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Clinical Risk Factors for Early Seizure Recurrence in Dogs Hospitalized for Seizure Evaluation

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Background: Epileptic seizures are a common cause for neurological evaluations in dogs.

Hypothesis/Objectives: To determine the timing, frequency, and risk factors for early seizure recurrence (ESR) among dogs admitted to the hospital for seizure evaluation and to facilitate rapid decision making about whether dogs should be placed in the intensive care unit (ICU) or day ward.

Animals: Nine-hundred twenty-two dogs referred for seizure investigation; 214 patients were included.

Methods: Retrospective study. Medical records between 2000 and 2017 were reviewed to determine risk factors for ESR. Findings were compared among dogs diagnosed with idiopathic epilepsy (IE), structural epilepsy (StE) and reactive seizures (RS), as well as in all selected cases together.

Results: Fifty percent of dogs had a seizure while hospitalized. In the group 53.1 and 52.2% in the StE group, whereas in the RS 40.44% had ESR. The average time to ESR was 7 hours. In IE group, abnormal postictal neurological examination with prosencephalon signs predicted ESR. In StE group, a single generalized or focal seizure 72 hours before hospital admission and abnormal neurologic examination predicted ESR. In the RS group, ERS was predicted by long-term antiepileptic monotheraphy. When all dogs were analyzed together, abnormal neurological examination, the occurrence of cluster seizures, status epilepticus, or combination of them 72 hours before presentation predicted ESR.

Conclusions and Clinical Importance: Epileptic seizures recurred in 50% of patients within a mean time of 7 hours. In general, when cluster seizures, status epilepticus or both occurred 72 hours before presentation and neurological examination was abnormal upon presentation, the dog should be placed in ICU for observation.

Key words: Epilepsy; Brain; Canine; ICU; Day ward.

The prevalence of idiopathic epilepsy (IE) has been estimated to be approximately 1–2% in a hospital-based population of dogs and cats in Germany,[1] 1.9% in a hospital-based population of dogs in Japan,[2] and in up to 5% of the overall canine population.[3–5] The prevalence is reported to be even higher for breeds exhibiting breed-specific genetic epilepsy,[6–9] making epilepsy 1 of the most common causes for referrals to veterinary neurologists.

Seizures frequently are associated with intracranial diseases such as neoplasia or inflammation (structural epilepsy),[10–14] but also can be a reaction to intoxication or other extracranial metabolic diseases (reactive seizures [RS]).[15] In many cases, mechanism of seizure occurrence is either genetic or unknown. In these cases, IE is a diagnosis of exclusion, based on normal interictal neurological examination, normal blood test results (tier 1 confidence level), normal magnetic resonance imaging (MRI) and normal cerebrospinal fluid (CSF) results (tier 2 confidence level) and electroencephalography results (tier 3 confidence level).[14–16] To make a diagnosis of IE, the above diagnostic evaluation is necessary. Patients often are admitted to the hospital for diagnostic testing during consultation hours or on an emergency basis. Little is known about the risk of early seizure recurrence (ESR) within the first 48 hours, and no risk factors for ESR have been identified among patients admitted to the hospital for seizure evaluation. Seizures may be detrimental, therefore, it is important to either treat them as early as possible or prevent them if possible.

Financial considerations and hospital administration play important roles for the clinical decision whether or not a canine patient admitted to the hospital for seizures should be placed in the intensive care unit (ICU) or a day ward. Our aim was, therefore, to identify patients with a high risk of seizure recurrence that should be placed in ICU. In such cases, higher hospitalization costs associated with the ICU would be justified as beneficial for the patient. Such recommendations are not available because previous studies did

Abbreviations:

MRI	magnetic resonance imaging
CSF	cerebrospinal fluid
ESR	early seizure recurrence
ICU	intensive care unit
IE	idiopathic epilepsy
RS	reactive seizures
StE	structural epilepsy
AED	antiepileptic drug
EED	electroencephalography
IVETF	International Veterinary Epilepsy Task Force

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not emphasize factors associated with the risk of seizure recurrence.[4,8]

Materials and Methods

Case Selection and Criteria

Medical records of all dogs presented to the Neurology Group, Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Germany, between 2000 and 2017 for the evaluation of seizures were retrospectively reviewed. The hospital database[a] was searched for the following words: dog, seizure, cluster seizures, status epilepticus, IE, reactive seizure, and structural epilepsy (StE). A total of 922 records was found (Figure 1).

Dogs were included in the study if they had undergone hospitalization for at least 48 hours, and if the database was complete and contained information regarding the timing and description of the last seizure episode, a neurological examination sheet, and a hospitalization sheet in which seizure occurrence was noted. Dogs must have had a diagnostic evaluation consistent with a tier 2 confidence level.[17]

The demographic data (age, breed) and clinical features of previous seizure occurrences (single generalized or focal seizure versus cluster seizures, status epilepticus), previous long-term antiepileptic treatment, and neurologic examination results were analyzed to assess potential risk factors associated with ESR. ESR was defined as a seizure recurrence during the first 48 hours postadmission.

Medical Records Review

Information obtained from the medical records data base included: history, signalment (with a focus on age and breed), and results of physical and neurological examinations. A detailed seizure description also was retrieved, including time of the last seizure event before presentation, information about whether the most recent seizure events were single, generalized focal seizures, cluster seizures, or status epilepticus; information regarding long-term antiepileptic treatment (mono- versus multidrug therapy); and, the occurrence of a seizure during hospitalization period.

An epileptic seizure was defined as excessive synchronous, usually self-limiting, epileptic activity of neurons in the brain. This activity results in a transient occurrence of signs, characterized by short episodes with convulsions of focal motor, autonomic, or behavioral features due to abnormal excessive, synchronous epileptic neuronal activity in the brain.[18] Generalized seizure was defined as event with more than minimal involvement of 2 cerebral hemispheres of tonic, clonic, or tonic-clonic character, with loss of consciousness and presence of salivation, defecation urination, or some combination of these.[18] Cluster seizures were defined as $\geq$2 seizures observed in a 24-hour period. Status epilepticus was defined as continuous epileptic seizures lasting $>$5 minutes, or $\geq$ discrete epileptic seizures between which incomplete recovery of consciousness occurred.[18]

Risk factors (variables) for ESR were as follows: age $>$6 years (H), age $<$6 months (I), presentation to the hospital on an emergency basis (J), presence of a single generalized seizure 72 hours before hospital admission (K), presence of cluster seizures, status epilepticus or both 72 hours before hospital admission (L), long-term antiepileptic monotherapy (M), long-term antiepileptic therapy, multiple drugs (N), abnormal neurological examination with prosencephalon signs including obtunded mental state and, lack of menace response (O), abnormal neurological examination with multifocal signs (P), abnormal neurological examination on presentation (Q), and abnormal neurological examination with asymmetric deficits.

A total of 214 records fulfilled the inclusion criteria Figure 1. Dogs were divided into 3 groups based on diagnosis and all 3 groups also

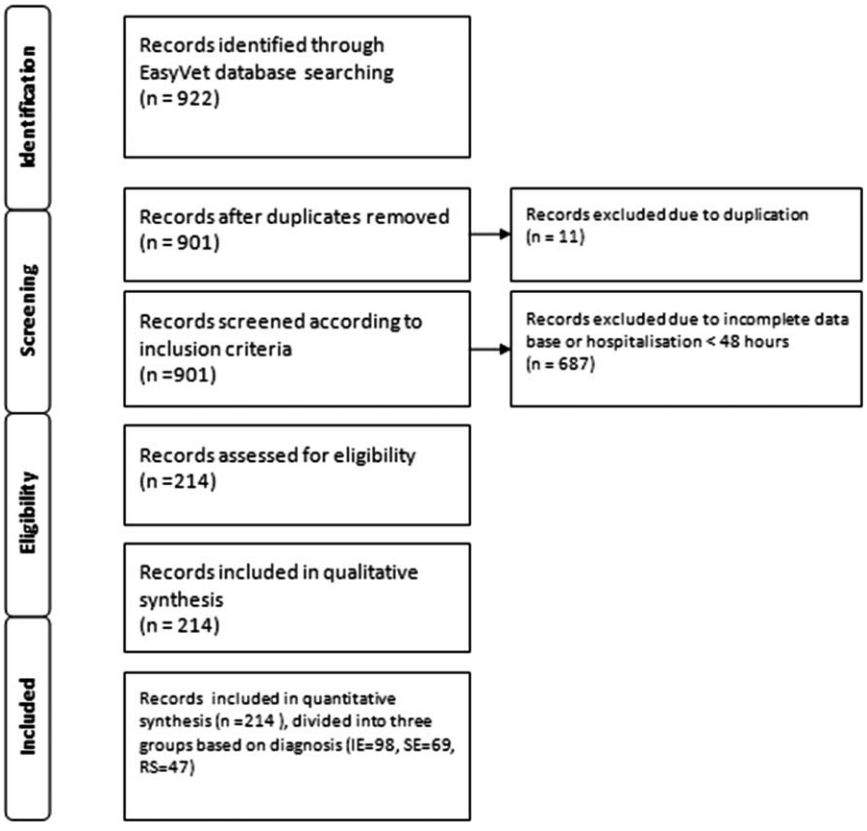

Fig 1. Study protocol for retrospective data analysis. IE, idiopathic epilepsy; StE, structural epilepsy; RS, reactive seizures.

were analyzed together. Group 1 (patients with idiopathic epilepsy IE which could be of genetic, suspected genetic, or unknown cause) consisted of 98 dogs. Diagnosis of IE was made when the dog was between 6 months and 6 years of age, had normal interictal physical and neurologic examination findings, no clinically relevant abnormalities on blood examination and urinalysis (tier 1 confidence level), and when bile acid stimulation test and MRI and CSF results were normal (tier 2 confidence level). Group 2 included 69 dogs with StE (caused by brain tumors, vascular diseases, anatomic anomalies, and immune-mediated diseases). Structural epilepsy was defined as epileptic seizures provoked by intracranial/cerebral pathology including vascular, inflammatory, infectious, traumatic, anomalous, developmental, neoplastic, or degenerative diseases confirmed by diagnostic imaging, CSF evaluation, or necropsy testing. Group 3 included 47 dogs with RS (hypoglycemia, intoxication, hepatic encephalopathy, electrolyte disorders were included). Reactive seizures were defined as seizures occurring as a natural response by the normal brain to a transient disturbances.[15,17,18]

Statistical Analysis

Data were analyzed using the software StatSoft 2011. Logistic regression was carried out to examine the relationship between ESR and potential explanatory risk factors H, I, J, K, L, M, N, O, P, Q, R. Correlation factors were established between variable G (determining if the seizure occurred) and the other variables (risk factors). When the seizure occurred in the hospital, variable G was assigned a value 1; if a seizure did not occur in the hospital, G was assigned a value of 0. Variables with $P < 0.05$ in the univariate analysis were included in the multivariate analysis. Statistical significance was set at $P < 0.05$. Data were analyzed with commercially available software program.[b]

Results

A total of 922 patient files was found as a result of the data base search. Of these patients, 214 fulfilled the inclusion criteria.

Among the 214 patients, 56 different breeds were reported. The most commonly represented breeds were as follows: 52 mixed breed dogs (51.9% of these had an epileptic seizure in the hospital), 13 Border Collies (76.9% had an epileptic seizure in the hospital), 12 Labrador Retrievers (33.3% had an epileptic seizure in the hospital), 12 Jack Russell terriers (75% had an epileptic seizure in the hospital), and 9 French bulldogs (55.5% had an epileptic seizure in a hospital).

Among 214 patients that fulfilled the inclusion criteria, 107 patients (50%) had a seizure while hospitalized. Of these 107 patients, 2 (1.8%) were below 6 months of age, 54 dogs (49.5%) were over 6 years, and 44 dogs (41.1%) were between 6 months and 6 years old. Fourteen dogs (13.0%) that experienced seizures in the hospital had been treated with a single long-term antiepileptic medication before presentation, whereas 8 dogs (7.5%) were treated with >1 long term antiepileptic medication before presentation. Twenty-six dogs (24.3%) experiencing an epileptic seizure while hospitalized had a single generalized or focal seizure 72 hours before presentation; 76 dogs (71.0%) experienced cluster seizures, status epilepticus, or both before hospital admission.

Upon neurological consultation, 65 dogs (60.7%) had an abnormal neurologic examination with prosencephalon signs, 16 dogs (15%) had multifocal intracranial deficits, 80 dogs (74.8%) had an abnormal neurological examination, and 15 dogs (14.0%) had an abnormal neurological examination with asymmetric deficits.

The 214 dogs in the study were divided into 3 different groups according to diagnosis. A total of 98 dogs (45.8% of the study group) were diagnosed with IE (tier 1 and tier 2 confidence levels), and 52 patients within this group (53.1%) experienced seizure recurrence. A total of 69 dogs (32.2%) were diagnosed with StE and 36 (52.2%) of these dogs had a seizure recurrence while hospitalized. Reactive seizures were diagnosed in 47 patients (22%) and 19 (40.4%) of these patients had a seizure while hospitalized. In dogs diagnosed with structural epilepsy that experienced seizure recurrence while hospitalized, the most common causes were intracranial neoplasia (62%), vascular inflammatory immune-mediated brain disease (35%), and the reminder consisted of vascular diseases and anatomic anomalies. Among dogs with reactive seizures, the conditions most commonly associated with seizure recurrence included hypoglycemia, electrolyte imbalances including calcium disorders, intoxications, and hepatic encephalopathy.

In the group with IE, 1 variable predicted the risk of ESR: abnormal neurologic examination with prosencephalon signs. In the StE group, the following variables predicted ESR: abnormal neurological exam, regardless of neurolocalization and symmetry, and a single generalized or focal seizure 72 hours before hospital admission. In the reactive seizure group, long-term antiepileptic monotherapy predicted ESR.

When all dogs were analyzed together (regardless of the underlying cause and diagnosis), the following variables predicted ESR: abnormal neurological examination (symmetric or asymmetric, multifocal, prosencephalon deficits) (Table 1).

The average time to recurrence of epileptic seizure was 7 hours after hospital admission. In 90% of cases, seizures recurred in the first 12 hours after hospital admission. In the remaining 10% of cases, the seizure recurred 12–48 hours after admission. Seizures recurred earliest in the reactive seizure group (average time, 3.8 hours after admission). In patients with StE, the average time to recurrence was 6.3 hours, whereas in the IE group the average time was 10.9 hours (Table 2).

Discussion

The purpose of our study was to investigate the rate, time, and probability of ESR and to identify risk factors related to the cumulative probability of recurrence within 48 hours. There are no guidelines based on clinical history and neurological examination that would guide a clinician's decision whether a patient should be placed in the ICU for observation or if the dog could be placed in a day ward during this hospitalization. This decision has an impact on patient health but also on the finances.

Seizures result from spontaneous excessive electrical discharges from a group of neurons in the cerebral cortex, and are caused by any mechanism that will disrupt the balance between neuronal excitation and inhibition. After neurons undergo a paroxysmal depolarization shift, a cascade of

Table 1. Occurrence of risk factors, expressed as %, among each group. Risk factors predicting seizure in each group are marked bold.

Risk Factors		IE, $n = 98$ %	StE, $n = 69$ %	RS, $n = 47$ %	All dogs, $n = 214$ %
H	Age <6 months (at the time of presentation)	0	1.4	14.9	4.7
I	Age >6 years	14.3	81.2	55.3	44.9
J	Presented as emergency	53.1	72.5	80.9	65.4
K	Single generalized or focal seizure 72 hrs before hospital admission	22.4	**29.0**	40.4	28.5
L	CS or SE 72 hrs before hospital admission	64.3	623	51.1	**60.7**
M	Long-term antiepileptic monotherapy	26.5	7.2	**8.5**	16.4
N	Long therapy antiepileptic therapy, multiple drugs	12.2	2.9	0	6.5
O	Abnormal neurological examination with prosencephalon signs	**58.2**	44.9	53.2	51.4
P	Abnormal neurological examination with a multifocal localization	0	29	12.8	12.1
Q	Abnormal neurological examination	59.2	**69.6**	59.6	**61.7**
R	Abnormal neurological examination with asymmetric deficits	0	23.2	2.1	7.9

IE, idiopathic epilepsy; StE, structural epilepsy; RS, reactive seizures group; ALL, all dogs analyzed together; %, percentage of dogs that experienced seizure recurrence and in which risk factor occurred; CS, cluster seizures; SE, status epilepticus.

cellular events occurs (eg, calcium cell influx, opening of sodium-gated channels) leading to repolarization and depolarization; if sustained, these changes can lead to irreversible cell damage and death.[16,19] Prolonged seizure activity in primates has been shown to cause damage in several brain areas, caused by neuronal cell necrosis, gliosis, and network reorganization leading to mirror epileptic focus formation or enlargement of the existing focuse.[20–23] The impact of seizures on brain function in the interictal phase may be important and occasionally can be identified using MRI.[24] In the canine brain, it has been documented that neuronal necrosis becomes more prominent and severe the longer seizure activity lasts. Therefore, it is of utmost importance for clinicians to prevent additional seizures during hospitalization.

In our study, the ESR rate was 50%, which leads to the conclusion that every other dog admitted to the hospital for seizure evaluation is at risk of experiencing seizure events, regardless of the underlying cause. Interestingly, in a recent study of reflex epilepsy, visits to the veterinary clinic were reported to be a possible trigger.[25] We cannot rule out that stress associated with a visit to the veterinary hospital leads to an increase in blood catecholamine and cortisol concentration. Panting leading to hypocapnia also may be a contributing factor inducing new seizure events.[26] Hypocapnia causes increased excitability of neurons that lowers seizure threshold, decreases brain-oxygen concentration and increases cellular acidity, decreases glucose availability for the brain by worsening control of blood glucose concentration, and decreases ability to resist stress caused by a weakened immune system.[26] Hypocapnia is a common sequel known in people in which stress-related seizures may occur,[26] and could have contributed in our study to the high ESR in dogs. A similar mechanism might have been a cause of ESR in dogs that have experienced seizures before hospitalization and suffered from cardiogenic pulmonary edema. A prospective study investigating the influence of sympathetic nervous system activation during status epilepticus or seizure activity on cardiopulmonary function in dogs to establish if catecholamines, cortisol, CO_2, O_2, or presence of pulmonary edema may have an influence on the ESR would be beneficial for better seizure treatment and management. Another question should be asked if cardiomyocytes may would be beneficial for better ESR understanding undergo damage as a result of repetitive seizure activity. Investigations on cardiac muscle injury markers for example, troponine I, ST segment elevation, and depression, alteration in QT intervals could help to determine if dogs undergoing repetitive seizures may benefit from medications supporting cardiac muscle function.

Table 2. Risk factors for early seizure recurrence (ESR) among each group and time of seizure recurrence.

	Selected Risk Factors	Mean Time of ESR (hours)	Minimal and Maximal Time for ESR (hours)
IE—idiopathic epilepsy group	• Abnormal neurologic examination with prosencephalon signs	10.9	1–41
StE—structural epilepsy group	• Abnormal neurological examination (symmetric or asymmetric multifocal, prosencephalon deficits) • Single generalized or focal seizure 72 hours before hospital admission	6.3	3–22
RS—reactive seizure group	• Long-term antiepileptic monotherapy	3.8	1–18
All dogs analyzed together	• Abnormal neurological examination (symmetric or asymmetric multifocal, prosencephalon deficits)	7	1–41

Early seizure recurrence rate in the human hospital population is reported to be between 30 and 65%,[27] which is similar to the rate observed in our study in dogs.

Dogs diagnosed with IE had the highest seizure recurrence rate (53.1%). The most strongly correlated risk factor was an abnormal postictal neurologic examination with prosencephalon signs. This finding is not surprising because cognitive deficits, motor deficits, postictal automatism, and vegetative signs all can be seen in the postictal period.[28,29] Among postictal cognitive deficits, the most commonly reported are visual deficits and abnormal alertness. In the veterinary patient, these are frequently detected as a lack of menace response, bumping into objects, and mentation changes.[28,30,31] In humans, the duration and severity of the postictal phase may depend on the preictal cognitive functioning level.[32] In humans, it also has been noted that the duration of postictal motor signs correlates with the presence of ictal motor signs.[33] In dogs, which have been discussed as a translational model for human epilepsy,[34] some also have longer postictal deficits than others and these dogs may be at higher risk of seizure recurrence when presented to the veterinary hospital. In our patients, seizures recurred at an average of 10.9 hours after presentation. Therefore, it is recommended to hospitalize these patients in the ICU for the first 24 hours.

In the group of dogs diagnosed with StE, the seizure recurrence rate was 52.2%. Seizures recurred at a mean time of 5.3 hours after presentation. Thus, clinicians should consider placing dogs in the ICU when any of the following risk factors are identified: abnormal neurologic examination (with any deficits observed) and a single generalized or focal seizure within the 72 hours before admission to the hospital.

Brain tumors are a well-known underlying cause for seizures, and seizures are the most common presenting signs.[10–12,15,29] In 1 report, 61.8% of dogs suffering from intracranial neoplasia developed seizures.[8] In another report, 51% of dogs with intracranial neoplasia developed seizures,[9] whereas other studies reported a seizure rate of 45% in dogs with intracranial neoplasia.[29,35] All of the above-mentioned studies found higher seizure activity rates than that observed in our study, but our study focused on short-term seizure recurrence in dogs that already had experienced a seizure before consultation. Interestingly, another study found that seizure severity in more than half of the dogs with intracranial neoplasia progressed to cluster seizures by the time the dogs underwent MRI[8] partly explaining our finding that abnormal neurologic examination with predominance of prosencephalon signs is a risk factor for seizure recurrence.

The reasons behind the abnormal neurologic examination and the mechanisms that promote tumor-related seizure activity most likely are multifactorial.[29,35,36] Neoplastic tissue can be an initiation site of seizure activity, particularly with gliomas.[8–10] Additionally extra- and intra-axial masses may alter surrounding brain tissue by the effect of peritumoral edema, leading to increased intracranial pressure, chaotic, and unbalanced vascular organization leading to vascular insufficiency or hemorrhage, hypoxia, peritumoral inflammation, and the release of metabolically active molecules.[8–10,36] Interestingly, the risk factor selected was an abnormal neurological examination with a predominance of prosencephalon signs rather than an abnormal neurological examination with asymmetric deficits or with deficits associated with a multifocal lesion. Thus, changes in the peritumoral microenvironment might promote ESR. Little data is available on seizure recurrence rates and times in dogs with immune-mediated brain diseases, but dogs presented with seizures, status epilepticus, or both decreased survival times.[12,29] Knowing what risk factors may increase the likelihood of seizure recurrence in a hospitalized population might further stimulate clinicians to start seizure treatment sooner. Cerebro-vascular accidents (ischemic and haemorrhagic) are known to cause sudden onset of disease, and affected patients also may present with seizures as the first neurologic sign. Vascular diseases frequently are localized in the cerebellum.[3,30] Therefore, these patients may present with signs of ataxia rather than seizures. No data in the veterinary literature describe seizure recurrence in these patients. In human literature, the risk factor that has been associated with a seizure recurrence in patients with vascular brain disease was the size of the hematoma, in patients suffering from intracerebral hemorrhage.[29] In our study, the number of dogs with vascular diseases was not large enough to obtain reliable data on ESR.

In the reactive seizure group, 40.4% of patients showed seizure activity within 48 hours of hospitalization. The mean recurrence time was 2.8 hours in this group, which is earlier than observed in other groups. All of the seizures observed in this group recurred within 12 hours of admission time. This is not a surprising finding, because 12 hours is an adequate time to obtain laboratory and imaging results in order to make a diagnosis and initiate appropriate treatment. The most significant risk factor in this group was long-term antiepileptic monotherapy, which might have been due to the fact that these dogs were not diagnosed correctly and had been treated symptomatically for seizures without addressing the underlying disease.

In dogs with RS, an abnormal neurological examination with asymmetric deficits was not a risk factor as expected, because dogs suffering from the RS are expected to have symmetrical signs.[30] However, abnormal neurological examination with multifocal or prosencephalon signs also was not a risk factor. Dogs suffering from RS were reported to have 1.57 higher odds of developing status epilepticus than dogs with IE and also were reported to have interictal neurological deficits, as substances constantly influence the nervous system by various ways, such as interfering with energy metabolism, osmolality, and acid base balance; decreasing inhibition; increasing excitation; and, inducing the production of endotoxin.[13,31] Among all groups, this group was the smallest because many cases did not fulfill the inclusion criteria (they were not hospitalized for 48 hours because they either were euthanized because of poor prognosis or the observation period in the hospital was even shorter). Evaluating dogs with RS and <48 hours of observation time may alter the trends observed in this study.

Our study had several limitations. First, some bias may be intrinsic to the retrospective design because patients with incomplete data had to be excluded. Because these are

unavoidable limitations of a retrospective study, a prospective study using a registry would be needed in the future, which should ideally be a multicenter study to include more patients. Such a large study could provide more accurate data regarding breed as a risk factor of ESR. Second, some patients that were staying in the day ward might have experienced unobserved seizures resulting in potentially lower ESR than reported in our study. The timeline of the study (2000–2017) also might have been a limitation as a consequence of possible changes in seizure treatment protocol (eg, introduction of IV levetiracteam for seizure treatment). Another limitation may be a fact that owners do not always witness their dogs' seizures because their dogs are not under constant surveillance. This fact might have falsely lowered the percentage of the following risk factors: presence of single generalized seizure 72 hours before hospital admission (K), and presence of clusters seizures, status epilepticus, or both 72 hours before hospital admission (L).

We analyzed all dogs together to evaluate for risk factors that could be identified on presentation, especially in the context of a referring veterinary practice with less experience in neurological consultations and also because of the fact that it usually takes time to obtain a final diagnosis The identified risk factors that should attract a clinician's attention and guide the decision to place the dog in ICU or to refer the dog to a specialist were abnormal neurological examination and presence of cluster seizures, status epilepticus, or both. Although the financial cost should not dictate the clinician's choice, the truth is that it does in many cases, because ICU hospitalization often is much more expensive than day ward care. In human medicine, the estimated cost of inpatient admission because of epileptic seizures is 4 billion dollars a year.[28] No financial data are available for veterinary medicine, but, in a Swedish population of insured dogs, 5013 claims were submitted for canine epilepsy between 1995 and 2006, accounting for 0.75% of all received claims upper index 37. In conclusion, our study helps to justify the higher ICU hospitalization cost when discussing treatment options with owners, especially in cases of dogs showing the described risk factors.

Footnotes

[a] EasyVet software, VetZ GmbH, Isernhagen, Germany
[b] Statistica 13, Zestaw plus (Krakow, Poland)

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Institutional Animal Care and Use Committee (IACUC) or Other Approval Declaration: Authors declare no IACUC or other approval was needed.

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