biopsy was performed in 7/127 dogs (5.5%) and in all cases it confirmed MUO diagnosis. Results of tests for infectious diseases were available for 75/127 (59.1%) dogs and all were negative.

Treatment was applied in 121/127 dogs (95.3%). Six untreated dogs died within 2 days of disease onset (four were euthanatized and two died during MRI examination). All 121 treated dogs received prednisolone – 37/121 dogs (30.6%) as a sole therapeutic agent and the remaining 84/121 dogs underwent 6 different treatment protocols based on various combinations of azathioprine, cytosine arabinoside, lomustine, cyclosporine, mycophenolate, and radiotherapy, of which the most common was the protocol including prednisolone and azathioprine (32/121 dogs; 26.4%) (Table S3).

Neurological signs resolved in 85/127 dogs (66.9%, 95% CI: 58.4%–74.5%); however, complete remission was observed in 45/127 dogs (35.4%, 95% CI: 27.7%–44.1%). During the observation period, death occurred in 53/127 dogs (the case fatality rate (CF) of 41.7%, 95% CI: 33.5%–50.4%). The overall survival time (time from the onset of MUO to death), calculated for 53 dogs whose exact time of death was known ranged from < 1 to 2257 days (6.2 years) with a median (IQR) of 71 (19–290) days. Two MUO-unrelated deaths occurred during MRI examination, due to complications of general anaesthesia rather than MUO itself. In the observation period, 74 dogs (58.3%) were lost to follow-up. The follow-up period for these dogs lasted from 14 to 3538 days (9.7 years) with a median (IQR) of 493 (335–1006) days.

Neurological assessment scales

The score that dogs with MUO were given ranged from 5 to 18 points (median 16 points, IQR 15–17 points) in the MGCS, from 0 to 12 points (median 5 points, IQR 3–6 points) in the NDS1, and from 0 to 18 points (median 6 points, IQR 3–9 points) in the NDS2 (Fig. S1). The scores obtained for each dog on the three scales were significantly mutually correlated: scores on the NDS1 and NDS2 were strongly positively correlated with each other ($R_s = 0.87$, $p < 0.001$) but strongly negatively correlated with scores on the MGCS ($R_s = -0.76$, $p < 0.001$ and $R_s = -0.70$, $p < 0.001$, respectively) (Fig. S2).

Prognostic factors

MUO-specific survival analysis

Median MSS of dogs with MUO when estimated based on all dogs (including censored) was 2257 days (6.2 years) with the 1st quartile (25% of dogs dead) of 162 days (Fig. 1). Most of deaths (46/53; 86.8%) occurred in the first year of observation (Fig. 2).

In the univariable analysis, neurological assessment scales were significantly but only weakly associated with MSS: an increase in MGCS was associated with longer MSS i.e. it was negatively associated with risk of MUO-related death (HR 0.82, 95% CI: 0.74–0.91; $p < 0.001$) whereas increase in NDSs was associated with shorter MSS i.e. it was positively associated with risk of MUO-related death (NDS1: HR 1.30, 95% CI: 1.14–1.49; $p < 0.001$ and NDS2: HR 1.19, 95% CI: 1.09–1.30; $p < 0.001$). Moreover, two other variables proved to be significantly associated with MSS: an increase in body

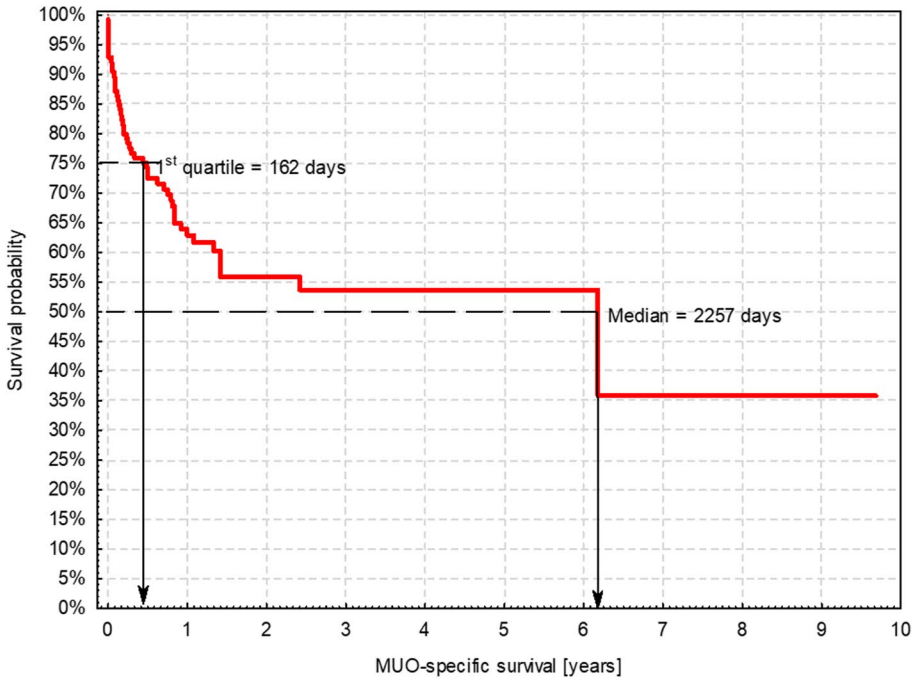

Fig. 1 Kaplan–Meier curve presenting meningoencephalitis of unknown origin (MUO)-specific survival of 127 Yorkshire Terriers with MUO

weight was weakly associated with longer MSS i.e. it was negatively associated with risk of MUO-related death (HR 0.69, 95% CI: 0.51–0.95; $p=0.020$) and the presence of only unilateral lesions in MRI was moderately associated with longer MSS i.e. it was negatively associated with risk of MUO-related death (HR 0.36, 95% CI: 0.17–0.77; $p=0.008$).. Age on admission, sex, brain region affected in MRI, and treatment protocol were not significantly associated with MSS (Table S4).

In the multivariable analysis, controlled for the treatment protocol, body weight, and the spread of lesions in MRI, two NDSs remained to be significantly associated with MSS and in both cases the associations were weak. An increase in these scales was weakly positively associated with the risk of MUO-related death (NDS1: HR 1.19, 95% CI: 1.03–1.39; $p=0.023$ and NDS2: HR 1.13, 95% CI: 1.02–1.25; $p=0.016$). The MGCS did not prove to be significantly associated with MSS. Furthermore, both the body weight and the spread of lesions remained significant in the multivariable analysis (Table S5).

Short-term prognosis – risk of death within first 7 days

During the first 7 days, 11/127 dogs died (8.7%), however, 2/11 dogs died during MRI, and they were not considered to be MUO-related deaths. Therefore, the MUO-related CF was 7.2% (95% CI: 3.8%–13.1%; 9/125 dogs).

None of the demographic or clinical variables were significantly linked to the risk of death of MUO within the first 7 days, except for the scores of all three neurological scales (Table S6). Their prognostic accuracy was highest for MGCS (AUROC 96.6%; 95% CI: 92.7%–99.9%), followed by NDS1 (AUROC 95.1%; 95% CI: 86.9%–99.9%) and NDS2 (AUROC 90.6%; 95% CI 79.6%–99.9%), however, the difference between them was not significant (Fig. 3). The optimal cut-off value was ≤ 14 points for MGCS, ≥ 7.5 points for NDS1, and ≥ 10 points for NDS2. At these cut-off values, MGCS had the highest prognostic sensitivity (PSe) while NDS1 had the highest prognostic specificity (PSp) (Table 1; Fig. S3). NDS1 appeared to be the most balanced prognostic test thanks to the highest simultaneous LR + and LR- (25.8 and 0.12, respectively). Assuming the CF in the first week of MUO is typically < 10%, only NDS1 offered higher than 50% probability of correct identification of the dog that will die within the first week (i.e. PPV). The two other scales had PPVs of only approximately 32%-37%. On the other hand, a dog negative in the scale was very likely to survive the first week regardless of the scale used (i.e. NPV of the negative result of each scale was 98%-100%) (Table 1).

Mid-term prognosis – probability of survival for 100 day

Excluding the 11 dogs that died during the first week, 114 dogs were observed until day 100: 19/114 dogs died of MUO (16.7%) and 95 were alive on day 100 (83.3%). The 100-day survival rate (S_{100}) was 76.0% (95% CI: 67.8%–82.6%; 95/125 dogs) (Fig. 2).

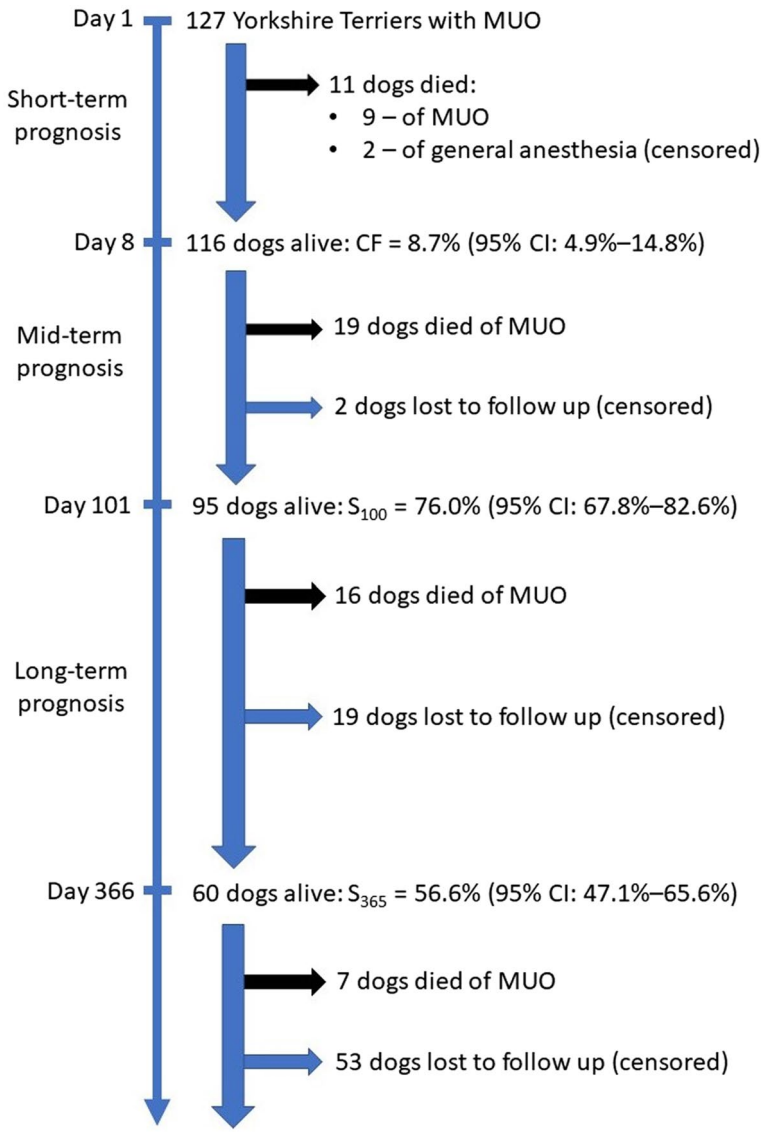

Fig. 2 Flowchart presenting change of the number of dogs with meningoencephalitis of unknown origin (MUO) in the subsequent time points of the study. Legend: CF stands for the case fatality rate. S_{100} and S_{365} correspond to the 100-day and 1-year survival rate, respectively. 95% CI stands for the 95% confidence interval

None of the three neurological scales was significantly associated with the probability of surviving the period between 8 and 100 days. One clinical variable, proved to be significantly and positively associated with a higher probability of survival in this period: unilateral brain lesions in MRI ($p=0.004$) (Table S7). In the multivariable analysis, only the spread of lesions in MRI was significantly associated with survival in this period and the association was very strong – controlled for the treatment protocol used, dogs with unilateral lesions in MRI had approximately 12-fold higher odds of surviving than dogs with bilateral lesions in MRI (adjusted odds ratio (OR_{adj}) 12.5; 95% CI: 1.60–97.4; $p=0.016$) (Table S8).

Long-term prognosis – probability of survival for 1 year

Ninety five dogs were observed until day 365; 35/95 died of MUO (36.8%) and 60/95 were alive at the end of the 1st year (63.2%). The 1-year survival rate (S_{365}) was 56.6% (95% CI: 47.1%–65.6%; 60/106 dogs) (Fig. S2). Survival rate calculated according to the most pessimistic and most optimistic scenario was 47.2% (95% CI: 38.8%–55.9%; 60/127 dogs) and 63.8% (95% CI: 55.1%–71.6%;

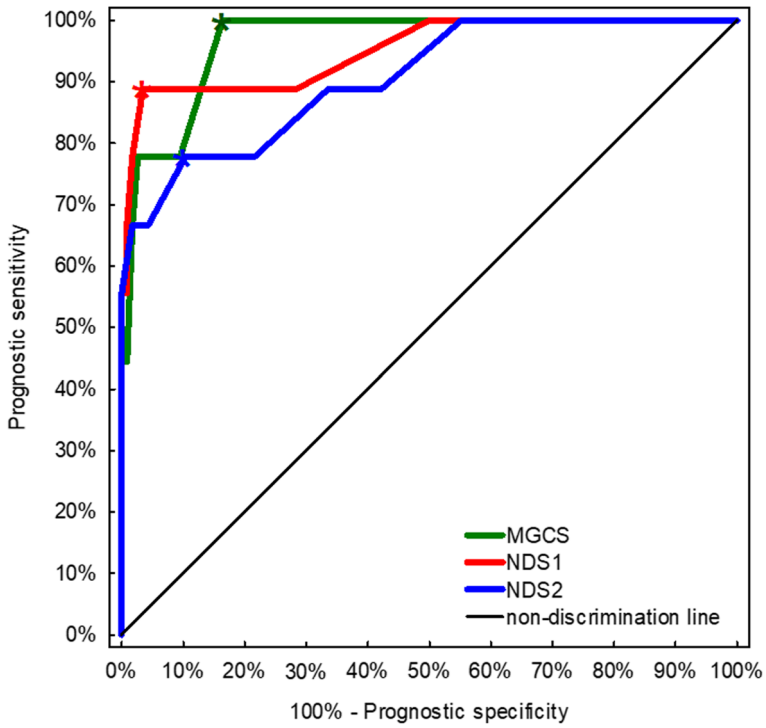

Fig. 3 Receiver operating characteristic (ROC) curve for the three neurological assessment scales. Legend: (MGCS – Modified Glasgow Coma Scale, NDS1 – Neuro Disability Scale according to Smith et al. (2009); NDS2 – Neuro Disability Scale according to Goncalves et al. (2023)). Asterisks indicate the most optimal cut-off values

Table 1 Short-term prognostic accuracy of the neurological assessment scales i.e. ability of the scales to predict death within first 7 days

Scale	AUROC (95% CI) [%]	Cut-off values	PSe (95% CI) [%]	PSp (95% CI) [%]	PPV (95% CI) [%]	NPV (95% CI) [%]	LR+ (95% CI)	LR- (95% CI)
MGCS	96.6 (92.7 – 99.9)	≤ 14	9/9 100 (70.1 – 100)	97/116 83.6 (75.8 – 89.3)	9 / 28 32.1 (17.9 – 50.7)	97 / 97 100 (96.2 – 100)	6.1 (4.0 – 9.2)	∞
NDS1	95.1 (86.9 – 99.9)	≥ 7.5	8/9 88.9 (56.5 – 98.0)	112/116 96.6 (91.5 – 98.7)	8 / 12 66.7 (39.1 – 86.2)	112 / 113 99.1 (95.2 – 99.8)	25.8 (9.6 – 69.4)	0.12 (0.02 – 0.73)
NDS2	90.6 (79.6 – 99.9)	≥ 10	7/9 77.8 (45.3 – 93.7)	104/116 89.7 (82.8 – 94.0)	7 / 19 36.8 (19.1 – 59.0)	104 / 106 98.1 (93.4 – 99.5)	7.5 (4.0 – 14.3)	0.25 (0.07 – 0.83)

AUROC area under receiver operating characteristic curve, *MGCS* Modified Glasgow Coma Scale, *NDS1* Neuro Disability Scale designed by Smith et al. (2009), *NDS2* Neuro Disability Scale designed by Gonçalves et al. (2023), *PSe* prognostic sensitivity, *PSp* prognostic specificity, *PPV* positive predictive value, *NPV* negative predictive value, *LR+* likelihood ratio of the positive result, *LR* likelihood ratio of the negative result, ∞ infinity, *95% CI* 95% confidence interval

81/127 dogs), respectively, which virtually perfectly corresponded to the 95% confidence limits of S_{365}.

In the univariable analysis, two factors proved to be significantly and positively associated with surviving the period between 8 and 365 days after the onset of MUO signs: body weight of ≥ 3.2 kg ($p = 0.002$) and the presence of unilateral lesions in MRI ($p = 0.019$); two other factors were significantly negatively associated with survival in this period: the presence of inflammatory pleocytosis in the CSF analysis ($p = 0.023$) and impaired cerebellar function in NDS2 ($p = 0.045$) (Table S9). The former factor could not be included in the multivariable analysis as the CSF analysis was available only for 65/95 dogs. The latter factor was dichotomized into normal and

impaired cerebellar function. In the multivariable analysis, dogs with body weight of ≥ 3.2 kg on admission had approximately sixfold higher odds of survival until day 365 (strong association: OR_{adj} 6.49, 95% CI: 1.79–23.5; $p = 0.004$), and dogs with unilateral lesions in MRI had approximately threefold higher odds of survival (moderate association: OR_{adj} 3.38, 95% CI: 1.03–11.1; $p = 0.045$), while dogs with impaired cerebellar function had approximately fivefold lower odds of survival (moderate association: OR_{adj} 0.21, 95% CI: 0.05–0.95; $p = 0.043$) (Table S10).

Discussion

The applicability of previously validated scoring systems, such as the NDS2, in predicting prognosis in YST with MUO was evaluated. Interestingly, the findings revealed that NDS2, along with two other tested scales, could not reliably predict mid-term or long-term outcomes in this specific breed. This may be attributed to the higher incidence of NE in YST, which is potentially associated with a more aggressive progression and a poorer overall prognosis compared to GME.

Our study shows that all three neurological scales are significantly associated with MSS and highly accurate predictors of death within the first week of MUO onset. The scores of NDS1 and NDS2 could be divided into categories based on survival quartiles to set hypothetical thresholds. As a consequence, they constitute an easily available, non-invasive, and inexpensive tool aiding clinicians in making important clinical decisions on admission. Noteworthily, no other factor recognized on presentation was significantly linked with the short-term prognosis. On the other hand, the neurological scales do not appear to be associated with either mid-term or long-term prognosis, which is not consistent with the findings of previous studies [27]. A possible reason for this inconsistency might be a smaller research group or breed-specific difference in prognosis.

When choosing the most clinically applicable scale, some important differences in the diagnostic performance of these scales should be considered. NPVs of all three scales are very high (98%–100%), which means that a dog testing negative on the scale (i.e., > 14 in MGCS, < 7.5 in NDS1, and < 10 in NDS2) is very likely to survive the first week. PPVs, however, are substantially lower. Only in the case of NDS1 did the PPV exceed 50%—it was 67%—which means that a dog with a positive NDS1 (≥ 7.5) result was 67% likely to die within the first week and still 33% likely to survive. MGCS and NDS2 had a PPV of only approximately 35%, so a dog with a positive result on either of these two scales was still more likely to survive the first week than to die. Predictive values are largely determined by the prevalence of the event of interest (in this case—death from MUO during the first week) in the population, i.e., CF [31]. Therefore, they should be interpreted in the context of the CF in the first week after MUO onset. As several studies have reported a higher CF than that observed in our study (20%–26%) [16, 32], it is important to remember that as the CF increases, the PPV will also increase, while the NPV will decrease. Therefore, to objectively describe the trustworthiness of the scales' results independently of CF, positive and negative likelihood ratios (LR + and LR–) are used instead of, or in addition to, predictive values [31, 33, 34]. The test is usually considered clinically useful when LR + > 10 or LR– < 0.1 [31, 34]. NDS1 virtually fulfils both criteria, which makes it the most versatile scale.

MGCS is an interesting case—97 of 97 dogs with an MGCS > 14 (good prognosis according to Platt et al. [23]) survived, which makes a negative MGCS result perfectly trustworthy (i.e., perfect NPV). On the other hand, only 9 of 28 dogs with an MGCS ≤ 14 died (PPV 32%), which makes a positive MGCS result a weak prognostic factor. However, all 4 dogs with an MGCS ≤ 8 (indicating a poor prognosis) died. Our study shows that initial triage using the MGCS, followed by further assessment of dogs with an MGCS score of 9–14 (guarded prognosis) coupled with NDS1 or NDS2, might be beneficial in terms of prognostic accuracy. MGCS is widely used for survival prognosis in veterinary medicine; however, it was initially designed for comatose patients with trauma, who are mostly in a severe neurological state. This is not true for most patients with MUO. In humans, the GCS has been applied successfully not only in acute inflammatory diseases of the CNS [19] but also in immune-mediated neuroinflammatory diseases, such as anti-N-methyl-D-aspartate receptor encephalitis [35]. The latter is a likely underlying cause of MUO in some dogs [20]. The focus of the MGCS is mostly on severe symptoms, and this area of concern is heavily graded, whereas patients in a good neurological condition are distributed in close proximity without much grading. This tendency was illustrated by the lack of a normal distribution, with strong left-hand asymmetry (Fig. S1), indicating that most dogs with MUO scored highly. The detailed assessment of severely affected patients may explain why MGCS had the highest prognostic accuracy in terms of short-term survival. In contrast to the MGCS, the NDSs are designed to test more subtle and disseminated lesions. For example, a focal forebrain lesion causing epileptic seizures as the only neurological sign would be scored at three possible grades in the NDSs (isolated seizures—1 point; cluster seizures—2 points; status epilepticus—3 points; in the NDS1 or controlled seizures—1 point; cluster/refractory seizures—2 points; status epilepticus—3 points; in the NDS2), but would not be scored at all in the MGCS as there is no category related to epilepsy. Such

a clinical picture in the early stages of MUO is seen frequently. Therefore, the NDSs might be more precise in less advanced stages of the disease. This might explain why the NDSs are better correlated with MSS than the MGCS.

Compared with NDS1, the complexity of NDS2 appeared to be advantageous in terms of accuracy, but not when considering difficulties in clinical utility due to greater time consumption and potentially longer learning curve. In conclusion, NDS1 appeared to be the most balanced scale in terms of prognostic potential and ease of use in the clinical environment, NDS2 had the strongest correlation with MSS, and MGCS had the highest prognostic accuracy in the short-term survival analysis. Considering these characteristics, none of the scales can be said to be definitely superior. However, in the clinical environment combining the scales might be beneficial in terms of making the most accurate prediction about death or survival. For this purpose, patient could be assessed firstly using MGCS and then NDS1.. A recent study, has revealed significant prognostic role of NDS2 in terms of 6-month survival [27]. The proposed cut-off value was 7 points and prognostic accuracy was relatively low (AUROC 71%, PSe 61%, PSp 67%).In our study NDS2 turned out not to be significantly associated with prognosis after 3 months or 1 year so it would likely be also insignificant after 6 months. This discrepancy may result from a huge difference in the study population size between the study of Gonçalves et al. [27] and ours – 447 versus 127. A study population size is a major factor influencing the power of statistical analysis – the study enrolling more patients is able to detect weaker effects as significant [31]. A prognostic tool with accuracy of 70% is unlikely however to be clinically meaningful.

Using NDS2, Gonçalves et al. found a significant difference between the scores of dogs that survived up to discharge and those that did not [17]. These results are consistent with our findings regarding short-term survival. Nevertheless, a correlation between the outcomes (good, fair, or poor) and the obtained scores was not found in that study [17]. In our study, we focused on the length of survival because it is objective and is the most commonly investigated final end-point in MUO prognostic studies. Owing to the different methodologies used, these results are difficult to compare. In another recent study by Lawn and Harcourt-Brown, obtundation at the presentation increased the odds of death by 6.6 times in the first 7 days after diagnosis [12]. In our analysis, we did not find mental status–associated scale elements superior to others in terms of short-term prognostication. We also did not find a significant correlation between mental status and mid-term prognosis, in contrast to the 1.9 times increased the risk of death 31–100 days after diagnosis in obtunded dogs described in the aforementioned study [12]. This finding may be influenced by the predominance of forebrain neurolocalization in the majority of our cases, as these patients are more likely to present with normal consciousness compared to those with brainstem neurolocalization.

In most studies, no association was found between MRI findings and survival [1]. However, Gonçalves et al. found that lower T2 lesion load was associated with longer survival, and higher T1 post-contrast lesion load was associated with relapse [14], Lowrie et al. found a negative impact of the loss of cerebral sulci and foramen magnum herniation on short-term survival [9] and Paušová et al. described focal brainstem lesions as a positive prognostic factor compared with forebrain multifocal lesions [13]. Therefore, the MRI lesion distribution was included in our analysis. The analysis did not reveal any significant differences in the brain region (forebrain, brainstem, or cerebellum) and focal vs. multifocal lesions, what is generally consistent with most studies. Interestingly, the spread of lesions (unilateral vs. bilateral) seemed to have an effect on mid- and long-term prognosis. Despite bilateral lesions being generally known to cause more severe clinical symptoms than unilateral, the approach of dividing cases into bi- or unilateral in MUO studies is novel. The better clinical condition of patients with brain lesions limited to one side is explained by reduction of a relative magnitude of the contribution to performance of the damaged side, allowing the intact side to dominate performance. In contrast, balanced bilateral damage distorts representations on both sides, which contribute equally, resulting in degraded performance [36]. Thus, the dogs with unilateral lesions were probably able to adapt, thanks to a functional half of the brain. Other factors associated with long-term outcomes in the multivariable analysis were body weight and impaired cerebellar function. The effect of body weight could be explained by the negative impact of the extreme miniaturization and potentially restricted genetic pool of these dogs on the their general condition and multiple comorbidities as well as difficulties with drug dosage [37–39]. However, effect of cerebellar function remains unclear and might be a coincidental correlation.

Limitations

This study has several limitations. The main limitation is that for some patients, not all data were available. The lack of histopathological confirmation in most cases and the absence of CSF analysis or inflammation as well as infectious disease testing in some cases, could result in a diagnostic bias. This bias can be reduced to a certain extent, by the breed homogeneity of the study population, as YST are highly predisposed to MUO [5, 28].

Additionally, excluding cases without CSF examination would introduce bias by disproportionately excluding the most severely affected patients with medical contraindications for CSF collection such as increased intracranial pressure. Regarding patients who had non-inflammatory CSF analysis results, in most cases, the reason was probably a previous steroid administration which was documented in all of these and likely suppressed CSF inflammation [40]. Moreover, CSF cytology has been shown to be normal in 12.5% dogs with NE [41], which almost perfectly corresponds with our findings (12% non-inflammatory CSF).

Another limitation is the lack of treatment standardization; the treatment protocols varied greatly as a result of patient-related factors (severity of clinical signs, response to treatment, relapses, and tolerability), owner-related factors (time restrictions and financial considerations) and treatment approach changing over a very long time period covered by the study (19-year period). The decision to euthanize was based primarily on the feelings and system of values of the caretaker of the animal, which in many cases resulted in different states of the disease being the reason for euthanasia. The aforementioned limitations are common in most studies on MUO thus emphasizing the need for prospective, standardized research.

Conclusion

The study provides strong evidence for a high short-term prognostic accuracy of the three neurological assessment scales in YST with MUO – the scales seem to be very useful in predicting survival within the first week of the onset of MUO. However, the scales do not appear to have prognostic value in the longer time frame. On the other hand, the presence of unilateral MRI changes and YST's body weight may assist with medium- and long-term prognosis. YST with unilateral lesions and higher body weight appear to have significantly better prognosis on day 100 as well as 1-year. Our study highlights the importance of breed-specific considerations in MUO prognosis.

Methods

Study design

This multicentre cohort study was designed as a retrospective review. It aimed to determine whether MGCS, NDS1, or NDS2 scores at admission were associated with the survival time of YST with MUO, and whether they play role in predicting the prognosis. The MGCS and NDS scores were calculated based on medical documentation of the initial neurological examination of patients by a neurology resident, PhD student, or neurologist in training and subsequent re-evaluation by a Diplomate of the European College of Veterinary Neurology. Demographic characteristics and clinical data that were not included in any of the aforementioned scales were added to the analysis to determine their significance and compare with findings of previous studies. For the sake of clinical applicability of results, we included only those factors that could be evaluated upon admission.

Patient selection

Medical records were searched at the Clinic for Dogs, Cats, and Horses of the Wrocław University of Environmental and Life Sciences (Wrocław, Poland), Clinic for Small Animals of the Leipzig University (Leipzig, Germany), and Neuroteam Specialist Clinic (Wrocław, Poland), between July 2004 and January 2023, that matched the inclusion criteria. The proposed antemortem MUO diagnostic criteria were as follows: (1) dogs older than 6 months of age; (2) multiple, single, or diffuse intra-axial hyperintensities on T2-weighted MRI; (3) pleocytosis on CSF analysis with > 50% monocytes/lymphocytes; and (4) absence of infectious diseases commonly occurring in a specific geographic area [41]. Owing to the retrospective nature of the study, not all criteria could be verified in every patient.

The inclusion criteria required sufficient documentation to support a highly probable diagnosis of MUO. This included age > 6 months, typical MRI findings, and mononuclear pleocytosis in the CSF. For cases with missing CSF examination, inclusion required age > 6 months, typical MRI appearance, and negative infectious disease testing. For cases with non-inflammatory CSF, inclusion required age > 6 months, typical MRI appearance, and either (a) MUO confirmation by brain biopsy and negative infectious disease testing from blood or (b) documented previous steroid administration and negative infectious disease testing. Additionally, all included cases required at least one neurological follow-up.

All dogs were older than 6 months, had MRI lesions typical for MUO, and underwent documented neurological examinations and follow-ups. CSF was considered inflammatory if > 5 cells/μL were present and/or protein concentration was > 0.3 g/L in cerebellomedullary cistern collection. Regarding dogs for whom CSF analysis was not available, the majority had medical contraindications for CSF collection (increased intracranial pressure, complications during anaesthesia), less often their owners refused to consent for the procedure. Due to the region of Europe where the study was conducted, most patients were tested for *Neospora caninum*, *Toxoplasma gondii*, *Ehrlichia canis*, and *Anaplasma phagocytophilum* (CSF PCR or blood serology) and all results were negative.

Scoring system

Based on documented neurological examinations, all dogs were scored on three ordinal assessment scales, so far developed or adapted in veterinary medicine: MGCS, NDS1, and NDS2. The scoring was conducted independently by two evaluators, both blinded to the outcomes. In cases where the scores differed, the discrepancies were reviewed and discussed until consensus was reached. The scoring systems of the scales are summarized in detail in Table S1. Briefly, the modified MGCS is a 14-point scale (minimum 3 points, maximum 16 points), where a high score is associated with a poor prognosis, which assesses three functional areas of the nervous system: motor activity, brainstem reflexes, and consciousness. The categorization of MGCS into scores indicating good (15–18), guarded (9–14), and poor (≤8) prognosis has been proposed [23]. NDS1 is a 21-point scale (minimum 0 points, maximum 20 points), negatively linked with the neurological status (i.e. it increases along with neurological disability), which also evaluates three functional areas of the nervous system: cranial nerves, mentation, and postural responses. NDS2 is a 22-point scale (minimum 0 points, maximum 21 points), also negatively linked with the neurological status, which investigates seven functional areas of the nervous system: ambulatory status, cerebral, cerebellar, brainstem and visual functions, postural abnormalities, as well as seizure presence and intensity. The scales vastly overlap one another.

Statistical analysis

Numerical variables were examined for normality of distribution using histograms and the Shapiro–Wilk W test. As the normality assumption was violated, data were presented as the median, interquartile range (IQR), and range, and compared between groups using the Mann–Whitney U test. Categorical variables were presented as counts (n) and proportions (%) in a group, and compared between groups using the likelihood-ratio G test or Fisher's exact test if the expected count in the contingency table was below five. The 95% confidence intervals (95% CI) for proportions were calculated using the Wilson score method [42]. The correlation between the neurological scales was determined using the Spearman's rank correlation coefficient (Rs). Strength of correlation was classed as follows [43]: Rs = 0.00 to 0.19 – very weak, 0.20 to 0.49 – weak, 0.50 to 0.69 – moderate, 0.70 to 0.89 – strong, and 0.90 to 1.00 – very strong.

In the MUO-specific survival (MSS) analysis, dogs were censored if they died from causes unrelated to MUO, were lost to follow-up, or were alive at the end of the observation period. The Cox proportional-hazard regression was used both in the univariable and multivariable MSS analysis and the effect size was presented as hazard ratios (crude, HR and adjusted, HR_{adj}) with 95% CI and it was categorized into weak (HR 0.5 to < 1 or > 1 to 2), moderate (HR 0.2 to < 0.5 or > 2 to 5), strong (HR 0.1 to < 0.2 or > 5 to 10), and very strong (HR < 0.1 or > 10) [44]. The multivariable MSS analysis was performed separately for each neurological scale, with all potentially confounding variables that had $p < 0.1$ in the univariable analysis entered according to the backward stepwise procedure. The Kaplan–Meier estimator plots were used to show survival functions [35].

Short-term prognosis was presented as the case fatality rate (CF) within the first 7 days of the onset of MUO signs (defined as the first neurological evaluation). Accuracy of neurological assessment scales in predicting MUO-related death within the first 7 days (short-term prognosis) was investigated using the area under ROC curve (AUROC) analysis. The optimal cut-off value was determined for each scale by maximizing the Youden's index, and the following measures of prognostic accuracy were calculated for the optimal cut-off value: prognostic sensitivity (PSe) defined as probability of positive result of a given scale in dogs that died within 7 days, prognostic specificity (PSp) defined as probability of negative result of a given scale in dogs that survived more than 7 days, and likelihood ratio of positive (LR+) and negative result (LR-) [33]. Positive predictive value (PPV) and negative predictive value (NPV) were also presented to illustrate how likely a patient with a positive scale result was to die within 7 days or how likely a patient with a negative scale result was to survive more than 7 days, respectively [31].

Mid-term and long-term prognosis were presented as 100-day and 1-year survival rate (S), respectively (S_{100} and S_{365}). S was calculated as the ratio of the number of dogs alive at the end of the period to the number of dogs alive at the beginning of this period. Dogs lost to follow-up in this period were excluded. However, to compensate for the influence of lost-to-follow-up dogs, S_{365} was additionally calculated in two extreme versions – most optimistic in which all dogs lost to follow-up were considered still alive and most pessimistic in which all dogs lost to follow-up were considered fatalities to MUO. Prognostic factors relevant in the three investigated periods were identified using the logistic regression – first univariable, and then multivariable, including hypothesized prognostic factors for which p-value in the univariable analysis was < 0.1 entered according to the backward stepwise procedure. The effect size was presented as odds ratios (crude, OR and adjusted, OR_{adj}) with 95% CI and it was categorized into weak (OR 0.5 to < 1 or > 1 to 2), moderate (OR 0.2 to < 0.5 or > 2 to 5), strong (OR 0.1 to < 0.2 or > 5 to 10), and very strong (OR < 0.1 or > 10) [44].

In the multivariable analyses treatment protocol was included by default to control for potential confounding effect of treatment. Treatment protocol was categorized into 3 classes: sole prednisolone (reference category), prednisolone and azathioprine, and other protocols. Goodness-of-fit of the multivariable logistic model was assessed using the Hosmer–Lemeshow $\chi 2$ test and Nagelkerke's pseudo-R^2 coefficient [45]. All statistical tests were two-tailed and the significance level (α) was set at 0.05 in all statistical tests except for the univariable analyses for which α was 0.1. The statistical analysis was performed using TIBCO Statistica 13.3 (TIBCO Software Inc., Palo Alto, CA, USA).

Abbreviations

CF	Case fatality rate
CI	Confidence interval
CSF	Cerebrospinal fluid
GCS	Glasgow Coma Scale
GME	Granulomatous meningoencephalitis
HR	Crude hazard ratio
HR_{adj}	Adjusted hazard ratio
IQR	Interquartile range
LR+	Likelihood ratio of positive result
LR-	Likelihood ratio of negative result
MGCS	Modified Glasgow Coma Scale
MRI	Magnetic resonance imaging
MSS	MUO-specific survival
MUO	Meningoencephalitis of unknown origin
NDS1	Neuro Disability Scale designed by Smith et al. (2009)
NDS2	Neuro Disability Scale designed by Gonçalves et al. (2023)
NE	Necrotizing encephalitis
NLE	Necrotizing leukoencephalitis
NPV	Negative predictive value
OR	Crude odds ratio
OR_{adj}	Adjusted odds ratio
PPV	Positive predictive value
S_{100}	Survival rate on day 100
S_{365}	Survival rate on day 365
YST	Yorkshire terrier

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12917-025-04594-2.

Supplementary Material 1. Supplementary Figure 1. Distribution of scores of the neurological assessment scales (MGCS – Modified Glasgow Coma Scale, NDS1 – Neuro Disability Scale according to Smith et al. (2009); NDS2 – Neuro Disability Scale according to Goncalves et al. (2023)) obtained by dogs with meningoencephalitis of unknown origin (MUO). Numbers above bars correspond to the number of dogs with a given score.

Supplementary Material 2. Supplementary Figure 2. Correlation between scores of the neurological assessment scales (MGCS – Modified Glasgow Coma Scale, NDS1 – Neuro Disability Scale according to Smith et al. (2009); NDS2 – Neuro Disability Scale according to Goncalves et al. (2023)) obtained by dogs with meningoencephalitis of unknown origin (MUO), presented as the Spearman's rank correlation coefficient (R_s) with 95% confidence intervals (95% CI). Description of data.

Supplementary Material 3. Supplementary Figure 3. Distribution of scores of the neurological assessment scales (MGCS – Modified Glasgow Coma Scale, NDS1 – Neuro Disability Scale according to Smith et al. (2009); NDS2 – Neuro Disability Scale according to Goncalves et al. (2023)) in dogs that died of meningoencephalitis of unknown origin (MUO) within the first 7 days after onset of the disease (n=9) and dogs that survived the first week (n=116). Two dogs that died of complications of general anesthesia were excluded from this analysis. The green broken lines indicate the most optimal cut-off values for the scales. Sign "+" denotes the result on the scale that indicates unfavorable short-term prognosis (i.e. likely death within the first week). Sign "-" denotes the result on the scale that indicates favorable short-term prognosis (i.e. likely survival for the first week).

Supplementary Material 4. Supplementary Table 1. Details of the neurological assessment scales.

Supplementary Material 5. Supplementary Tables 2-10.

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Authors' contributions
LB was the major contributor to the references and manuscript. LB, AB, MW, MP, EG, AC, AO and TF examined the patients neurologically and collected the clinical data. LB, AB and MW assessed the patients on the scoring systems. MC analysed the data. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study has been granted an exemption from requiring ethics approval, according to the decision (9/2024) of the Animal Welfare Advisory Team Supervisor of Wroclaw University of Environmental and Life Sciences. In accordance with the Experiments on Animals Act from January 15th, 2015 (Journal of Laws of the Republic of Poland, 2015, item. 266), concerning the welfare of the animals used for research or teaching purposes, the restrictions defined in the law shall not apply to clinical veterinary studies carried out according to Article 37ah-37ak of the Act from September 6th, 2001 – Pharmaceutical Law (Journal of Laws from 2008, No. 45, item 271 as amended in item 4). Hence, ethical review and approval was not required for this animal study as the study was retrospective. Additionally, MRI and CSF examinations are standard diagnostic procedures performed in diagnosis of central nervous system diseases in companion animals. Informed written consent for all medical procedures was obtained from all owners. The animals were handled according to high ethical standards and national legislation. Decision to euthanise was made by the animal's owner in consultation with the veterinarian and performed in accordance with the national law. The medicament used (pentobarbital) is registered for euthanasia reasons and was administered IV as the second step after sedation or general anaesthesia.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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