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Incidence of postoperative complications and outcome of 48 dogs undergoing surgical management of insulinoma

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Abstract

Background: Information regarding outcome of dogs undergoing surgical management for insulinoma is based on studies of a small number of dogs.

Objectives: To report the outcomes of dogs undergoing surgery as treatment for insulinoma, the prevalence of postoperative diabetes mellitus (DM) in this group and to determine if development of DM can be predicted.

Animals: Forty-eight client-owned dogs, with a histopathological diagnosis of insulinoma, from three European referral hospitals.

Methods: Retrospective observational study. Dogs were identified from a search of electronic hospital records. Cox's regression was used to determine factors associated with postoperative survival and relapse, and logistic regression was used to determine factors associated with the development of DM.

Results: Median survival time (MST) was 372 days (range 1-1680 days), with dogs with stage I disease having the longest survival time. Stage I dogs had MST of 652 days (range 2-1680 days), whereas dogs with either stage II or III disease had MST of 320 days (range 1-1260 days; P = 0.045). Postoperative hyperglycemia was identified in 33% (16/48) of the dogs, of which 9 (19% of the total population) developed persistent DM. No factors that could be used as predictors for development of DM were identified.

Conclusions and clinical importance: Stage of disease and postoperative hypoglycemia were associated with greater odds of relapse and decreased survival time; these could be used when discussing prognosis. In this study, postoperative DM developed more commonly than previously reported, but no factors were identified that might be useful predictors.

KEYWORDS
diabetes mellitus, hyperglycemia, hypoglycemia, pancreatectomy

1 | INTRODUCTION

Insulinoma is the most common endocrine pancreatic tumor in dogs.[1,2] Neoplastic beta cells are capable of producing and releasing insulin independently of blood glucose,[3] leading to hyperinsulinemia and hypoglycemia, that can be life-threatening. Clinical signs result from neuroglycopenia and increased insulin antagonistic counterregulatory hormone production.[4,5] Insulinomas are usually malignant and they are thought, in almost all dogs, to have metastasized at the time of diagnosis,[1] although visible metastases are found in only approximately 50% of cases at surgery.[6] The common sites of metastasis are regional lymph nodes, liver, and lungs, with less common sites including the spleen, mesentery, gastrointestinal tract, kidney, spinal cord, and bone.[2,7,8]

Surgical management is the treatment of choice and involves partial pancreatectomy to remove the primary tumor and any visible metastases, with longer median survival times in dogs treated surgically compared to dogs treated medically.[9,10] In 2 studies, the median survival time of dogs undergoing partial pancreatectomy was 381 days and 785 days, respectively, [9,10] compared with 74 days and 196 days, respectively, in those treated with medical treatment alone. [9,10] As a result, surgical management is often recommended[11,12] for dogs with World Health Organization (WHO) stage I (local disease confined to the pancreas) or stage II disease (presence of locoregional metastasis). Medical management is considered for nonsurgical candidates such as those with the presence of distant metastasis, a large pancreatic mass, proximity of the pancreatic mass to the pancreatic blood supply, important comorbidity or when the owner declines surgery.[13]

A common postoperative complication with partial pancreatectomy is pancreatitis.[13] Diabetes mellitus (DM) can also occur and is thought to develop because of atrophy of the nonneoplastic pancreatic beta cells secondary to chronic hyperinsulinemia. Some dogs develop transient hyperglycemia, whereas a smaller number of dogs develop persistent DM requiring long-term administration of insulin.[1] In human medicine, prevalence of postpancreatectomy DM varies from 5 to 78% depending on the heterogeneity of the population studied.[14] The largest study revealed a median prevalence of 23%.[15] Factors that affect the development of DM after pancreatectomy in people are: age, pancreatic resection type, resection volume ratio, and high body mass index.[14.] Approximately 10% of dogs develop DM after pancreatectomy,[7] with clinical signs generally occurring when 80%-90% of pancreatic tissue is excised.[16,17]

Given the limited information on factors associated with postsurgical outcome in dogs with insulinoma, the aims of this were to report the outcomes in a group of dogs undergoing surgical management of insulinoma, and to determine the prognostic factors associated with survival. A further aim was to report the prevalence of persistent DM in this group and to determine if the development of DM could be predicted by pre-, peri- or post-operative factors. In this respect, we hypothesized that DM would be common, as it is in human medicine.

2 | MATERIALS AND METHODS

2.1 | Study design and ethics

This was a retrospective observational study examining factors associated with survival in dogs with histologically confirmed insulinoma. The study was approved by the University of Liverpool Research Ethics Committee (VREC659), and all owners gave written consent.

2.2 | Case identification and eligibility criteria

Eligible dogs were identified from a search of electronic hospital records at 3 European referral hospitals; institution 1 was The Small Animal Teaching Hospital, University of Liverpool, Neston, UK; institution 2 was Willows Veterinary Centre & Referral Service, Solihull, UK; and institution 3 was Centro Specialistico Veterinario, Milan, Italy. Cases seen from November 2004 to June 2017 were identified. To be eligible for inclusion, dogs had to have clinical signs consistent with hypoglycemia, and clinical investigations suggestive of insulinoma including normal or increased serum insulin concentration at the time of hypoglycemia, low serum fructosamine concentration, increased insulin: glucose ratio, and a pancreatic mass identified on diagnostic imaging. In addition, dogs had to have had thoracic and abdominal imaging and undergone abdominal surgery to excise a pancreatic mass, confirmed to be insulinoma on subsequent histological and, in some cases, immunohistochemical examination. Dogs that were diabetic before developing insulinoma were excluded given that one of the aims of the study was to identify the prevalence of postoperative DM. Additionally, complete clinical records had to be available in order to determine postoperative outcome.

2.3 | Data collection

Data gathered from medical records included signalment (age, sex, neuter status, weight, and breed), clinical signs at the time of presentation and clinicopathological investigations (including complete blood count, serum biochemistry, glucose concentration, fructosamine, and serum insulin concentration). The preoperative diagnostic imaging findings, one or more of radiography, ultrasonography, and computed tomography (CT) reports generated by a specialist in veterinary diagnostic imaging were reviewed, and the presence of a pancreatic mass or lesion consistent with metastatic disease were noted. The reports were generated at the time each dog had diagnostic imaging (radiographs and ultrasound or CT), at which time the diagnostic imager had access to the history of the dog and the suspected diagnosis that is, they were not blinded. Surgical reports were reviewed and compared with the preoperative imaging findings. The histopathology reports, generated by a specialist in veterinary anatomical pathology, of the primary tumor and possible metastatic lesions were reviewed, as well as the records of hospitalization until the time of discharge. The histopathology reports were generated at the time of the

sample(s) was submitted, at which time the anatomical pathologist had access to the history of the dog and the suspected diagnosis and therefore were not blinded. A presumptive diagnosis of postoperative pancreatitis was made in dogs based on clinical signs of abdominal pain, nausea, vomiting, and anorexia, as well as increased serum canine pancreatic-specific lipase (cPL) concentration and diagnostic imaging. In the previous literature, such a diagnosis is usually based on clinical impression of the attending clinician, as neither serum cPL nor diagnostic imaging, alone or in combination is completely reliable in a dog that has undergone partial pancreatectomy in the preceding days.[13] In all cases, postoperative ileus as a cause of similar clinical signs was excluded based on documentation of peristalsis on abdominal ultrasonography. Analgesia was adjusted in dogs in which opioid treatment was thought to have contributed to the clinical signs.

2.4 | Outcome measures

The primary outcome measures of the study were time to relapse of clinical signs (time to progression) and time to death (survival time). For time to relapse, the time in days between surgery and the first report of clinical signs of recurrent hypoglycemia was calculated from the clinical records. For time to death, the time between surgery and death was calculated, again based on clinical records, and cases were included whether they died or were euthanized. The main secondary outcome measure studied was development of postoperative DM, defined as persistent hyperglycemia requiring long-term (>9 days) insulin treatment. This time frame was elected as previous human studies suggest transient hyperglycemia resolves after 9 days in 90% of human patients after pancreatectomy.[18]

2.5 | Statistical analysis

Statistical analyses were performed with 2 computer software packages (Stats Direct version 3.0.171; Stats Direct Ltd. JMP version 14.3.0, SAS Institute Inc.) and $P < .05$ was chosen to determine statistical significance, with 2-sided analyses used throughout. Cox proportional hazards models were created to determine which variables were associated with time to relapse of clinical signs and time to death. For time to relapse, the time in days between the surgery and the first report of clinical signs was calculated, again from clinical records. Associated variables were assessed both in terms of "all-cause mortality" and deaths related only to the insulinoma. Variables tested included institution, breed, age, sex, neuter status, presence of clinical signs, duration of clinical signs before diagnosis, weight at presentation, blood glucose concentration at presentation, serum insulin concentration at presentation, insulin:glucose ratio at presentation, tumor size, location of tumor within the pancreas, WHO stage, postoperative glycemic status, and occurrence of postoperative complications. To account for possible clustering as a result of the multicentered nature of the study, institution was included as a fixed effect in all analyses; for this, dummy variables were created for institution 2 and

institution 3, with institution 1 as the reference category. Continuous explanatory variables tested included age (in months), body weight at presentation (in lb), duration of clinical signs before diagnosis (in days), blood glucose concentration (in mg/dL), serum insulin concentration (in mIU/L), insulin:glucose ratio (in mU/mg), and tumor size (in mm). Categorical variables were tested in a binary format, with a single binary variable used for sex (male: 1; female: 0) and neuter status (neutered: 1; intact: 0). Single binary variables (present: 1; absent: 0) were also used both for individual clinical signs (seizures, ataxia, weakness, collapse) and for postoperative complications (all complications, diabetes mellitus only, and suspected pancreatitis only). For breed, separate binary variables were created for the 3 most popular breeds (mixed breed, boxer, and West-Highland white terrier) whereas, for WHO stage, a binary variable was created for dogs classed as stage II or III (with stage 1 used as the reference category). A similar approach was used for location of the tumor within the pancreas (left lobe, right lobe or body, with left lobe as the reference category) and postoperative glycemic status (hypoglycemia, normoglycemia, and hyperglycemia, with normoglycemia as the reference category).

Initially, each variable was tested separately using simple regression. Multiple logistic regression models were then built, which initially included the variables identified as $P < .1$ on simple regression analysis. Competing models were tested in a backward and forward stepwise fashion, with additional of removal of variables, and the best fit model was chosen using the corrected Akaike Information Criterion (AICc) and Bayesian Information Criterion (BIC). With this approach, if removal of any effect yielded a model with lower AICc and BIC, the variable with the least effect was removed, until the model with the smallest AICc and BIC was found. Contingency tables were used to assess the independence of each factor compared with other factors in the model. Log(−log[survival]) versus log(time) plots were visually inspected to confirm that proportional hazards assumption was not violated for each explanatory variable in the final model. Results are expressed as risk ratios (RR), along with the associated 95% confidence interval (95% CI), and P-value.

Simple logistic regression was used to determine associations between the development of DM postoperatively and the variables described earlier, with the exception of postoperative glycemic status given its direct relationship to the outcome variable. For each variable, odds ratios (OR), Wald-based 95% confidence intervals (95% CI), and the associated P-value (based upon the Wald Chi-square test) were calculated. Model fit was assessed by calculating McFadden's pseudo R^2 value (the proportion of the total uncertainty that is attributed to the model fit, defined as the ratio of the difference to the reduced negative log-likelihood values), the area under receiver operating characteristic curves (where a value of 1.0 indicates a perfect fit, whereas a value near 0.5 indicates that the model cannot discriminate among groups), and the lack-of-fit test from the "Fit Model" platform of the computer software (also known as the "goodness of fit test," which indicates whether the model fits the data). In a similar manner to that used with the survival analysis, multiple regression models were built for factors identified as $P < .1$ on simple regression analysis, with competing models tested in a backward and forward stepwise fashion using AICc and BIC.

3 | RESULTS

3.1 | Animals

A total of 49 dogs underwent surgery and were diagnosed with insulinoma by histopathology at 1 of the 3 referral centers during the time period of the study. One dog was excluded because of a pre-existing diagnosis of DM. Therefore, 48 dogs were finally included in the study (Table 1) with 27 male dogs (57%) and 21 female dogs (43%). The median age at diagnosis was 7.8 years (range 4 to 11 years). Of the 27 male dogs, 21 (78%) were neutered and 6 (22%) were intact; of the 21 female dogs, 20 (95%) were neutered and 1 was intact (5%). Breeds represented included crossbreed (9; 19%), boxer (8; 17%), West Highland white terrier (8; 17%), English springer spaniel (4; 8%), Border collie (2; 4%), and 1 each of 17 other breeds. The median weight was 58 lb (26.3 kg), ranging from 15 lb (6.8 kg) to 97 lb (44.0 kg). Eleven (23%) dogs had weight recorded before the clinical signs developed and at the time of diagnosis, and weight gain was observed in all but 1 dog.

3.2 | Clinical signs

The median duration of clinical signs was 29 days (range 1-280 days). Reported clinical signs included generalized (18 dogs; 37%) or focal (6 dogs; 12%) seizures, ataxia (15 dogs; 31%), weakness (14 dogs; 29%), and collapse (12 dogs; 25%). Forty-four dogs (92%) had signs suggestive of neurological dysfunction (as detailed individually earlier). The 4 dogs (8%) without signs of neurological dysfunction presented with nonspecific signs, predominantly lethargy.

3.3 | Laboratory testing

Blood glucose concentration was measured in all dogs at the time of presentation and hypoglycemia was defined as a blood glucose concentration less than 60 mg/dL (3.3 mmol/L). Forty-four dogs (92%) were hypoglycemic, whereas the remaining 4 dogs (8%) dogs had a low-normal blood glucose concentration. Median blood glucose concentration was 34 mg/dL (1.8 mmol/L) (range 21-58 mg/dL [1.2-3.2 mmol/L]) for hypoglycemic dogs, and 61 mg/dL (3.4 mmol/L) (range 60-67 mg/dL [3.3-3.7 mmol/L]) for normoglycemic dogs. Serum insulin concentration was measured in 42 dogs (87%); median insulin concentration was 36.9mIU/L (range 9-29). The insulin:glucose ratio was suggestive of insulinoma (>30 mU/mg) in 20 dogs (42%) cases. Fructosamine concentration was measured in 7 (15%) dogs, 2 of which had concentrations below the reference interval, and the remaining 5 had concentrations within the reference interval. The median fructosamine concentration was 255 μmol/L (range 225-295).

3.4 | Staging and surgical procedures

Contrast-enhanced thoracic and abdominal CT was performed in 43 dogs (90%). Findings included pancreatic nodules of varying size

TABLE 1 Signalment and clinical signs for the dogs in the study (mean values for age, body weight, duration of signs, blood glucose, serum insulin, and insulin:glucose ratio)

Variable	Institution 1 UK	Institution 2 UK	Institution 3 Italy
Number	25	12	11
Age (months)	101	82	100
Sex	14 M 11 F	9 M 3 F	4 M 7 F
Breed	7 Cross breed	3 WHWT	3 WHWT
	4 Boxer	2 ESS	3 Boxer
	2 WHWT	1 Boxer	1 Cross breed
	2 ESS	1 Cross breed	1 AST
	2 Border Collie	1 GSD	1 Belgian shepherd
	1 Greyhound	1 Labrador	
	1 Irish Setter	1 Golden Retriever	1 Istrian hound
	1 GWHP	1 JRT	1 Lhasa Apso
	1 YSD	1 Rottweiler	
	1 Bearded Collie		
	1 GSP		
	1 Lurcher		
	1 FCR		
Bodyweight (kg)	60.2 (27.3 kg)	58.2 (26.4 kg)	57.3 (26 kg)
Duration of signs (days)	42	12	60
Seizures	6	8	3
Ataxia	5	4	4
Weakness	10	2	2
Collapse	6	2	2
Blood glucose (mg/dL)	36 (2 mmol/L)	35 (1.9 mmol/L)	36 (2 mmol/L)
Serum insulin (mIU/L)	31.7	44.5	37.2
Insulin: glucose (mU/mg)	0.9	1.8	0.7

Abbreviations: AST, American Staffordshire terrier; ESS, English springer spaniel; F, female; FCR, Flat-coated retriever; GSP, German shepherd dog; GWHP, German wirehaired pointer; JRT, Jack Russell terrier; M, male; WHWT, West Highland west terrier; YSD, Yugoslavian shepherd dog.

(42), loco-regional lymphadenomegaly (27), and hepatic nodules (3). In 5 dogs (12%) that were diagnosed with presumed metastatic lesions based on CT findings (regional lymphadenopathy and hepatic nodules), these changes were benign based on histopathology; in 7 dogs (16%) pancreatic or loco-regional metastatic lesions were missed on CT; in 1 dog, no pancreatic lesion was seen but a pancreatic mass was identified during exploratory celiotomy, which was performed because of the clinical suspicion of insulinoma. The remaining 5 dogs (10%) had thoracic and abdominal radiography and abdominal ultrasonography, which identified a pancreatic mass. Based on WHO staging, 16 dogs (33%) were

stage I, 28 dogs (58%) were stage II, and 4 dogs (8%) were stage III (Table 2).

A midline celiotomy was performed in all dogs. In 4 dogs (8%), a visible distinct mass was not present; however, palpation of the pancreas revealed nodular thickening consistent with possible neoplastic tissue, which was subsequently excised. Assessment of the regional lymph nodes and other intraabdominal organs was performed: if any evidence of metastatic disease was suspected, local lymphadenectomy and (in 4 cases) partial liver resection were performed. Local lymph nodes were only excised if there was evidence of a gross abnormality (eg, change in color, size, shape, or consistency) or a concern of metastasis based on diagnostic imaging (eg, contrast uptake).

All samples were submitted for histopathological examination. Of all 48 dogs, 16 (33%) underwent partial pancreatectomy alone, excision of local lymph nodes was required in 28 dogs (58%), whereas 4 dogs (8%) underwent resection of distant metastatic lesions (partial liver lobectomy). A single pancreatic mass was present in all but 1 dog, which had 2 lesions, 1 of which was identified as a pancreatic adenoma on histopathological examination. Tumor size was assessed in 46 dogs (96%) with 34 measuring <20 mm (range 3-18 mm), 10 measuring 20-39 mm and 2 measuring >40 mm (42 and 50 mm, respectively). Pancreatic lesions were identified in the left limb in 24 dogs (51%), in the right limb in 16 dogs (34%) and in the body in 7 dogs (15%). In 1 dog the location of the tumor was not stated in the medical record.

3.5 | Postoperative complications

Postoperative care consisted of regular assessment of blood glucose concentration at the time of completing surgery and every 4 hours thereafter, or more frequently if there was a clinical indication. For those dogs that developed hyperglycemia postoperatively,

TABLE 2 Surgical findings, postoperative complications and survival for the dogs in the study

Variable	Institution 1 UK	Institution 2 UK	Institution 3 Italy
Stage			
I	10	4	2
II	13	7	8
III	2	1	1
Tumor size (mm)	16	11	12
Tumor location			
Left lobe	13	7	4
Body	2	1	2
Right Lobe	9	4	5
Postoperative glycemic status			
Hypoglycemia	4	1	6
Normoglycemia	11	6	4
Hyperglycemia	10	5	1
Postoperative complications			
All complications	10	2	2
Diabetes mellitus	6	2	1
Suspected pancreatitis	5	0	0
Time to relapse (days)	365	270	1
Time to death (days)			
All cause	392	616	180
Insulinoma-related	140	616	180

TABLE 3 Final multiple Cox regression models for time to relapse and time to death

Parameter	Risk ratio	95% CI*	P value
Time to relapse			
Institution			
1	1.000	-	-
2	1.17	0.46-3.00	0.74
3	1.14	0.36-3.67	0.82
Stage			
I	1.00	-	-
II and III	3.75	1.40-10.04	<0.001
Postoperative glycemic status			
Hypoglycemia	4.54	1.63-12.61	0.0044
Normoglycemia	1.00	-	-
Hyperglycemia	0.32	0.16-0.97	0.045
Suspected post-op pancreatitis	6.72	1.50-30.21	0.013
Time to death (insulinoma-related)			
Institution			
1	1.000	-	-
2	1.21	0.45-3.30	0.71
3	0.81	0.26-0.54	0.72
Stage			
I	1.000	-	-
II and III	2.64	1.02-6.86	0.045
Postoperative glycemic status			
Hypoglycemia	4.96	1.69-14.50	0.0035
Normoglycemia	1.00	-	-
Hyperglycemia	0.70	0.24-2.00	0.50
Suspected post-op pancreatitis	11.84	2.27-61.86	0.0034
Time to death (all cause)			
Institution			
1	1.000	-	-
2	0.75	0.29-1.90	0.54
3	0.61	0.21-1.79	0.36
Stage			
I	1.000	-	-
II and III	2.26	0.95-5.36	0.064
Postoperative glycemic status			
Hypoglycemia	4.41	1.58-12.28	0.0046
Normoglycemia	1.000	-	-
Hyperglycemia	1.24	0.49-3.13	0.65
Suspected post-op pancreatitis	7.55	1.87-30.43	0.0045

short-acting insulin was administered; dogs with persistent hyperglycemia characterized by over 48 hours of hyperglycemia were transitioned to long-acting insulin (porcine lente) as required. Dogs that remained hypoglycemic (11; 23%) for longer periods of time (ie, several days) were treated with a 5% dextrose solution and, when there was hypoglycemia persisting for over 1 week postoperatively, medical management with prednisolone alone or prednisolone and diazoxide was started.

Sixteen of the 48 dogs (33%) developed postoperative hyperglycemia, of which 9/48 (19%) required long-term administration of exogenous insulin, and 7/48 (15%) had transient hyperglycemia. Three (3/48; 6%) of the dogs with postoperative hyperglycemia had suspected

TABLE 4 Logistic regression to determine factors associated with postoperative diabetes mellitus

Parameter	R^2	AUC	Lack of fit	Odds ratio	95% CI*	P value
Age (months)	0.118	0.694	0.721	0.99	0.95-1.03	.64
Institution	0.113	0.672	NC			
1				1.00		
2				0.63	0.11-3.73	.61
3				0.00	-	.99
Breed						
Mixed breed	0.113	0.681	0.791	1.15	0.18-7.58	.88
Boxer	0.178	0.738	1.000	0.00	-	1.00
WHWT	0.146	0.684	0.046	3.78	0.44-32.72	.23
Sex	0.168	0.773	0.093			
Female				1.00	-	
Male				0.91	0.05-1.47	.13
Neuter status	0.114	0.673	0.834			
Intact				1.00	-	
Neutered				1.19	0.11-12.69	.88
Body weight (lb)	0.196	0.772	0.839	0.93	0.85-1.01	.06
Duration of signs (days)	0.119	0.696	0.440	1.00	0.98-1.01	.62
Clinical signs						
Seizures	0.125	0.716	0.076	0.51	0.07-3.42	.50
Ataxia	0.128	0.709	0.993	2.00	0.37-10.83	.42
Weakness	0.140	0.716	0.377	2.49	0.48-13.04	.28
Collapse	0.146	0.733	0.866	0.29	0.03-2.75	.23
Glucose at diagnosis	0.138	0.730	0.834	0.49	0.12-2.10	.30
Insulin at diagnosis	0.131	0.725	0.567	1.00	0.99-1.01	.58
Insulin: glucose	0.125	0.743	0.556	1.04	0.78-1.40	.79
Stage	0.113	0.681	0.806			
I				1.00	-	
II and III				1.05	0.21-5.13	.96
Tumor size (mm)	0.121	0.702	0.957	0.98	0.90-1.06	.56
Tumor location	0.27	0.722	0.791			
Left lobe				1.000	-	
Body				1.61	0.12-21.98	.72
Right lobe				0.57	0.09-3.53	.55
Suspected postoperative pancreatitis	0.132	0.703	NC	4.11	0.56-29.96	.16

Note: R^2: McFadden's pseudo R^2 value, the proportion of the total uncertainty that is attributed to the model fit, defined as the ratio of the difference to the reduced negative log-likelihood values. AUC: area under receiver operating characteristic curve, which is an indicator of the goodness of fit for the model; a value of 1 indicates a perfect fit, whilst a value near 0.5 indicates that the model cannot discriminate among groups. Lack of fit: lack of fit (also known as goodness of fit) test, which indicates whether the model fits the data; the value indicated is the P-value for the test, with small values indicating a significant lack of fit. 95% CI: Wald-based 95% confidence intervals of the odds ratio for each variable. P-value: determined by the Wald Chi square test. NC: Lack of fit could not be computed for this model.

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pancreatitis and systemic inflammatory response syndrome (SIRS) and died within 48 hours of surgery.

Median survival time (MST) of dogs with persistent DM was 224 days (range 28-1680 days) and all required long-term insulin treatment. MST of dogs with transient hyperglycemia was 420 days (range 224-1260 days). MST of the 11/48 dogs (23%) with postoperative hypoglycemia was 180 days (range 14-672 days).

Within 48 hours of surgery, 5/48 dogs (10%) developed suspected postoperative pancreatitis, of which 3/48 (6%) met the criteria for SIRS. The survival time of dogs with concurrent SIRS was less than or equal to 2 days.

Insulinoma progression was documented in 20/48 dogs (42%), with a median disease-free interval of 275 days (range 1-980 days).

3.6 | Factors associated with time to recurrence

Relapse occurred in 20/48 dogs (42%). Treatment postrelapse was variable, possibly including additional surgery, medical treatment (prednisolone either given alone or in combination with diaxozide) or euthanasia based on owner discretion. Given the diversity of treatment received, differences in treatment were not explored statistically. Using Cox's proportional hazards regression analysis (Table 3), stage, postoperative glycemic status, and the suspected development of pancreatitis postoperatively were all positively associated with recurrence. The risk of relapse was greater for dogs classified as either stage II or III (RR 3.75, 95% CI 1.40-10.04) compared with stage I, for dogs that developed postoperative hypoglycemia (RR 4.54, 95% CI 1.63-12.61), and for dogs that developed suspected postoperative pancreatitis (RR 6.72, 95% CI 1.50-30.21) although it should be emphasized that the number affected was small (5 dogs).

3.7 | Factors associated with survival time

The median duration of follow-up was 15 months (ranging from 1 month to 3 years). During this period 34 dogs died or were euthanized, with 13 dogs (38%) dying or being euthanized as a result of insulinoma recurrence. Cause of death in the other dogs included disseminated hemangiosarcoma, uncontrolled seizures (intracranial neoplasm), hyperadrenocorticism, or other reasons. Using Cox's proportional hazards regression analysis (Table 3), stage, postoperative glycemic status, and the development of suspected postoperative pancreatitis were all associated with the risk of dying from insulinoma. The risk of death was greater for stage II or III dogs (RR 2.64, 95% CI 1.02-6.86) compared to stage I. When analyzing the impact of the postoperative glycemic status, the risk of recurrence was greater for dogs that remained or became hypoglycemic within the first 24 hours (RR 4.96, 95% CI 1.69-14.50) compared with normoglycemic dogs, but there was no difference between those that developed hyperglycemia and normoglycemic dogs (RR 0.70, 95% CI 0.24-2.00). Dogs that developed suspected postoperative pancreatitis had a greater risk of recurrence compared with those that did

not (RR 11.84, 95% CI 2.27-61.86). However, it should again be emphasized that the number of affected dogs was small (5), and also that the 3 dogs developing suspected pancreatitis and SIRS that died postoperatively were included in the survival analysis. Similar results were seen when all-cause mortality was assessed (Table 3).

3.8 | Factors associated with postoperative DM

Logistic regression was used to determine factors associated with the odds of developing persistent DM in the postoperative period (Table 4). Using simple regression analysis, there were no factors that were significant in their own right and, given that none qualified (at P < .1) for inclusion in multiple regression modeling, no models were built.

4 | DISCUSSION

In this study, the postoperative complications and survival times of dogs undergoing surgical management of insulinoma were assessed, along with factors associated with relapse and survival. Stage of the disease and postoperative hypoglycemia were associated with a greater odds of relapse and decreased survival time. Although there was also an association with suspected pancreatitis, the clinical importance of this is not clear. Such information will be valuable to clinicians because they could be taken into account when discussing prognosis with clients. Postoperative diabetes mellitus developed more commonly than previously reported, and all affected dogs required on-going exogenous insulin treatment. No factors were identified that might be useful predictors of postoperative DM.

Various clinical signs are reported with insulinoma, most of them because of the resulting neuroglycopenia.[19] In this study, 44 dogs (92%) presented with neurological signs; the most common of which were generalized and focal seizures, although ataxia, weakness, and collapse were also seen (Table 1). Hypoglycemia was also identified in 44 dogs (92%), with the remaining dogs having a blood glucose concentration within the reference interval. Insulin:glucose ratio is reported to aid in the diagnosis of insulinoma in dogs, although poor sensitivity and specificity are reported.[20] Some studies suggest a ratio over 30 μIU/L is diagnostic for insulinoma,[21,22] whereas others have suggested poor sensitivity,[1,21] and associations between abnormal insulin:glucose ratios and other causes of hypoglycemia have been reported.[5,21,22] Given that only 20 dogs (42%) in the current study had an insulin:glucose ratio > 30 mIU/L, our findings might question the suitability of this test for the diagnosis of insulinoma.

Intraoperatively, tumors were localized in the left pancreatic limb (51%), right pancreatic limb (34%), and pancreatic body (15%; Table 2). This is in agreement with what it has been previously reported, pancreatic lesions are more commonly located in the limbs (left: 44%, right: 35%) and less frequently in the body (14%).[6] In all cases, pancreatic tumors were resected and there was no significant association between the location of the pancreatic tumor and time to relapse or survival

time. Tumor size has previously been reported to be a negative prognostic indicator, and larger tumors are associated with shorter survival in human studies.[23] In this study, there was no association between tumor size and prognosis.

Close monitoring of blood glucose concentration is recommended after partial pancreatectomy for insulinoma.[13] Persistent postoperative hypoglycemia has been associated with a poorer prognosis, because it is suggestive of an incompletely excised tumor or the presence of metastasis. Postoperative hyperglycemia after partial pancreatectomy for treatment of insulinoma is commonly described.[22] Although its duration and significance in human medicine is unclear, most studies suggest it is usually transient and self-resolves in 3 to 9 days.[18] In a recent study in people, the prevalence of hyperglycemia was 36%,[24] and no significant difference in age, sex, tumor size, or surgical approach were noted between human patients with normoglycemia and those that were hyperglycemic during the postoperative period.[24] In dogs, postoperative transient hyperglycemia has been commonly recognized, and it has been associated with a better prognosis,[12] whereas the development of permanent DM is believed to be uncommon.[7] In our study, postoperative hyperglycemia was identified in 16 dogs (33%), of which, 7/48 had transient hyperglycemia and 9/48 developed persistent DM. The percentage of dogs that developed hyperglycemia requiring chronic exogenous insulin (19%) was greater than previously reported, and similar to the reported rate in humans (23%).[15] Transient hyperglycemia was identified as a positive prognostic factor in this study as previously reported,[25] supported by a median survival time of 420 days compared to 224 days for those dogs with DM and 180 days for dogs with postoperative hypoglycemia. DM occurred in 19% of cases, which is higher than in previous reports where a prevalence of approximately 10% was reported.[7] This finding suggests that permanent insulin treatment might be required for a substantial number of dogs undergoing surgery. Further, dogs developing DM had decreased median survival times when compared to dogs with transient hyperglyemia (224 days versus 420 days, respectively). However, the fact that no variables were identified that were associated with its development suggests that it is difficult for clinicians to predict in which cases it will occur.

Pancreatitis is another well-recognized complication of pancreatectomy, with 10% of dogs reportedly affected.[1,9,13,25,26] In this study, 10% of dogs had suspected postoperative pancreatitis and, when this developed, its presence was negatively associated with survival, most notably in dogs with clinical findings consistent with SIRS. This effect on survival was strong, despite the small number of dogs (5) affected. Nonetheless, it should be emphasized that pancreatitis was not definitely proven, as this would be difficult to achieve in dogs that had recently undergone pancreatectomy. Diagnosis was largely based on clinical signs (abdominal pain, nausea, vomiting, and anorexia), with possible addition of increased CPL concentration, supportive diagnostic imaging findings or both. As the result, suspected postoperative pancreatitis might have been under- or over-diagnosed. For example, the clinical signs in some cases could have been because of postoperative ileus or an adverse effect of opioid analgesia, however attempts were made to exclude this where possible.

Median survival time for dogs with insulinoma undergoing surgical treatment was 372 days, which is equivalent to median survival times

previously reported.[9,10] Stage of the disease can be determined preoperatively and has been reported to be a good prognostic factor in dogs with insulinoma.[21] Dogs with stage I disease have been reported to have the longest disease-free interval, whereas those with stage III disease have significantly shorter survival times.[21] Similarly, in this study, stage of the disease was associated with survival time, most notably for dogs with either stage II or stage III disease. Dogs with stage I disease had a median survival time of 652 days, whereas dogs with stage II or III disease had a median survival time of 320 days. One limitation of this study was the fact that few dogs had stage III disease and, as a result, these dogs could not be assessed separately.

This study has several limitations. First, although this is technically the largest study of dogs undergoing surgical management of insulinoma, the number of cases included was still small and only 6 more than a previous study.[25] Second, given the retrospective and observational design, statistical significance does not necessarily imply causation. Further, for some variables such as suspected postoperative pancreatitis, the number of dogs affected was small and, as a result, the findings should be interpreted cautiously. As discussed above, the diagnosis was only presumptive and the clinical findings might have arisen for other reasons such as abdominal pain postsurgery, increased serum cPL as a result of surgery. As such, suspected postoperative pancreatitis could have been over or, more likely, under diagnosed, particularly considering it was only documented in 1 of the 3 centers included in the study. Whereas suspected postoperative pancreatitis had a statistically significant effect on time to relapse and survival based on the data, the number of affected dogs was small (5) and further work would be required to determine whether suspected postoperative pancreatitis has a genuine effect on outcome measures.

Third, both the retrospective nature and also the fact that it was a multicenter study would likely lead to inconsistencies in diagnostic approach and management, as well as in the data recorded (in particular postoperative care). Fourth, the median duration of follow-up was 15 months (ranging from 1 month to 3 years) and, therefore, the low rate of recurrence for this disease might be an underestimate. One specific concern would be that there might have been insufficient time for some dogs to relapse, most notably those dogs with a short follow-up time. However, there was no significant difference in dogs that died versus those that did not (Mann-Whitney P = .85 for insulinoma-related death; P = 0.71 for all-cause mortality). This suggests that the duration of follow-up in the dogs that did not relapse in their follow-up was not considerably shorter than in those that did. Further, time to relapse or censoring was significantly shorter in dogs that relapsed than in dogs that did not (Mann-Whitney P = .02); this would suggest that the short follow-up times almost invariably occur in dogs that relapse quickly (as supported by the statistics of time to death or censoring or time to relapse). Indeed, of the 16 dogs with a follow-up time of <100 days, all but 1 had relapsed within their follow-up period. Finally, because this was a referral population, it might not be fully representative of cases seen in primary care practice. That said, because surgical management of insulinoma is usually undertaken in referral centers, these findings are likely to be helpful for primary care veterinarians when discussing possible outcomes of referral surgical management with owners.

In summary, this study examined postoperative complications, relapse and survival times of dogs undergoing surgical management of insulinoma. Stage of the disease and postoperative hypoglycemia were associated with a greater odds of relapse and decreased survival time. Although there was also an association with suspected pancreatitis, the clinical importance of this is not clear. Development of DM after surgery for insulinoma might be more common than previously reported, and affected dogs have a worse prognosis than dogs with only transient hyperglycemia. Such information might aid clinicians in predicting prognosis in the future.

CONFLICT OF INTEREST DECLARATION

Alexander J. German is an employee of the University of Liverpool, but his post is financially supported by Royal Canin, which is also owned by Mars Petcare. Alexander J. German has also received financial remuneration for providing educational material, speaking at conferences and consultancy work for Mars Petcare; all such remuneration has been for projects unrelated to the work reported in this manuscript. The other authors do not have a conflict of interest to declare.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study was approved by the University of Liverpool Research Ethics Committee (VREC659), and all owners gave written consent.

HUMAN ETHICS APPROVAL DECLARATION

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

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