

Clinical characteristics of, prognostic factors for, and long-term outcome of dogs with multiple acquired portosystemic shunts: 72 cases (2000–2018)

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OBJECTIVE

To identify clinical characteristics of, prognostic factors for, and long-term outcome of dogs with multiple acquired portosystemic shunts (MAPSSs) and determine whether survival time was associated with previous portosystemic shunt attenuation.

ANIMALS

72 client-owned dogs with MAPSSs.

PROCEDURES

Medical records of dogs in which MAPSSs had been diagnosed between January 2000 and August 2018 were reviewed for signalment, historic and diagnostic findings, management methods, and outcome.

RESULTS

Median survival time of dogs ($n = 23$) that died of causes related to MAPSSs was 580 days (range, 156 to 1,363 days). Factors significantly associated with dying of MAPSS-related versus unrelated causes included body weight, albumin concentration at the first and last recheck examinations, and cholesterol, total solids, and glucose concentrations at the last recheck examination. Dogs not receiving medical management or without signs of depressed mentation at the time of initial presentation were less likely to die of causes related to MAPSSs. Patient status (alive vs dead of causes related to MAPSSs vs dead of causes unrelated to MAPSSs vs dead of unknown causes) was not significantly associated with survival time.

CONCLUSIONS AND CLINICAL RELEVANCE

Survival time for dogs with MAPSSs was not shortened by previous portosystemic shunt attenuation surgery and was not different when death was versus was not related to MAPSSs. Dogs with MAPSSs that had progression of biochemical changes consistent with liver dysfunction were more likely to die of causes related to MAPSSs and were unlikely to live a normal lifespan.

Portosystemic shunts (PSSs) are vascular anomalies that establish a direct communication between the portal venous system and systemic circulation, bypassing the liver. These shunts can be further classified into congenital extrahepatic PSSs, congenital intrahepatic PSSs, single acquired PSSs, and multiple acquired (MAPSSs).^{1–3} Congenital PSSs occur secondary to inappropriate closure of the fetal vasculature, whereas acquired PSSs develop as a compensatory response secondary to portal hypertension or increased resistance in the portal system.^{4–7}

Formation of MAPSSs has been documented in 2% and 10% of dogs, respectively, following attenuation or ligation of a congenital extrahepatic or intrahepatic PSS and is a result of severe portal hypertension.^{8–13} In younger animals, MAPSSs commonly occur secondary to hepatoportal fibrosis (idiopathic noncirrhotic portal hypertension) or primary hepatic anomalies.^{2,7,14–16} Severe hepatic disease such as chronic hepatitis and fibrosing hepatic

cirrhosis is a more common cause of MAPSSs in older animals.^{2,4,17}

Clinical signs and changes in hematologic and biochemical factors of dogs with MAPSSs do not vary greatly from those for dogs with congenital PSSs, aside from the development of ascites (reported in 44% to 73% of dogs with MAPSSs) secondary to severe hypoalbuminemia and portal hypertension.^{5,6,15,18,19} Dogs with MAPSSs can have a history of neurologic (eg, abnormal mentation, hepatic encephalopathy, or seizures), gastrointestinal tract (eg, inappetence, diarrhea, vomiting, or weight loss), or urinary tract (eg, polyuria and polydipsia) abnormalities.^{7,20–23} Common hematologic and biochemical changes include microcytic, hypochromic anemia; high liver enzyme activities; low glucose, BUN, albumin, and cholesterol concentrations; hyperammonemia; and high pre- and postprandial bile acids concentrations.^{7,20,23}

A definitive diagnosis of MAPSSs is made through advanced imaging or exploratory laparotomy. Visualization of multiple, extrahepatic, tortuous vessels near the kidneys is characteristic of MAPSSs seen during exploratory laparotomy.^{7,15,20–24} Computed tomographic angiography, trans-splenic portal scintigraphy, and contrast-enhanced portal magnetic resonance angiography are all well-described modalities in diagnosing MAPSSs.^{25–30} Diagnosis of MAPSSs with trans-splenic portal scintigraphy is based on the identification of several discrete anomalous vessels in various locations, hepatofugal blood flow caudal to the cranial margin of the kidneys, or evidence of bolus fragmentation.^{26,27} One study²⁷ reported a high accuracy (13/14 cases) of trans-splenic portal scintigraphy in diagnosing MAPSSs, with none of the dogs with congenital PSSs having hepatofugal blood flow caudal to the cranial margin of the kidneys. Accuracy of abdominal ultrasonography to detect MAPSSs is variable and dependent on user experience.^{31–34} Compared with abdominal ultrasonography, computed tomographic angiography is 5.5 times as likely to detect PSSs and has a sensitivity of 96% for detection of PSSs.³¹

Treatment of MAPSSs is aimed at alleviating clinical signs and is similar to medical management of congenital PSSs.^{2,9,15,20,21,23,24} In a single case series²⁴ of dogs treated with medical management (ie, protein-restricted diets, antimicrobials, and diuretics), 62% survived to discharge after the initial hospitalization, but only 7% were alive at the median follow-up time of 41 months (range, 1 to 54 months). Dogs that were euthanized or died for reasons related to hepatic disease had a median survival time of 6.5 months.²⁴ To the authors' knowledge, there is a paucity of available information on long-term outcome of dogs with MAPSSs and on factors predisposing dogs to a poor outcome.

The objectives of the study reported were to document clinical characteristics and long-term outcome of dogs with MAPSSs and prognostic factors associated with outcome. We also wanted to determine whether survival time was associated with previous PSS attenuation. We hypothesized that dogs that developed MAPSSs following previous extrahepatic or intrahepatic PSS attenuation or that developed MAPSSs as a result of acquired hepatic disease would have shorter survival times, compared with survival times for dogs that developed MAPSSs secondary to congenital hepatic abnormalities.

Materials and Methods

Case selection criteria

Medical records at the University of Tennessee Veterinary Teaching Hospital were searched to identify dogs in which a diagnosis of MAPSSs had been made between January 2000 and August 2018. Dogs were eligible for inclusion in the study if a definitive diagnosis of MAPSSs was recorded in the medical

record; the diagnosis had been confirmed by means of exploratory laparotomy, trans-splenic portal scintigraphy, or computed tomographic angiography (alone or in combination); and follow-up information ≥ 6 months after the initial examination was available. Dogs were excluded if the diagnosis had been made only through abdominal ultrasonography or transcolonic scintigraphy, the diagnosis of MAPSSs had not been confirmed, or medical records lacked follow-up information for at least 6 months for dogs that were still alive, information on management recommendations following the diagnosis of MAPSSs, or physical examination findings. Additionally, dogs were excluded from the study if they were lost to follow-up between 6 and 24 months after MAPSSs were diagnosed.

Medical records review

Details collected from the medical record included signalment, body weight, and presenting complaint as documented in medical records or referral paperwork. Presenting complaints were reclassified by the authors into the following categories based on notations in the medical records: suspect PSS, hepatic dysfunction, toxin ingestion, suspect MAPSS formation, ascites, and unrelated. The presenting complaint was categorized as PSS if referral paperwork, patient history, or owner-mentioned suspicion that a PSS was suspected. Presenting complaint was categorized as hepatic dysfunction if hepatic enzyme activities were high or results of hepatic function tests were abnormal, but no notation of PSS was found, or if referral paperwork mentioned suspected hepatic dysfunction.

Information collected before initial presentation from referral documents provided in the medical records included clinical signs, duration of clinical signs, diet history, and previous treatments administered. Clinical signs exhibited before presentation were assigned to the following categories: no clinical signs, hepatic encephalopathy (if documented as such in the medical record), seizures, gastrointestinal tract signs (eg, vomiting, diarrhea, regurgitation, or anorexia), urinary tract signs (eg, polyuria, polydipsia, cystic calculi, stranguria, or hematuria), lethargy, and ascites.

Information collected at the time of initial presentation included physical examination findings and abnormalities, including neurologic signs, at presentation, and clinicopathologic abnormalities, including hematologic and serum biochemical abnormalities and abnormal pre- and postprandial bile acids concentrations, plasma ammonia concentration, and protein C activity. Neurologic signs exhibited at presentation were categorized as normal, depressed mentation, ataxia, hepatic encephalopathy, or obtunded mentation. Comorbidities, including life-threatening conditions, were diagnosed based on notations in the medical record and previous treatments. Results of clinicopathologic testing performed during the initial

hospital visit when the diagnosis of MAPSSs was made were recorded, along with diagnostic imaging results and whether uroliths were identified. The modality used to confirm the diagnosis of MAPSSs was documented based on notations in the medical record.

The authors attempted to classify the cause of the MAPSSs based on patient history, available diagnostic test results, and notations of etiology in the medical record. The following classifications were used to define the etiology of MAPSSs: secondary to previous surgical PSS attenuation, hepatic toxin exposure, primary hepatic disease, congenital disorder (eg, microvascular dysplasia or portal vein hypoplasia), and unknown. Etiology secondary to previous PSS attenuation was based on a history of previous PSS attenuation with no documented evidence of MAPSSs at the original procedure but a subsequent diagnosis of MAPSSs. Because dogs with a PSS can have histologic evidence of microvascular dysplasia or portal vein hypoplasia, PSS attenuation was classified as the primary cause of MAPSSs in dogs with these histologic abnormalities at the time of PSS attenuation surgery. The etiology of the MAPSSs was classified as microvascular dysplasia or portal vein hypoplasia if results of histologic examinations performed by a board-certified veterinary pathologist were available for review and documented compatible findings, including arteriolar duplication and reduplication, portal endothelial hyperplasia, portal hypoperfusion, and portal venous hypoplasia.^{35,36} Other hepatic histologic abnormalities were classified separately as listed in the medical records as cirrhosis, hepatitis, copper hepatopathy, lipogranulomas, and fibrosis. Dogs with evidence of multiple hepatic abnormalities were assigned to all qualified groups. Histopathology reports were then reclassified in an attempt to define the likely etiology of MAPSSs. Primary hepatic disease was defined as various forms of hepatitis or chronic fibrosis (cirrhosis). Additional etiologies were classified as hepatic toxin exposure (ie, owner-reported history of exposure with subsequent development of MAPSSs), congenital disorder (ie, a congenital hepatic anomaly that could result in portal hypertension, such as microvascular dysplasia or portal vein hypoplasia, or idiopathic noncirrhotic portal hypertension), and unknown cause (ie, no history of congenital PSS attenuation and no histologic abnormalities or historical factors that could account for development of MAPSSs).

Follow-up information was obtained either by reviewing medical records at the authors' hospital or through referral records obtained from the primary veterinarian. Results of recheck clinicopathologic testing performed at the first and second or final recheck examination were recorded. Clinical signs and medical management information 6 months following the diagnosis were recorded when available.

Outcome

Current patient status was defined as alive, dead (died or euthanized), or lost to follow-up. Patients lost

to follow-up after 24 months were included in the study but excluded from survival analyses owing to the inability to accurately determine survival time. Survival time since diagnosis was calculated from the date of definitive diagnosis to the date of last contact with the owner or primary veterinarian. Cause of death was recorded as related to MAPSSs, likely related to MAPSSs, unlikely related to MAPSSs, or information not provided. Death related to MAPSSs and death likely related to MAPSSs were identified as such on the basis of signs of severe or progressive liver dysfunction such as hypoalbuminemia, hepatic encephalopathy or nonresponsive seizures, icterus, ascites, and gastrointestinal hemorrhage. Deaths confirmed by referring veterinary hospital records but without information pertaining to cause of death or euthanasia were classified as "information not provided."

Statistical analysis

Descriptive statistics were calculated. The Shapiro-Wilk normality test was used to determine whether continuous data were normally distributed, with normally distributed continuous variables reported as mean \pm SD and continuous variables that were not normally distributed reported as median and range. Categorical data are expressed as counts and percentages.

Logistic regression analysis was used to evaluate whether signalment, historical findings, physical examination abnormalities, medical management, results of clinicopathologic testing, cause of MAPSSs, and results of follow-up clinicopathologic testing were associated with the binary response variable of death related to MAPSSs (ie, death related or likely related to MAPSSs) versus death unrelated to MAPSSs (ie, death unlikely related to MAPSSs). Median survival times were estimated with the Kaplan-Meier method. Cox proportional-hazards model analysis was conducted to evaluate whether current patient status (alive vs dead of causes related to MAPSSs vs dead of causes unrelated to MAPSSs vs dead of unknown causes) was associated with survival times. Dogs that were classified as lost to follow-up after 24 months were not included in the logistic regression analysis or survival time analysis.

All statistical analyses were performed with standard software (SAS, version 9.4; SAS Institute Inc). Values of $P \leq 0.05$ were considered significant.

Results

Animals

A total of 113 medical records were reviewed, and 72 dogs met the criteria for inclusion in the study. Of the 72 dogs included in the study, 31 (43.1%) were male (9 sexually intact and 22 castrated) and 41 (56.9%) female (9 sexually intact, and 32 spayed). Median age at the time of initial diagnosis of the MAPSSs was 30.8 months (range, 3 to 97 months), and the median body weight was 7.61 kg (range 1.02 to

34 kg). Multiple breeds were represented, with Yorkshire Terriers ($n = 20$), mixed breed dogs (13), Maltese (5), Miniature Schnauzers (4), Toy Poodles (3), and Beagles (3) being the most common. The remaining 24 dogs represented 16 breeds, with 16 small-breed dogs and 8 large-breed dogs. Sex, breed, and age were not significantly associated with whether death was related versus unrelated to MAPSSs. However, body weight was significantly ($P = 0.01$) associated with whether death was related to MAPSSs (OR for each 1-kg increase in body weight, 1.082; 95% CI, 1.016 to 1.152). Mean \pm SD body weight was 11.39 ± 11.35 kg for dogs for which death was related to MAPSSs and was 5.83 ± 5.73 kg for dogs for which death was unrelated to MAPSSs.

Medical history information was available for all 72 dogs. Fourteen (19.4%) dogs did not have any clinical signs; for the remaining 58 (80.6%) dogs, clinical signs included gastrointestinal signs (38/58 [65.5%]), followed by hepatic encephalopathy (23/58 [39.7%]), lethargy (20/58 [34.5%]), urinary tract signs (19/58 [32.8%]), seizures (6/58 [10.3%]), and ascites (6/58 [10.3%]). Clinical signs had been present for 0 to 3 months (36/58 [62.1%]), 6 to 12 months (18/58 [31.0%]), or > 12 months (4/58 [6.9%]).

Sixty-two of the 72 (86.1%) dogs received previous medical or surgical treatment for management of a suspected PSS before admission. Twenty (27.8%) dogs had undergone previous surgical management of a PSS, including extrahepatic PSS attenuation ($n = 18$) with an ameroid ring constrictor (16) or silk suture (2) and intrahepatic PSS attenuation with cellophane banding (2). At the time of presentation, 55 dogs were receiving medical management for a suspected PSS, including 42 (58.3%) dogs that received only medical management and 13 (18.1%) dogs that had previously undergone PSS attenuation. The most common medical management documented at initial presentation included lactulose (38/55 [69.1%]), antimicrobials (33/55 [60.0%]), nutraceuticals (20/55 [36.3%]), and acid suppressants (10/55 [18.2%]).

Information on diet was available for all 72 dogs, with 40 (55.6%) dogs being fed a commercial liver-specific diet, 25 (34.7%) being fed a commercial, nonliver-specific diet, 4 (5.6%) being fed a nutritionist-developed formulated diet, and 3 (4.2%) being fed a home-cooked diet. On the basis of history recorded in the medical record at the time of initial presentation, 32 of 55 (58.1%) dogs had no recorded response to medical management, 17 (30.9%) showed improvement of clinical signs after starting medical management, and 6 (10.9%) showed no improvement. Dogs that were not receiving medical management before or at the time of initial presentation were significantly ($P = 0.04$) less likely (OR, 0.333; 95% CI, 0.113 to 0.980) to die of causes related to MAPSSs than were dogs that were receiving medical management.

Initial presentation

The chief presenting complaint as documented in the medical records was most commonly a suspected single congenital PSS (38/72 [52.8%]). Chief presenting complaints for the remaining dogs were suspected MAPSSs (16/72 [22.2%]), hepatic dysfunction (10/72 [13.9%]), concerns unrelated to MAPSSs (6/72 [8.3%]), and ascites (2/72 [2.78%]). No physical examination abnormalities were documented in 43 of the 72 (59.7%) dogs, whereas 29 (40.3%) had documented abnormalities including neurologic abnormalities ($n = 14$) such as depressed mentation (11), encephalopathy (2), and obtundation (1); underweight (10); ascites (5); poor muscle mass (2); poor haircoat (2); hypersalivation (1); and other signs unrelated to MAPSSs (11). Potentially life-altering systemic comorbidities unrelated to the liver were present in 16 of the 72 (22.2%) dogs. Dogs without mild neurologic signs (ie, depressed mentation) at the time of initial presentation were significantly ($P = 0.02$) less likely (OR, 0.203; 95% CI, 0.052 to 0.787) to die of causes related to MAPSSs than were dogs that had neurologic abnormalities (ie, hepatic encephalopathy and obtundation) at the time of initial presentation.

Sixty-five of 72 (90.3%) dogs had a CBC, serum biochemical panel, or venous blood gas analyses performed at the time of initial presentation (**Table 1**). None of the clinicopathologic findings were significantly associated with whether dogs died of causes related or unrelated to their MAPSSs.

Diagnosis and initial recommendations

Advanced imaging aided in the diagnosis of MAPSSs in 71 of the 72 (98.6%) dogs. The diagnosis of MAPSSs was confirmed by means of trans-splenic portal scintigraphy in 35 of the 72 (48.6%) dogs, exploratory laparotomy in 28 (38.9%), and computed tomographic angiography in 9 (12.5%). Mean \pm SD shunt fraction for dogs that underwent trans-splenic portal scintigraphy was $80.4 \pm 18.3\%$ (range, 12 to 97.2%). Common scintigraphic findings in dogs that underwent trans-splenic portal scintigraphy included hepatofugal flow caudal to the spleen or cranial margin of the kidney ($n = 31$), biphasic or bolus fragmentation (21), findings different from findings of scintigraphy performed before shunt attenuation (7), multiple anomalous vessels (5), and slow absorption or a prolonged spleen-to-heart transit time (3). Twenty-nine of 35 (82.9%) dogs in which the diagnosis was confirmed by means of trans-splenic portal scintigraphy underwent additional imaging, and in all 29, the radiology report provided by a board-certified veterinary radiologist documented the diagnosis of MAPSSs.

Hepatic biopsy specimens from 31 of the 72 (43.1%) dogs were submitted for histologic examination, and the most common finding was portal vein hypoplasia or microvascular dysplasia (27/31, 87.1%). Additional histopathologic findings included lipogranulomas (3 [9.7%]), noncirrhotic fibrosis (3 [9.7%]), active hepatitis (2 [6.5%]), and cirrhosis (2 [6.5%]).

Table 1—Results of clinicopathologic testing in 72 dogs with multiple acquired portosystemic shunts.

Variable	Initial presentation		First recheck examination		Second or final recheck examination		Reference range
	No. of dogs	Mean \pm SD	No. of dogs	Mean \pm SD	No. of dogs	Mean \pm SD	
Total solids (g/dL)	42	5.41 \pm 0.76	45	5.76 \pm 0.87	42	6.02 \pm 0.87 ^a	5.4–6.8
Hct or PCV (%)	28	41.7 \pm 7.7	35	44.8 \pm 7.76	34	44.6 \pm 10.6	40.5–59.9
WBCs ($\times 10^3$ cells/ μ L)	36	14.1 \pm 9.7	35	12.6 \pm 6.3	36	14.3 \pm 11.3	4.7–15.2
Neutrophils ($\times 10^3$ cells/ μ L)	36	10.1 \pm 8.8	34	9.18 \pm 5.9	35	9.93 \pm 9.4	2.41–10.88
Glucose (mg/dL)	49	94.7 \pm 19.98	42	99.5 \pm 27.9	42	88.3 \pm 20.3 ^a	82–132
BUN (mg/dL)	48	9.29 \pm 8.2	45	9.9 \pm 8.8	42	14.4 \pm 23.5	7–37
Creatinine (mg/dL)	48	0.48 \pm 0.19					0.3–1.1
ALT (U/L)	48	319.0 \pm 393.4	47	183.1 \pm 188.7	43	222.2 \pm 258.3	18–100
ALP (U/L)	48	308.3 \pm 661.7	45	233.2 \pm 557.8	43	254.8 \pm 520.9	13–240
GGT (U/L)	6	10.2 \pm 4.9	27	6.7 \pm 5.2	25	7.6 \pm 5.9	0–5
AST (U/L)	46	93.6 \pm 74.4	22	75.4 \pm 66.1	24	69.8 \pm 60.9	9–63
Cholesterol (mg/dL)	47	165.7 \pm 94.2	36	172.6 \pm 136.8	33	213.8 \pm 124.9 ^a	130–354
Albumin (g/dL)	48	2.78 \pm 0.58	45	2.75 \pm 0.6 ^a	43	2.8 \pm 0.6 ^a	3.2–4.3
Globulin (g/dL)	48	2.66 \pm 0.58	44	3.1 \pm 0.6	43	3.2 \pm 0.68	1.9–3.1
Total bilirubin (mg/dL)	47	0.38 \pm 0.74	37	0.26 \pm 0.23	38	0.28 \pm 0.23	0.1–0.6
Bile acids (μ mol/L)							
Preprandial	17	101.2 \pm 104.7	7	111.1 \pm 80.3	5	127.9 \pm 83.3	0–10
Postprandial	17	145.6 \pm 136.7	8	258.9 \pm 138.3	4	285.2 \pm 300.9	0–30
Protein C (%)	23	30.7 \pm 16.2	1	42	0	NA	75–135
Ammonia (μ g/dL)	11	121.4 \pm 90.6	5	164.6 \pm 122.9	3	1,343.3 \pm 962.3	0–16

ALP = Alkaline phosphatase. ALT = Alanine transaminase. AST = Aspartate transaminase. GGT = γ -Glutamyltransferase. NA = Not applicable.

^aValues differed significantly ($P < 0.05$) between dogs that died of causes related to the acquired portosystemic shunts and dogs that died of unrelated causes.

None of the samples had obvious evidence of copper hepatopathy. Urolithiasis was identified in 22 of the 72 (30.5%) dogs on the basis of exploratory laparotomy and diagnostic imaging findings. Results of urolith composition analysis were available for 7 of these 22 (31.8%) dogs, with urate stones identified in 6.

Overall, the cause of MAPSSs could not be determined in 22 of the 72 (30.6%) dogs. The most commonly determined etiologies for MAPSSs were an underlying primary hepatic anomaly such as portal vein hypoplasia or microvascular dysplasia (26/72 [36.1%]) or previous PSS attenuation (20/72 [27.8%]). Additional etiologies included primary liver disease (5/72 [6.9%]) and liver toxin (unspecified but strongly suspected by a board-certified veterinary pathologist; 2/72 [2.78%]). Formation of MAPSSs may have been multifactorial in 3 (4.2%) dogs.

During hospitalization for the initial presentation, 2 dogs experienced cardiopulmonary arrest and died, and an additional 2 dogs were euthanized intraoperatively. For the surviving 68 (94.4%) dogs, treatment recommendations included a specific commercial (61/68 [89.7%]) or formulated (3/68 [4.4%]) diet, lactulose (54/68 [79.4%]), nutraceuticals (38/68 [55.9%]), antimicrobials (31/68 [45.6%]), acid suppressants (23/68 [33.8%]), and anticonvulsants (3/68 [4.4%]). No significant associations were detected between diagnostic imaging modality, diagnostic imaging findings, shunt fraction determined by means of portal scintigraphy, presence of urolithiasis, histopathologic findings, suspected cause of MAPSSs, or medical management or dietary recommendations

and the likelihood of death related versus unrelated to MAPSSs.

Follow-up results

Additional clinicopathologic testing was performed at some time during the follow-up period in 52 of the 68 (76.5%) dogs that survived to discharge. Within 3 weeks after diagnosis of MAPSSs, an additional 4 of the 68 (5.9%) dogs that survived to discharge had died or were euthanized without undergoing additional diagnostic testing.

Results of clinicopathologic testing performed during the first recheck appointment following the diagnosis of MAPSSs and results of testing performed during the second or final recheck appointment were recorded (Table 1). Mean \pm SD time from diagnosis to the first follow-up clinicopathologic testing was 411 \pm 547.2 days. Serum albumin concentration was significantly ($P = 0.007$) lower in dogs that died of causes related to MAPSSs than in dogs that died of unrelated causes (Table 2), and dogs with higher serum albumin concentrations were significantly (OR for each 1 g/dL increase in serum albumin concentration, 0.158; 95% CI, 0.041 to 0.604) less likely to die of causes related to MAPSSs. No other clinicopathologic test results from the first recheck appointment were significantly associated with dying of causes related to MAPSSs.

Mean \pm SD time from diagnosis to the second or final follow-up clinicopathologic testing was 1,286 \pm 956 days. Serum albumin, cholesterol, glucose and total solids concentrations were all significantly

Table 2—Serum biochemical values that differed significantly between dogs in Table 1 that died of causes related to multiple acquired portosystemic shunts and dogs that died of unrelated causes.

Variable	Dogs that died of causes related to their shunts	Dogs that died of unrelated causes	P value
First recheck examination			
Albumin (g/dL)	2.38 ± 0.61	2.93 ± 0.51	0.007
Second or final recheck examination			
Albumin (g/dL)	2.32 ± 0.72	2.95 ± 0.46	0.01
Cholesterol (mg/dL)	128.9 ± 62.4	256.3 ± 127.5	0.007
Glucose (mg/dL)	77.5 ± 23.2	93.1 ± 17.2	0.03
Total solids (g/dL)	5.4 ± 0.94	6.3 ± 0.70	0.009

associated with dying of causes related versus unrelated to MAPSSs (Table 2). Dogs with higher serum albumin concentration (OR for each 1 g/dL increase in serum albumin concentration, 0.169; 95% CI, 0.044 to 0.657), higher serum cholesterol concentration (OR for each 1 mg/dL increase in serum cholesterol concentration, 0.981; 95% CI, 0.968 to 0.995), higher serum glucose concentration (OR for each 1 mg/dL increase in serum glucose concentration, 0.962; 95% CI, 0.929 to 0.996), or higher total solids concentration (OR for each 1 g/dL increase in total solids concentration, 0.215; 95% CI, 0.068 to 0.686) were significantly less likely to die of causes related to MAPSSs. No other clinicopathologic test results from the second or final recheck appointment were significantly associated with dying of causes related to MAPSSs.

Information on clinical signs 6 months after the diagnosis of MAPSSs was available for 26 dogs. Twelve of the 26 (46.2%) did not have associated clinical signs, 7 (26.9%) had gastrointestinal tract signs, and 4 (15.4%) had hepatic encephalopathy. Medical management 6 months after the diagnosis of MAPSSs included lactulose (33/49 [67.3%]), nutraceuticals (18/49 [36.7%]), and antimicrobials (18/49 [36.7%]). None of these variables were statistically associated with dying of causes related to MAPSSs.

Outcome and survival time

Twenty-two of 72 (30.5%) dogs were still alive at the time of the study, 12 (16.7%) had been lost to follow-up > 24 months after diagnosis, and 38 had died (12/72 [16.7%]) or been euthanized (26/72 [36.1%]). For dogs that were still alive at the time of the study, median survival time was 999.5 days (range, 341 to 3,236 days). Twenty-three of 38 dogs died or were euthanized for reasons related to MAPSSs. For these dogs, median survival time was 580 days (range, 156 to 1,363 days), with 14 of the 23 (60.8%) dogs alive > 330 days after the diagnosis and 6 (26.1%) alive > 1,582 days after the diagnosis. The cause of death or euthanasia for dogs that were dead for reasons related to MAPSSs was progressive hepatic disease (ie, icterus, ascites, edema, or hypoalbuminemia; $n = 7$), persistent gastrointestinal tract signs and anorexia (6), hepatic encephalopathy (5), seizures (3), duodenal ulceration (1), and failure to thrive (1).

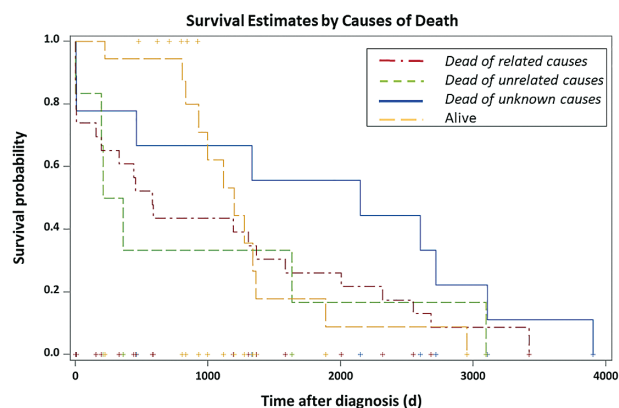


Figure 1—Kaplan-Meier survival analysis curves for 60 dogs with multiple acquired portosystemic shunts that were still alive at the time of the present study ($n = 22$), had died or been euthanized for reasons related to the shunts (23), had died or been euthanized for reasons unrelated to the shunts (6), or had died or been euthanized for unknown reasons (9). Patient status (alive vs dead of causes related to the shunts vs dead of causes unrelated to the shunts vs dead of unknown causes) was not significantly ($P = 0.385$) associated with survival time.

Six of 37 (16.2%) dogs died or were euthanized for reasons unrelated to MAPSSs. For these dogs, median survival time was 284.5 (range, 1 to 3,095 days), with 2 of the 6 (33.3%) dogs alive > 360 days after the diagnosis. The cause of death or euthanasia for these dogs was immune-mediated thrombocytopenia ($n = 1$), septic peritonitis (1), trauma (1), neoplasia (1), and progressive renal disease (2).

Information regarding the cause of death or euthanasia was not available for 9 of 37 (24.3%) dogs. Median survival time for these dogs was 2,146 days (range, 4 to 3,107 days).

Current patient status (alive vs dead of causes related to MAPSSs vs dead of causes unrelated to MAPSSs vs dead of unknown causes) was not significantly ($P = 0.385$) associated with survival time (Figure 1).

Discussion

In the present study, various factors were associated with an increased odds of dogs with MAPSSs dying of causes related versus unrelated to

their shunts. However, survival time was not significantly different between dogs that died of causes related to MAPSSs and dogs that died of causes unrelated to MAPSSs. A previous study²⁴ reported that dogs with MAPSSs, especially those that developed MAPSSs secondary to primary liver disease, had a poor prognosis because of progressive clinical signs associated with portal hypertension. This finding was not repeatable in our study and dogs in the present study that died of causes related to MAPSSs had a longer median survival time (580 days) than did the dogs in that previous study (median survival time, 195 days). However, most dogs in the present study were young when MAPSSs were diagnosed, and median survival time was not consistent with a typical life expectancy. Additionally, biochemical changes consistent with progressive hepatic dysfunction such as hypoalbuminemia, hypoglycemia, and hypocholesterolemia were significantly associated with the likelihood of dying for reasons related to MAPSSs. Therefore, it can be assumed that dogs with MAPSSs, particularly those with progressive biochemical signs of hepatic dysfunction, have a poor long-term prognosis. Our study hypothesizes that dogs with previous PSS attenuation and those with acquired hepatic disease would have shorter survival times were rejected, and although reasons for these findings are unclear, they suggest that the main effects on survival time in dogs with MAPSSs are related to progressive hepatic dysfunction.

The most commonly determined etiologies for MAPSSs in the present study were an underlying primary hepatic anomaly such as portal vein hypoplasia or microvascular dysplasia (26/72 [36.1%]) and previous PSS attenuation (20/72 [27.8%]). Although previous studies^{2,15,36} evaluating dogs with portal vein hypoplasia or microvascular dysplasia did not include those with MAPSSs, the dogs in those studies were reported to have a more favorable long-term outcome. Previous reports^{9,37} detail MAPSS formation following PSS attenuation and suggest that possible sequelae to MAPSS formation could range from no clinical signs to death or euthanasia. Only 3 of the 20 (15.0%) dogs in the present study in which the etiology of their MAPSSs was previous PSS attenuation underwent liver biopsy following diagnosis of MAPSSs. Therefore, it was impossible to determine in most cases whether there were persistent liver abnormalities that may have caused the MAPSSs as opposed to PSS attenuation itself. The literature is variable and sparse as to prognosis following a diagnosis of MAPSSs in dogs with these conditions. Additionally, 22 of 72 (30.5%) dogs in the present report were still alive at the study conclusion, and median survival time for these dogs (999.5 days) was longer than median survival time in a previous study³⁸ of dogs with congenital PSSs that received only medical management (2.3 years). These results suggest there is a subset of dogs with MAPSSs that have the potential for a long survival time.

Trans-splenic portal scintigraphy, which was used to confirm the diagnosis in 35 of the 72 (48.6%) dogs in the present study, has been previously reported to be useful in the diagnosis of PSSs and MAPSSs.^{26–28,37} Although less common outside of academic institutions, trans-splenic portal scintigraphy has been shown to be 100% sensitive in diagnosing congenital PSSs, making it an inexpensive and fast diagnostic tool, compared with computed tomographic angiography.²⁸ In a previous study,²⁷ common scintigraphic findings in 14 dogs with MAPSSs included hepatofugal flow caudal to the cranial margin of the kidneys (13/14), multiple distinct shunting vessels (9/14), and a longer transit time from the spleen to the heart.²⁷ In the present study, hepatofugal flow caudal to the cranial kidney margin was documented in most dogs (31/35) and multiple distinct shunting vessels were identified in 5. In addition, 21 dogs in the present study had evidence of bolus fragmentation, 3 had a prolonged spleen-to-heart transit time, and 7 had alterations in the scintigraphic pattern from before to after congenital PSS attenuation. Morandi et al²⁷ reported an accuracy of 92.9% associated with trans-splenic portal scintigraphy, but it is possible that MAPSSs is an underdiagnosed condition if this modality is used alone and these findings are typically not noted.

Synthesis of proteins, especially albumin, is one of the many important functions of the liver. Hypoalbuminemia is not specific for hepatic disease but can occur with severe hepatic failure.^{14,17,39} Hypoglycemia is a common finding in dogs with PSSs and is thought to be related to impaired hepatic production, a reduced response to glucagon, or decreased glycogen stores.¹⁶ Hypoglycemia, although rare, can also be seen with acute liver failure and end-stage chronic hepatic disease and is considered a negative prognostic indicator.^{16,40} The liver is also responsible for synthesis of cholesterol from chylomicrons and lipoproteins, and hypocholesterolemia is often seen in dogs with PSSs and in about 40% of dogs with chronic hepatitis, especially in those with cirrhosis.⁴¹ In these instances, hypocholesterolemia is likely secondary to decreased production or increased incorporation of cholesterol with bile acids.¹⁶ Although hypoproteinemia, hypoalbuminemia, hypoglycemia, and hypocholesterolemia are all characteristic findings of PSSs, these findings are also all seen with loss of 70% to 80% of hepatic functional capacity.^{40,42} We suspect that the progressive hypoalbuminemia, hypoglycemia, hypocholesterolemia, and hypoproteinemia seen on recheck clinicopathologic testing in the present study were most suggestive of progressive or end-stage hepatic disease, which would account for the association with an increased odds of dying of causes related to MAPSSs.

Historically, medical management, including lactulose, antimicrobials, acid suppressants, and a protein-restricted diet, is recommended to control clinical signs associated with MAPSSs and is the mainstay of PSS management.⁹ Typically, medications are

administered in an attempt to control and minimize the production of ammonia, reducing the likelihood and severity of hepatic encephalopathy.⁹ Interestingly, no specific medication following the diagnosis of MAPSSs was associated with the odds of dying of causes related to the shunts in the dogs in the present study. However, dogs that were receiving medications as a part of their medical management at the time of initial presentation had an increased odds of death related to MAPSSs, compared with dogs not receiving medications. It could be assumed that dogs being administered medications for the management of clinical signs before diagnosis may have had more advanced disease or were more dependent on medical management, compared with dogs without clinical signs.

In dogs, hepatic encephalopathy occurs after > 70% of functional hepatic mass is lost. Although the condition is not entirely understood, it is believed to be secondary to circulating neurotoxins that can impair neuron and astrocyte function, cause an inflammatory response, and alter the permeability of the blood-brain barrier, impairing cerebral function.^{43–46} Clinical signs associated with hepatic encephalopathy are variable and can range from excitatory activity, such as seizures, to inhibitory activity, such as lethargy, ataxia, and unresponsiveness.^{3,11,24} Interestingly, dogs in the present study with more severe neurologic signs did not have an increased odds of death related to MAPSSs when compared to dogs with mild neurologic signs such as depressed mentation. This could be explained by the small number of dogs with hepatic encephalopathy, compared with the number with depressed mentation only.

Higher body weight on initial presentation increased the odds of death related to MAPSSs in the dogs in the present study, which was contrary to findings in previous reports^{47,48} in which dogs that had a lower body weight had a worse outcome following attenuation of an intrahepatic or extrahepatic PSS. The reason behind these findings is not entirely understood; however, medium- to large-breed dogs seem to be more predisposed to primary hepatic diseases with a poorer prognosis, such as copper-associated chronic hepatitis, compared with small-breed dogs, which are more commonly affected by portal vein hypoplasia and microvascular dysplasia.^{49,50} Another consideration would be the effect of ascites on body weight in this population of dogs, as theoretically dogs with a large volume of ascites could have a higher body weight secondary to fluid accumulation. Unfortunately, the volume of ascites in the affected dogs was not measured, so any further characterization of this association is not possible, and the presence of ascites was not significantly associated with the likelihood of death related to MAPSSs.

The primary limitations of the present study were related to its retrospective nature. Follow-up times and data recorded during recheck examinations varied widely among dogs, and information

that was available varied depending on the detail and completeness of medical records, attending clinician, and owner compliance. Therefore, complete medical records were not available for every dog. Survival times should be interpreted in light of the fact that 22 of the 72 (30.5%) dogs were still alive at the conclusion of the study and that 12 (16.7%) dogs were lost to follow-up evaluation after 24 months and thus were not included in survival analyses. Given the paucity of information regarding dogs with MAPSSs in the published literature, we believe that the dogs lost to follow-up after 24 months add valuable information even if survival time could not be determined, especially since the survival time of at least 24 months was longer than the median survival time of dogs that died of causes related to MAPSSs. To our knowledge, the present study was the first in the recent literature to describe a large cohort of dogs with MAPSSs and their outcome following diagnosis. However, it would be ideal to have a larger sample size followed up in a prospective manner to better characterize survival time in dogs with this condition. In addition, it is difficult to know how owner perceptions of a dog's prognosis and quality of life might have affected the decision to euthanize individual dogs and ultimately the median survival time for this population of dogs.

To the authors' knowledge, the present study was the first to evaluate a large population of dogs with MAPSSs and the long-term effects of MAPSSs on survival time. Dogs receiving medical management at the time of presentation, presumably because of clinical signs related to MAPSSs, were more likely to die of causes related to their shunts than were dogs not receiving medical management. Dogs without depressed mentation at initial presentation had a decreased likelihood of dying of causes related to MAPSSs, and dogs with a higher body weight and progressively lower hepatic function were more likely to die of causes related to their shunts. In general, dogs in this study were young, and those that had a progression in biochemical test results consistent with hepatic dysfunction were unlikely to live a normal lifespan. The information presented here may help guide clinicians in providing prognostic information to owners of dogs with MAPSSs.

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