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ORIGINAL ARTICLE – CLINICAL

Prognostic factors for short-term survival of dogs that experience postattenuation seizures after surgical correction of single congenital extrahepatic portosystemic shunts: 93 cases (2005-2018)

Ronan A. Mullins MVB, DECVS[1] | Carlos Sanchez Villamil DVM[1] | Laura E. Selmic BVetMed (Hons) MPH, DACVS-SA, DECVS[2] | Michael S. Tivers BVSc (Hons) PhD, DECVS[3] | J. Brad Case DVM, MS, DACVS[4] | Ameet Singh BSc, DVM, DVSc, DACVS[5] | Kelley M. Thieman Mankin DVM, MS, DACVS[6] | Davina M. Anderson MA, VetMB, PhD, DSAS(ST), DECVS[7] | Robert N. White BSc (Hons), BVetMed, DSAS(ST), DECVS, SFHEA[8,9] | Kathryn M. Pratschke MVB, MVM, DECVS[10] | Hilde de Rooster DVM, MVM, PhD, DECVS[11] | Anne Kummeling DVM, PhD, DECVS[12] | Donald A. Yool BVMS, PhD, DECVS, SFHEA[13] | Melanie Olive DVM[14] | Jean-Philippe Billet Dr vét DECVS[14] | Ines Gordo DVM, MS[15] | Herve Brissot DV, DECVS[15] | Cameron Broome BVSc (Hons), DVCS, FANZCVS[10] | Barbara M. Kirby DVM, MS, DACVS, DECVS[1]

[1]Section of Veterinary Clinical Sciences, University College Dublin, Belfield, Dublin, Ireland

[2]Department of Veterinary Clinical Sciences, The Ohio State University, Columbus, Ohio

[3]Bristol Veterinary School, University of Bristol, Langford House, Langford, Bristol, United Kingdom

[4]Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, Florida

[5]Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Ontario, Canada

[6]Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Texas

[7]Anderson Moores Veterinary Specialists, Hursley, Winchester, United Kingdom

[8]Willows Veterinary Centre and Referral Service, Solihull, West Midlands, United Kingdom

[9]School of Veterinary Medicine & Science, University of Nottingham, Sutton Bonington Campus, Loughborough, United Kingdom

[10]University of Glasgow, School of Veterinary Medicine, Bearsden, Glasgow, United Kingdom

[11]Small Animal Department, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

[12]Department of Clinical Sciences, Faculty of Veterinary Medicine, Utrecht University, The Netherlands

[13]The Royal (Dick) School of Veterinary Studies, Easter Bush Campus, Midlothian, Edinburgh, United Kingdom

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[14]Centre Hospitalier Vétérinaire Atlantia, Nantes, France

[15]Pride Veterinary Centre, Derby, Derbyshire, United Kingdom

Correspondence: Ronan A. Mullins, Section of Veterinary Clinical Sciences, University College Dublin, Belfield, Dublin 4, Ireland.
Email: ronan.mullins@ucd.ie

Present address
Dr. Tivers, Paragon Veterinary Referrals, Paragon Business Village, Red Hall Crescent, Wakefield, WF1 2DF, United Kingdom
Dr. Broome, Veterinary Referral Hospital, Melbourne, Victoria, Australia
Dr. Yool, University of Glasgow Small Animal Hospital, School of Veterinary Medicine, College of Medical, Veterinary & Life Sciences, 464 Bearsden Road, Glasgow G61 1QH
Dr. Sanchez Villamil, Department of Clinical Science and Services, Royal Veterinary College, University of London, London, United Kingdom
Dr. Brissot, Azurvet, Saint-Laurent-du-Var, France

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Abstract

Objective: To identify prognostic factors for short-term survival of dogs that experience seizures within 7 days after surgical correction of single congenital extrahepatic portosystemic shunts (cEHPSS).

Study design: Multi-institutional retrospective study.

Sample population: Ninety-three client-owned dogs.

Methods: Medical records at 14 veterinary institutions were reviewed to identify dogs that underwent surgical attenuation of a single cEHPSS from January 1, 2005 through February 28, 2018 and experienced postattenuation seizures (PAS) within 7 days postoperatively. Logistic regression analysis was performed to identify factors associated with 1-month survival. Factors investigated included participating institution, signalment, shunt morphology, concurrent/historical conditions, presence of preoperative neurologic signs, presence of preoperative seizures, aspects of preoperative medical management, surgical details including method and degree of shunt attenuation, type of PAS (focal only or generalized ± focal), drugs administered as part of the treatment of PAS, and development of complications during treatment of PAS.

Results: Thirty (32.3%) dogs survived to 30 days. Seventy-six (81.7%) dogs experienced generalized PAS. Factors positively associated with short-term survival included having a history of preoperative seizures ($P = .004$) and development of focal PAS only ($P = .0003$). Most nonsurvivors were humanely euthanized because of uncontrolled or recurrent seizures.

Conclusion: Dogs that experienced PAS that had a history of preoperative seizures and those that experienced focal PAS only had significantly improved short-term survival.

Clinical significance: The results of this study provide information that will help in the counseling of owners who seek treatment for PAS after surgical correction of cEHPSS.

1 | INTRODUCTION

Development of postattenuation seizures (PAS) is a well-recognized complication of surgical correction of portosystemic shunts in dogs,[1-26] with often fatal consequences.[1-3,8-10,12,15,18,21,22] These seizures have an incidence of up to 4.7%–8.1% reported in the recent literature[18,21,22] and occur almost exclusively within 5 days postoperatively.[1-26] The etiopathogenesis of PAS is not well understood. Proposed theories include a decline in systemic concentrations of endogenous benzodiazepines/benzodiazepine-like substances, hypoglycemia, electrolyte derangements (hypocalcemia and hypokalemia), hypoxemia, exacerbation of hepatic encephalopathy, an unknown perioperative metabolic event, sudden correction of an adapted to altered metabolic state, systemic hypertension, concurrent brain disease, intraoperative hypotension, and prolonged surgical and anesthetic times.[2,3,9,10,21,23,27] However, none of these has been consistently identified in previous studies.[1-25] For instance, PAS have been reported in the face of normal to only mildly elevated ammonia concentrations[2,7,9,10,17,20,22] and normal glucose[7-10,17,20,21,23] and electrolyte concentrations.[17,20]

Large-scale studies in which risk factors for PAS have been investigated are lacking.[9,22] In a recent study by Strickland et al,[22] increasing age and the presence of hepatic

encephalopathy immediately preoperatively were identified as risk factors for postoperative neurologic signs and seizures. Occurrence of PAS has not been definitively shown to be associated with shunt morphology (intrahepatic or extrahepatic or individual submorphologies), presence of preoperative seizures, or method or degree of shunt attenuation.[2,3,6,9,11,14-19,21,22] Certain breeds have been suggested as being at greater risk of PAS including pugs,[6,9,23] Maltese terriers,[1,2] and Jack Russell terriers.[14]

On the basis of a limited number of case reports, small case series, and isolated cases within retrospective studies, a guarded prognosis is typically provided after development of PAS.[1-3,8-10,12,15,18,21,22] The largest cohort of dogs affected by PAS in a published study (in which 12 dogs with PAS were described) was reported by Strickland et al.[22] In that study,[22] which included dogs with congenital extrahepatic portosystemic shunts (cEHPSS) and congenital intrahepatic portosystemic shunts (cIHPSS), only seven of 12 dogs that experienced PAS survived to discharge. A number of authors, however, have reported a more favorable prognosis.[7,17,20,21] In one study,[21] dogs that experienced PAS that had a history of preoperative seizures had improved survival compared with those that had not had a history of preoperative seizures. There are also reports of a more favorable outcome after treatment of PAS with administration of continuous rate infusion (CRI) of propofol.[7,17,20] A limitation of these reports, however, has been the small study samples and the fact that other antiepileptic drugs were administered concurrently with propofol CRI, which makes interpretation difficult.

The objective of the study reported here was to identify prognostic factors for short-term survival of dogs that experienced PAS within 7 days after surgical correction of single cEHPSS. We hypothesized that, having received prophylactic levetiracetam (LEV), treatment of PAS with propofol CRI, having experienced PAS/undergone surgery in the second half of the study period and development of focal PAS only would be positively associated with short-term survival.

2 | MATERIALS AND METHODS

2.1 | Inclusion and exclusion criteria

Medical records at 14 institutions were retrospectively reviewed to identify dogs that underwent surgical attenuation (suture ligation [SL], thin film banding [TFB], or ameroid ring constrictor [ARC] placement) of a single cEHPSS from January 1, 2005 through February 28, 2018 and experienced PAS within 7 days postoperatively. Exclusion criteria included dogs with cIHPSS, dogs that did not undergo shunt attenuation because of apparent concurrent portal vein aplasia, and dogs that were lost to follow-up prior to 30 days postoperatively. Dogs that experienced onset of seizure activity after 7 days postattenuation were excluded.

2.2 | Data collection

Data retrieved from medical records of dogs that met inclusion criteria included breed, age, sex/neuter status, and bodyweight at surgery; year of surgery; shunt morphology (portocaval, portoazygos or portophrenic); concurrent/historical conditions at presentation; presence and type of preoperative neurologic signs and seizures; abnormal preoperative physical examination findings; method of shunt identification (abdominal ultrasound, computed tomography angiography [CTA], magnetic resonance imaging [MRI], intraoperative portovenography [IOPV], nuclear scintigraphy); details of preoperative medical management; prophylactic LEV or other antiseizure medications; method (SL, TFB or ARC) and degree (complete, partial, or none) of acute intraoperative shunt attenuation; timing and type of PAS (focal only or generalized ± focal); electrolyte (sodium, potassium and chloride), glucose, and ammonia concentrations about the time of PAS occurrence; antiseizure medications administered as part of treatment of PAS; complications experienced during treatment of PAS; and whether the dog survived to 1 month. Regarding preoperative medical management, dogs were recorded as having received at least 1 week's duration of preoperative lactulose or not and at least 1 week's duration of antimicrobials or not. Preoperative diet type was also recorded. Dogs were divided into four groups with respect to prophylactic treatment with LEV: received no LEV (LEV^{-}); received LEV at ≥20 mg/kg every 8 hours for ≥24 hours preoperatively or 60 mg/kg IV loading dose of LEV perioperatively, and continued at ≥20 mg/kg every 8 hours postoperatively (LEV1); received LEV at <20 mg/kg every 8 hours for <24 hours preoperatively, or continued at <20 mg/kg every 8 hours postoperatively (LEV2); and received LEV postoperatively only (but prior to postoperative seizure activity) according to the same preoperative protocol of group LEV1 (LEV3). Short-term survival was defined as survival to 30 days. For dogs that did not survive to 30 days, whether the dog had died naturally or had been humanely euthanized and the cause/reason were recorded. A complication was defined as any unanticipated event that altered the course of PAS treatment.

2.3 | Statistical analyses

Continuous variables were tested for normality by using graphical methods, skewness, kurtosis, and Shapiro–Wilk

test. Normally and nonnormally distributed continuous variables were presented as mean and SD and median and range, respectively. Categorical variables were presented as frequency and percentages (with 95% confidence interval [CI]). Comparison of electrolyte, glucose, and ammonia concentrations between survivors and nonsurvivors and dogs with and without a history of preoperative seizures were made by using the independent samples *t* test or Mann–Whitney *U* test, depending on normality of the data. Univariable logistic regression analysis was performed to assess for factor association with 1-month survival. Factors assessed included contributing institution, breed, sex/neuter status, age, and bodyweight at surgery; year of surgery; shunt morphology; presence of preoperative neurologic signs; presence of preoperative seizure activity; presence of concurrent/historical conditions at presentation; whether the dog received a minimum of 1 week's duration of preoperative lactulose; whether the dog received a minimum of 1 week's duration of preoperative antimicrobials; LEV group (LEV^{-}, LEV1, LEV2 or LEV3); method of shunt attenuation and degree of acute intraoperative shunt attenuation (complete, partial or none); whether the dog developed generalized or focal PAS only; and whether the dog experienced a complication during treatment of PAS. The second half of the study period was defined as January 1, 2012 onward. Additional factors that were assessed included treatment of PAS with propofol CRI, alfaxalone CRI, benzodiazepine, LEV, phenobarbital, potassium bromide, α-2 agonist, gabapentin/pregabalin, flumazenil, and mannitol. Multivariable logistic regression analysis was performed to assess all variables identified with $P < .2$ in the univariable analysis. Backward selection was used with a retention α of .05 for variables to be retained in the model. This allowed calculation of adjusted odds ratios and 95% CI. Statistical analysis was performed in SAS version 9.4 (SAS Institute, Cary, North Carolina). Statistical significance was set at $P < .05$.

3 | RESULTS

Ninety-three dogs were included in the study. Details of 75 dogs are the subject of another report. Details of 16 dogs have partially been reported previously.[17,18,20,21,26]

3.1 | Signalment

Breeds included mixed breed (n = 18), Yorkshire terrier (n = 15), bichon frise (n = 12), pug (n = 9), shih tzu (n = 8), Maltese terrier (n = 6), Jack Russell terrier (n = 6), miniature schnauzer (n = 5), Chihuahua (n = 4), dachshund (n = 3), West Highland white terrier (n = 2), and one each of Norfolk terrier, border terrier, Brussels griffon, Coton De Tulear, and setter. There were 31 (33.3%) spayed females, 13 (14.0%) intact females, two (2.2%) unspecified females, 28 (30.1%) castrated males, and 19 (20.4%) intact males. Median (range) age was 34 (5-124) months. Median (range) weight was 6 (1.4-21.0) kg.

3.2 | Year of surgery

Thirty-three (35.5%) dogs experienced PAS from January 2005 through December 2011 (first half of study period), and 60 (64.5%) dogs experienced PAS from January 2012 through February 2018.

3.3 | Historical neurologic signs and seizures

Preoperative neurologic signs were recorded in 73 of 93 (78.5%) dogs. Preoperative seizures were recorded in 16 of 93 (17.2%) dogs. The most common neurologic signs included reduced mentation (n = 46), pacing/wandering/compulsive walking (n = 15), ataxia (n = 12), abnormal behavior/behavior change (n = 11), head pressing (n = 9), hypersalivation/drooling (n = 9), circling (n = 8), disorientation (n = 5), and four each of increased/inappropriate sleeping/sleepy, apparent blindness, and weakness.

3.4 | Concurrent/historical conditions at presentation

Concurrent/historical conditions at presentation were recorded in 27 of 93 (29.0%) dogs and most commonly included urolithiasis (n = 19); urinary tract infection (n = 8); cardiac murmur (n = 4); unspecified brachycephalic airway syndrome; and one each of urinary sediment/crystalluria, pattern baldness, distichiasis, and cryptorchidism. Two dogs had previously undergone cEHPSS attenuation 7 and 16 months prior but did not experience PAS after initial surgery.

3.5 | Method of shunt identification and morphology

Shunts were identified preoperatively by ultrasonography (n = 75), CTA (n = 31), nuclear scintigraphy (n = 3), and/or MRI (n = 1). Seventeen dogs underwent IOPV. Shunt morphology was available for 89 of 93 (95.7%) dogs and included portocaval (n = 67), portoazygos (n = 16), and portophrenic (n = 6).

3.6 | Preoperative medical management

Ninety-one (97.8%) dogs received preoperative medical management, which included combinations of antimicrobials, lactulose, and a protein-restricted diet. One dog did not receive preoperative medical management. For the remaining dog, this information could not be confirmed. Seventy-eight (83.9%) dogs received at least 1 week of preoperative antimicrobial. Eighty-one (87.1%) dogs received at least 1 week of preoperative lactulose. Fifty-seven dogs received a prescription hepatic diet, eight dogs received an unspecified protein-restricted diet, and five dogs received a protein-restricted renal diet. Other diets included hypoallergenic (n = 3), vegetarian (n = 2), homemade protein-restricted (n = 2); one dog received a gastrointestinal diet, and one dog received a homemade chicken and vegetable diet. For the remaining dogs, the type of diet was not recorded.

3.7 | Prophylactic LEV or other antiseizure medications

Fifty (53.8%) dogs had received prophylactic LEV. One of these dogs had received additional prophylactic treatment with phenobarbital (3 mg/kg every 12 hours) and potassium bromide (8 mg/kg every 24 hours) for 3 months preoperatively. Forty-three (46.2%), 22 (23.7%), 25 (26.9%) and three (3.2%) dogs were included in groups LEV^{-}, LEV1, LEV2 and LEV3, respectively.

3.8 | Preoperative physical examination findings

Preoperative physical examination findings were available for 86 of 93 (92.5%) dogs. Abnormal findings were recorded in 48 of 86 (55.8%) dogs and most commonly included reduced/altered mentation/lethargy (n = 22), underweight/suboptimal body condition (n = 16), small stature (n = 7), ataxia (n = 6), circling (n = 4), pacing/wandering (n = 3), and cardiac murmur (n = 3).

3.9 | Method and degree of shunt attenuation

Shunts were attenuated by using TFB (n = 36: partial attenuation [n = 20], no attenuation [n = 16]), ARC (n = 33: no attenuation [n = 33]), SL (n = 23: complete attenuation [n = 20], partial attenuation [n = 3]), and combination of TFB and suture (n = 1: partial attenuation [n = 1]).

TABLE 1 Electrolyte, ammonia, and glucose concentrations of all affected dogs

Parameter	Overall, n = 93	Survivors, n = 30	Nonsurvivors, n = 63	*P*-value	Dogs with history of preop seizure activity, n = 16	Dogs with no history of preop seizure activity, n = 77	*P*-value
Sodium (mmol/l), median (range)	143.5 (135.1-171.0), n = 44 Recorded as normal, n = 3	144.0 (137.0-155.0), n = 17	142.5 (135.1-171.0), n = 27	.81	144.4 (137.0-151.4), n = 11	143.0 (135.1-171.0), n = 33	.44
Potassium (mmol/l), mean ± SD	4.0 ± 0.4, n = 44 Recorded as normal (n = 3)	4.1 ± 0.5, n = 17	4.0 ± 0.4, n = 27	.69	4.1 ± 0.7, n = 11	4.0 ± 0.3, n = 33	.82
Chloride (mmol/l), mean ± SD	114.4 ± 6.2, n = 33 Recorded as normal, n = 2 Recorded as high, n = 1	114.6 ± 3.5, n = 14	114.2 ± 7.7, n = 19	.81	115.1 ± 4.8, n = 8	114.1 ± 6.7, n = 25	.70
Ammonia (μmol/l), median (range)	32.3 (0.0-261.6), n = 38 Recorded as within normal limits (n = 6) Recorded as high (n = 1)	28.8 (5.0-93.0), n = 14	39.5 (0.0-261.6), n = 24	.35	46 (13.0-104.0), n = 6	32.3 (0.0-261.6), n = 32	.60
Glucose (mmol/l), median (range)	5.3 (1.1-11.1), n = 50 Recorded as normal (n = 2)	5.5 (2.4-7.2), n = 20	5.2 (1.1-11.1), n = 30	.40	5.8 (3.9-7.2), n = 10	5.2 (1.1-11.1), n = 40	.13

Abbreviation: Preop, preoperative.

3.10 | Type and timing of PAS

Seventy-six (81.7%) dogs were recorded as having developed generalized PAS, while 17 (18.3%) dogs developed focal PAS only. Among the 76 dogs that experienced generalized PAS, 13 (17.1%) were recorded as having experienced focal PAS that later progressed to generalized despite treatment. Postattenuation seizures commenced after a median (range) of 48 (3-144) hours postoperatively. Seventy-three (78.5%) dogs developed PAS while hospitalized. Twenty (21.5%) dogs displayed neurologic signs/commenced seizure activity postdischarge.

3.11 | Electrolyte, glucose, and ammonia concentrations at the time of PAS

Electrolyte, glucose, and ammonia concentrations overall (when available), among survivors and nonsurvivors and dogs with and without a history of preoperative seizures

TABLE 2 Reason for euthanasia, cause of natural death, and complications during treatment of PAS

Event	Explanation
Cause of natural death[a]	Cardiorespiratory arrest, n = 5 Aspiration pneumonia, n = 1 Suspect cerebrocortical necrosis secondary to severe hypernatremia and hyperchloremia, n = 1 Spontaneous death, n = 1 Heart failure, pulmonary edema, n = 1
Reason for euthanasia[a]	Uncontrolled or recurrent seizures, n = 24 Persistent seizures and poor prognosis, n = 8 Uncontrolled seizures ± financial limitations to ascertain whether seizures would eventually cease, n = 5 Respiratory arrest, n = 2 Poor mentation, n = 1 Blind, unable to stand, welfare concerns, n = 1 Disorientated, vocalizing, and nonresponsive, n = 1 Seizures, suspected aspiration pneumonia, n = 1 Seizures, hypoventilation, and poor prognosis, n = 1 Seizures, unresponsive, and fulminant liver failure, n = 1 Suspected portal hypertension, n = 1 Aspiration pneumonia, n = 1 Uncontrolled neurologic signs, n = 1 Uncontrolled seizures and pulmonary edema, n = 1 Unsuccessful reanimation, n = 1 Seizures, coma, n = 1
Complications during treatment of PAS	Aspiration pneumonia, n = 4 Pyrexia, respiratory arrest and aspiration pneumonia, n = 1 Aspiration pneumonia and suspect thromboembolic event, n = 1 Acute renal failure, cardiogenic edema, and pneumonia, n = 1 Repeated respiratory arrest, n = 1 Hypoventilation requiring mechanical ventilation, n = 1 Hypoventilation requiring mechanical ventilation, suspected vagal event, hypertension and tachycardia, respiratory arrest, n = 1 Fulminant liver failure, n = 1 Hyperthermia, tachycardia, hematochezia suspected related to portal hypertension, no mesenteric congestion at revision coeliotomy, n = 1 Sepsis suspected to be associated with gastrostomy tube, n = 1 Sepsis, systemic inflammatory response syndrome, disseminated intravascular coagulation, suspect pneumonia, requirement for mechanical ventilation, n = 1 Pulmonary edema, n = 1 Pulmonary edema, hypothermia, and hyperthermia, n = 1

Abbreviation: PAS, postattenuation seizure.

[a]Not recorded if died or euthanized (n = 3).

TABLE 3 Univariable regression analysis of variables potentially associated with survival to 30 days

Variable	Category[a]	n	%[a]	Survivors, n[a]	Nonsurvivors, n[a]	*P*-value
Center						.48
Age	Median (range), mo	93	34 (5-124)	34.5 (5-64)	34 (6-124)	.15
Weight	Median (range), kg	93	6 (1.4-21)	6.0 (1.4-8.9)	6.0 (1.8-21.0)	.16
Breed	Mixed breed	18	19.4	4	18	.98
	Yorkshire terrier	15	16.1	7	8	
	Bichon frise	12	12.9	6	6	
	Shih tzu	8	8.6	1	7	
	Maltese terrier	6	6.5	1	5	
	Pug	9	9.7	3	6	
	Miniature schnauzer	5	5.4	2	3	
	Jack Russell terrier	6	6.5	2	4	
	Dachshund	3	3.2	0	3	
	Chihuahua	4	4.3	1	3	
	West Highland white terrier	2	2.2	1	1	
	Norfolk terrier	1	1.1	1	0	
	Border terrier	1	1.1	1	0	
	Brussels griffon	1	1.1	0	1	
	Coton De Tulear	1	1.1	0	1	
	Setter	1	1.1	0	1	
Sex	ME	19	20.4	6	13	.64
	MN	28	30.1	6	22	
	FE	13	14.0	5	8	
	FS	31	33.3	12	19	
	UF	2	2.2	1	1	
Shunt morphology	Portocaval	67	72.0	24	43	.99
	portoazygos	16	17.2	6	10	
	Portophrenic	6	6.5	0	6	
	Unspecified	4	4.3	0	4	
Concurrent/historical conditions	Yes	27	29.0	9	18	.89
	No	66	71.0	21	45	
Preoperative neurologic signs	Yes	73	78.5	27	46	.07
	No	20	21.5	3	17	
Preoperative seizures	Yes	16	17.2	12	4	.0003
	No	77	82.8	18	59	
Preop antimicrobials for minimum of 1 wk	Yes	78	83.9	29	49	.18
	No	13	13.9	1	12	
	Unknown	2	2.2	0	2	
Preop lactulose for minimum of 1 wk	Yes	81	87.1	30	51	.99
	No	10	10.7	0	10	

TABLE 3 (Continued)

Variable	Category[a]	n	%[a]	Survivors, n[a]	Nonsurvivors, n[a]	*P*-value
	Unknown	2	2.2	0	2	
Prophylactic LEV	LEV-	43	46.2	15	28	.2
	LEV1	22	23.7	10	12	
	LEV2	25	26.9	4	21	
	LEV3	3	3.2	1	2	
Year of surgery	2005	2	2.2	0	2	.94
	2006	3	3.2	2	1	
	2007	1	1.1	0	1	
	2008	5	5.4	1	4	
	2009	2	2.2	0	2	
	2010	10	10.8	6	4	
	2011	10	10.8	3	7	
	2012	14	15.1	5	9	
	2013	12	12.9	4	8	
	2014	6	6.5	1	5	
	2015	12	12.9	3	9	
	2016	12	12.9	3	9	
	2017	3	3.2	1	2	
	2018	1	1.1	1	0	
Surgery from January 1, 2012 onward	Yes	60	64.5	18	42	.53
	No	33	35.5	12	21	
Method of shunt attenuation	SL	23	24.7	6	17	.52
	TFB	36	38.7	10	26	
	ARC	33	35.5	14	19	
	SL and TFB	1	1.1	0	1	
Degree of Intraop attenuation	None	49	52.7	17	32	.87
	Partial	24	25.8	7	17	
	Complete	20	21.5	6	14	
Type of postattenuation seizures	Generalized	76	81.7	16	60	<.0001
	Focal only	17	18.3	14	3	

Abbreviations: ARC, Ameroid ring constrictor; F, female; FE, female entire; FS, female spayed; Intraop, intraoperative; LEV; levetiracetam; ME, male entire; MN, male neutered; Preop, preoperative; SL, suture ligation; TFB, thin film banding; UF, unspecified female.
[a]Except for age and weight.

are presented in Table 1. No differences in these parameters were identified between survivors vs nonsurvivors or dogs with a history of preoperative seizures vs dogs without a history of preoperative seizures (Table 1).

3.12 | Treatment of PAS

Ninety (96.8%) dogs received treatment for PAS. One dog that experienced focal PAS only did not receive any antiseizure treatment. An additional dog that experienced focal PAS only did not receive any additional treatment apart from continued administration of LEV. One dog that experienced a generalized seizure at home was already receiving LEV but did not receive any additional treatment. Specific details of drugs administered as part of the treatment of PAS were available for all but one dog. One dog that was receiving prophylactic LEV experienced generalized PAS treated by the primary veterinarian. Specific details regarding additional

antiseizure medications administered were not available. Among 20 (21.5%) dogs that commenced seizure activity postdischarge, nine (45.0%; 9.7% of all dogs) were treated for PAS by their local veterinarian, eight (40.0%; 8.6% of all dogs) were re-presented to the participating institution, two (10%) were treated initially by the local veterinarian and subsequently re-presented, and the remaining dog was treated for generalized PAS with continued administration of LEV by the owner at home.

3.13 | Focal seizures only

Dogs that experienced focal PAS only were treated with LEV (n = 15; 10 dogs were already receiving prophylactic LEV: LEV1 [n = 6], LEV2 [n = 4]), benzodiazepines (n = 9), propofol CRI (n = 6), phenobarbital (n = 6), potassium bromide (n = 3), flumazenil (n = 2), α-2 agonist (n = 1), and/or gabapentin (n = 1). One dog was taken back to surgery to have the TFB removed because of concerns over possible portal hypertension; moderate

TABLE 4 Univariable analysis of drugs administered as part of treatment of PAS

Variable	Category	n	%	Survivors, n	Nonsurvivors, n	*P*-value
Propofol CRI	Yes	49	52.7	12	37	.21
	No	43	46.2	18	25	
	Unknown	1	1.1	0	1	
Alfaxalone CRI	Yes	3	3.2	0	3	>.99
	No	89	95.7	30	59	
	Unknown	1	1.1	0	1	
Mannitol	Yes	16	17.2	3	13	.44
	No	76	81.7	27	49	
	Unknown	1	1.1	0	1	
Benzodiazepines	Yes	45	48.4	11	34	.27
	No	47	50.5	19	28	
	Unknown	1	1.1	0	1	
Levetiracetam	Yes	64	68.8	22	42	.52
	No	29	31.2	8	21	
Phenobarbital	Yes	55	59.1	16	39	.68
	No	37	39.8	14	23	
	Unknown	1	1.1	0	1	
Potassium bromide	Yes	13	14.0	7	6	.23
	No	79	85.0	23	56	
	Unknown	1	1.1	0	1	
α-2 agonist	Yes	8	8.6	4	4	.56
	No	84	90.3	26	58	
	Unknown	1	1.1	0	1	
Gabapentin/pregabalin	Yes	4	4.3	2	2	.45
	No	88	94.6	28	60	
	Unknown	1	1.1	0	1	
Flumazenil	Yes	2	2.2	2	0	.98
	No	91	97.8	28	63	
	Unknown	1	1.1	0	1	
Complication during treatment of PAS	Yes	16	17.2	2	14	.08
	No	77	82.8	28	49	

Abbreviations: CRI: continuous rate infusion; PAS, postattenuation seizures.

TABLE 5 Multivariable logistic regression model assessing relationship with outcome of survival to 30 days

Variable	Category	OR	95% CI	*P*-value
Preop seizures	Yes	7.6	1.9-30.3	.004
	No	Reference		
Type of PAS	Focal only	14.4	3.4-60.2	.0003
	Generalized ± focal	Reference		

Abbreviations: CI, confidence interval; OR, odds ratio; PAS, postattenuation seizures; Preop, preoperative.

liver congestion was noted at surgery but without congestion of mesenteric vessels. The dog was euthanized intraoperatively at the request of the owners.

3.14 | Generalized seizures

Dogs that experienced generalized PAS were treated with LEV (n = 49; 34 were already receiving prophylactic LEV: LEV1 [n = 16], LEV2 [n = 21], LEV3 [n = 3]), phenobarbital (n = 49; one dog was already receiving prophylactic phenobarbital), propofol CRI (n = 43), benzodiazepines (n = 36), mannitol (n = 16), potassium bromide (n = 10; one dog was already receiving prophylactic potassium bromide), α-2 agonist (n = 7), alfaxalone CRI (n = 3), and/or gabapentin/pregabalin (n = 3).

3.15 | Development of complications during treatment of PAS

Sixteen (17.2%) dogs experienced one or more significant complications during treatment of PAS within 30 days postoperatively (Table 2). The most common complication was development of aspiration pneumonia.

3.16 | Short-term survival

Thirty (32.3%) dogs survived to 30 days. Sixteen (21.1%) of 76 dogs that experienced generalized (+/− focal) PAS survived to 30 days, whereas 14 (82.4%) of 17 dogs that experienced focal PAS only survived to 30 days. Among those that did not survive, 50 (79.4%) were humanely euthanized (generalised PAS [n = 48]; focal PAS only [n = 2]), nine (14.3%) died (generalized PAS [n = 9]), and one (1.6%) suffered cardiorespiratory arrest and was successfully resuscitated but later euthanized (generalized PAS [n = 1]). For the remaining three (4.8%) dogs, it was not recorded whether they had died or been euthanized. The most common reason for euthanasia was uncontrolled or recurrent seizures (Table 2). Median (range) survival time of nonsurvivors was 4 (1-20) days (recorded as 2-3 weeks postoperatively [n = 1]). Among those that survived to 30 days, 16 experienced generalized PAS, 14 experienced focal PAS only. Sixty dogs that did not survive to 30 days experienced generalized PAS, while three dogs experienced focal PAS only. Cause of natural death and reasons for humane euthanasia are presented in Table 2.

3.17 | Prognostic factors associated with short-term survival

Results of univariable analysis are presented in Tables 3 and 4. Prophylactic treatment with LEV, surgery performed in the second half of the study period, and treatment of PAS with propofol CRI were not associated with short-term survival. Factors associated with short-term survival in the multivariable analysis included having a history of preoperative seizures ($P = .004$) and type of PAS ($P = .0003$; Table 5). Dogs with a history of preoperative seizures had 7.6-fold (95% CI: 1.9-30.3) increased odds of survival to 30 days compared with those without a history of preoperative seizures, with adjustment for PAS type. Dogs that developed focal PAS only had increased odds of survival (odds ratio = 14.4, (95% CI: 3.4-60.2)) compared with those that experienced generalized PAS, with adjustment for preoperative seizure activity.

4 | DISCUSSION

The main findings of this study are (1) that affected dogs that had a history of preoperative seizures and those that experienced focal PAS only had significantly increased odds of survival to 30 days and (2) having received prophylactic treatment with LEV, treatment of PAS with propofol CRI and having experienced PAS/undergone surgery in the second half of the study period were not associated with improved short-term survival.

In a recent study by Brunson et al,[21] dogs that experienced PAS that had a history of preoperative seizure activity had a sevenfold increased probability of survival compared with those that had not had a history of preoperative seizure activity. Similarly in our study, such dogs had an almost eightfold increased odds of survival to 30 days. One possible explanation for this is that PAS experienced by both of these subsets of dogs have a different etiopathogenesis or that

some dogs with a history of preoperative seizure activity have continuation of these seizures postoperatively. We did not find support for hyperammonemia to be responsible for PAS in such affected dogs in our study, which is in line with reports by several other investigators.[2,7,9,10,17,20,22] It is well recognized that ammonia concentrations and severity of encephalopathy do not always correlate, emphasizing the importance of other neurotoxic substances.[28] In a study by Strickland et al,[22] the presence of hepatic encephalopathy immediately preoperatively was identified as a risk factor for PAS; however, similar to our results, postoperative ammonia concentrations were normal to mildly elevated in all dogs for which it was available.

Dogs that experienced focal PAS only in our study had a 14.4-fold increased odds of short-term survival compared with those that experienced generalized PAS. Whether focal PAS in such affected dogs represent a less aggressive form of neurologic dysfunction, has a different etiopathogenesis, or would have progressed to generalized PAS without antiseizure treatment is unknown. Seventeen percent of dogs that developed generalized PAS in our study were recorded as having experienced initial focal PAS, which provides evidence that these may be a precursor to generalized PAS in some cases. In a study by Mehl et al,[15] all dogs that experienced focal PAS only survived to discharge, while all those that experienced generalized PAS within 7 days postoperatively died during hospitalization. Most dogs that failed to survive to 30 days in our study were humanely euthanized, most commonly because of uncontrolled or recurrent seizures (Table 2). It is possible that factors such as client unwillingness to continue treatment, financial constraints, or an attending clinician's perception of a poor prognosis for neurologic recovery significantly influenced the decision to euthanize. It may be anticipated that generalized PAS is more challenging to abolish, more distressing for the pet owner to observe, and associated with a greater treatment cost and the perception of a poorer prognosis for recovery, all of which may provoke a decision to euthanize.

Only one-third of dogs that experienced PAS in our study survived to 30 days, which is in line with previous reports of 0% to 58.3% in the literature.[2,3,9,15,18,21,22] The large proportion (81.7%) of dogs in our study that experienced generalized PAS had a strong influence on the low short-term survival rate because such dogs had significantly decreased odds of survival in the multivariable analysis.

We hypothesized that having undergone surgery/experienced PAS in the second half of the study period would be positively associated with short-term survival. This was based on the premise that, with greater experience in treating PAS and advances in critical care medicine, short-term survival would be improved. This was not supported by the results of our study. Possible explanations for this may be related to factors such as a perceived poor prognosis for neurologic recovery, factors outside of the control of the attending clinician including client unwillingness to pursue treatment and financial constraints, and the overall infrequent occurrence of PAS. In our study, the maximum number of cases of PAS seen by any institution in a single year was four, with most institutions seeing a maximum of one or two cases per year.

Administration of several antiepileptic drugs including benzodiazepines,[2,3,9-12,14,15] barbiturates,[2,3,6-12,14,15] and propofol[7,10,14,17] has been described for the treatment of PAS in previous reports. There are, however, no large-scale studies in which researchers have compared outcomes of affected dogs treated with various antiepileptic drugs, likely because of the infrequent occurrence of these seizures and subsequent small case numbers within individual institutions.[22] In our study, none of these antiepileptic drugs, including propofol CRI, was associated with short-term survival. Because of the nonprospective nature of our study, treatment of PAS with propofol CRI was not randomized. Therefore, it is likely that it will have been administered to the most severely affected cases in our study. While there are reports of a more favorable prognosis with administration of propofol CRI,[7,17,20] individual numbers are small and may represent a positive outcome publication bias. Previous studies have reported conflicting results regarding the possible protective effect of LEV against development of PAS.[18,21,22,26] Approximately half of the dogs in our study received prophylactic LEV. The recommended dose of LEV is 20 mg/kg orally every 8 hours for a minimum of 24 hours preoperatively.[27] On the basis of the known pharmacokinetics of the drug (albeit in healthy dogs), continuation of the drug at the same dose during the first 7 days postoperatively should be considered.[29] Several dogs in our study received less standardized protocols of LEV (groups LEV2 and LEV3). No group, however, was of prognostic significance. It is possible that dogs that develop PAS despite receiving prophylactic treatment with LEV are biased toward more severe postattenuation neurologic dysfunction, although this is purely speculative. It also raises the question whether continued treatment of such dogs with LEV after development of PAS is likely to be of benefit.

This study has a number of important limitations. Similar to all retrospective studies, the accuracy of the presented data relies on the completeness of the medical records. Seventy-five of the dogs of the present report are the subject of another study which investigated the effect of prophylactic treatment with LEV on the incidence of PAS in dogs that underwent cEHPSS attenuation.[26] Because of the infrequent occurrence of PAS, the present

study would not have been possible without the inclusion of such dogs. This was a multicenter study involving multiple surgeons, with differences in case management and experience in treating PAS. Treatment of PAS with different antiepileptic drugs was not randomized but rather based on clinician preference. Drug dosages and infusion dose rates were not standardized. We did not record individual doses of various antiepileptic drugs used to treat PAS because these will have varied widely even within individual dogs, with most dogs receiving numerous boluses of individual drugs along with variable rates of CRI. Other factors including the attending clinician's perception of prognosis for neurologic recovery after development of PAS, the extent to which the seizures were treated, cost of treatment, and client willingness to treat seizures could not be controlled because of the retrospective nature of the study. The authors acknowledge that several of the dogs included in this study may have experienced prodromal neurologic signs prior to seizure onset; however, because of the retrospective nature of the study, the exact timing and details of such sign may not have been accurately recorded in the medical record. Additionally, the timings of when the antiseizure medications were started in relation to prodromal neurologic signs or following the occurrence of actual seizures was not possible to determine from the retrospective nature of our study. The classification of seizures as focal or generalized in this study reflects what was recorded in the medical record. Assignment of a dog as having experienced a seizure was based on the attending clinician's/criticalist's interpretation of the neurologic signs manifested. However, it is important to note that all dogs were treated at academic teaching hospitals or referral institutions by multidisciplinary staff with extensive experience in treating dogs with portosystemic shunts and their complications. Finally, just under 10% of dogs that experienced PAS in this study were not treated for PAS at the operating institution, and the impact of this on the survival of such dogs is unknown.

The overall short-term survival rate in this study was low, with just under one-third of dogs surviving to 30 days. Affected dogs that had a history of preoperative seizures or experienced focal PAS only had significantly improved short-term survival. The results of this study provide information that will help in the counseling of owners who seek treatment for cEHPSS for their animals and may serve as a basis for further investigation regarding prevention or treatment of PAS in the future.

CONFLICT OF INTEREST

The authors report no conflicts of interest related to this report.

ORCID

Ronan A. Mullins https://orcid.org/0000-0003-1159-2382
Laura E. Selmic https://orcid.org/0000-0001-6695-6273
Michael S. Tivers https://orcid.org/0000-0001-7047-9334
Ameet Singh https://orcid.org/0000-0002-8095-9339
Robert N. White https://orcid.org/0000-0002-3507-278X
Kathryn M. Pratschke https://orcid.org/0000-0002-1468-9967
Hilde de Rooster https://orcid.org/0000-0001-8087-256X
Donald A. Yool https://orcid.org/0000-0002-3562-9111

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