SYSTEMATIC REVIEW

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Treatment of congenital extrahepatic portosystemic shunts in dogs: A systematic review and meta-analysis

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Abstract

Background: Several options have been proposed for the treatment of congenital extrahepatic portosystemic shunts (cEHPSS) in dogs, but formal comparisons among different treatment options are currently unavailable. A previous evidence-based review (2012) found low quality of evidence for papers assessing the treatment of cEHPSS in dogs.

Objectives: To assess the quality of evidence available in the treatment of cEHPSS, summarize the current state of knowledge with respect to outcome after cEHPSS management, and compare different treatment techniques.

Animals: Not used.

Methods: A bibliographic search was performed without date or language restrictions. Studies were assessed for quality of evidence (study design, study group sizes, subject enrollment quality, and overall risk of bias) and outcome measures reported (perioperative outcome, clinical outcome, and surgical or interventional outcome), all reported with 95% confidence intervals. A network meta-analysis was performed.

Results: Forty-eight studies were included. Six retrospective studies (grade 4b) compared 2 techniques and 7 were abstracts (grade 5). The quality of evidence was low and risk of bias high. Regarding surgical outcome, statistically significant superiority of ameroid constrictor over thin film band was observed (*P* = .003). No other comparisons were statistically significant.

Conclusions and Clinical Importance: The evidence base of choice of treatment of cEHPSS in dogs remains weak despite recent publications on the subject. Ameroid is superior to thin film band in causing EHPSS closure. Blinded randomized studies comparing different treatment modalities, which routinely include postoperative imaging to assess cEHPSS closure and acquired portosystemic shunt development are essential.

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1 | INTRODUCTION

The first study reporting congenital extrahepatic portosystemic shunt (cEHPSS) management in dogs was published in 1976 and since that time, several medical and surgical or interventional approaches have been suggested and applied.[1-6] Although surgical or interventional treatment is recommended over medical management,[7] not all patients are ideal surgical or interventional candidates. Treatment options might be influenced by the owner's financial capacity, patient's clinical signs and concomitant diseases, anesthetic risk, and shunt morphology.[8] In the past, complete ligation was the treatment of choice in dogs that tolerated complete cEHPSS occlusion intraoperatively, with maximum attenuation of a cEHPSS in a single procedure based on portal pressure measured during the procedure and subjective visual criteria during shunt occlusion.[9,10] In recent years, gradual occlusion methods (thin film band, ameroid constrictor, and coil embolization) have become popular in an attempt to minimize the risk of perioperative complications, life-threatening portal hypertension, and to treat the high percentage of dogs that do not tolerate acute shunt occlusion.[2,4,9] In order to elect the best treatment modality for cEHPSS, comparison of the different available techniques and their overall outcome is needed. In 2012, an evidence-based review based on English language peer-reviewed papers assessed the quality of evidence.[6] Our study differs from the previous study because we applied an intensive search without date (until 2018) or language restrictions, employed the use of 95% confidence intervals (CI) in data assessment, and performed a network meta-analysis (NMA) to compare different techniques. Our goal was to provide an updated and extended evaluation, comparing current published evidence on the different treatment options for dogs with cEHPSS based on objective criteria, in order to provide small animal clinicians with evidence-based information about the available treatment modalities and associated short- and long-term outcomes. To do so, we used a PICO framework to develop the literature search strategy. The PICO acronym stands for: P, patient, problem, or population; I, intervention; C, comparison, control, or comparator; and O, outcome. Hence, our PICO question was "What is the best treatment technique in the short and long-term for the treatment of cEHPSS in dogs?"

2 | MATERIALS AND METHODS

2.1 | Search strategy

The literature search aimed to identify all studies evaluating the clinical effectiveness of medical, surgical, or interventional treatment of cEHPSS in dogs. Article selection and data extraction were performed by the primary author (G.S.) and assisted by the coauthors (N.D. and F.M.). When conflicts existed, studies were evaluated based on the inclusion criteria below:

- Criterion 1: Type of study: peer-reviewed studies and congress abstracts. Clinical trials and case series were included if these described >5 dogs.
- Criterion 2: Case diagnosis: dogs with cEHPSS, either with or without clinical signs related to the cEHPSS, were included. Confirmation of the cEHPSS by portovenography, computed tomography angiography (CTA), portal scintigraphy, abdominal ultrasonography, magnetic resonance angiography (MRA), or identification of the shunt vessel during surgery was essential. Dogs were excluded if the type of shunt (extrahepatic versus intrahepatic) was not defined. Dogs with a diagnosis of up to 2 cEHPSS were included.
- Criterion 3: Treatment: dogs managed by medical treatment, surgical, or interventional or both were included. Medical treatment consisted of dietary treatment, lactulose, antibiotic treatment, or some combination of them. For dogs that underwent surgical or interventional treatment, only the outcomes and follow-up from the first intervention were considered. The type of surgery had to be clearly documented.
- Criterion 4: Outcome: studies had to include (or provide enough information to deduce) perioperative outcome and long-term clinical, surgical, or interventional follow-up, with description of general patient condition and survival time. Improvement or worsening of the patient's general condition, assessed by a clinician or the owner, had to be reported. Studies selectively reporting on cEHPSS complications or management of these complications were excluded. Studies in which outcomes for multiple surgical or interventional treatments (eg, ameroid constrictor and ligation) could not be differentiated were excluded. Studies describing cEHPSS and intrahepatic portosystemic shunts (IHPSS) together were excluded if the different shunt types (cEHPSS versus IHPSS) could not be distinguished with regard to outcome, except for studies in which the IHPSS cases did not exceed 5% of the total population.

Electronic search engines for publication databases, reference lists of published papers, and proceedings of relevant scientific conferences were used to search all possible pertinent papers. The utilized databases were PubMed (www.ncbi.nlm.nih.gov/PubMed) and Web of Science (www.webofknowledge.com). Electronic searches were undertaken until October 20, 2018, by the primary author (G.S.) and 2 of the coauthors (N.D. and F.M.) independently without date or language restriction. Details of the search strategy are presented in Supporting Information S1. Articles searched from reference lists of publications and proceedings from 1990 to 2018 (or the first meeting after 1990) of major internal medicine and surgery conference meetings (European College of Veterinary Internal Medicine - Companion

Animals Congress, American College of Veterinary Internal Medicine Forum, European College of Veterinary Surgery Annual Scientific Meeting, and American College of Veterinary Surgery Veterinary Symposium). Other proceedings were included if manual search or electronic search identified pertinent information. All results returned from electronic, manual, and reference list searches were recorded and analyzed.

2.2 | Study selection

Studies written in languages other than English were assessed by a veterinarian fluent in the language of publication (Portuguese, Greek, Dutch, German, French, and Spanish). A 2-stage screening process was used by the primary author (G.S.).[11] All studies that fulfilled criterion 1 and reported findings on cEHPSS in dogs were analyzed based on title and abstract. Stage 2 identified papers that fulfilled criteria 2, 3, and 4. These were evaluated in detail for the type of paper, diagnostic methods used, treatment method, perioperative outcome, clinical outcome, surgical or interventional outcome, and follow-up time (see below for definitions).

2.3 | Assessment of quality of evidence

For every study selected, a modified Preferred Reporting Items for Systematic reviews and Meta-Analyses classification was performed similar to a previous study.[11] Studies were assessed for the level of evidence based on a modified "Oxford Centre for Evidence-Based Medicine" grading system. The grading system was modified to remove categories that were not applicable to the present study. Furthermore, "grade 4" evidence was subdivided in to 3 subgroups to allow greater differentiation among the evidence available, similar to a previous publication[6] (Table 1). A fusion of original "grade 4c" and "grade 4d" subgroups was performed, becoming simply "grade 4c," as both refer to case series from which the treatment technique can be identified and outcome assessed. Abstracts were included in "grade 5." A 3-part system of evidence quality assessment consisting of study group size, subject enrollment quality, and overall risk of bias was used to characterize the strengths and weaknesses of each study.[11]

2.4 | Study group sizes

Depending on the number of subjects per group, each study was categorized using the following system: (1) *large*: >50 subjects per group; (2) *moderate*: 20-50 subjects per group; (3) *small*: 10-19 subjects per group; and (4) *very small*: <10 subjects per group.[11]

2.5 | Subject enrollment quality

Studies were classified as "clearly characterized" (ie, cEHPSS diagnosis was based on imaging techniques or on cEHPSS identification during surgery with available outcomes for the cEHPSS) or as "mixed characterization" (ie, the study had clear characterization of the cEHPSS, but reported combined outcomes for dogs with IHPSS and cEHPSS). If the

TABLE 1 Levels of evidence

Grade	Description
1a	Systematic review with homogeneity of RCT
1b	Individual RCT (with narrow confidence interval)
2a	Systematic review (with homogeneity) of cohort studies[a]
2b	Individual cohort studies (including RCT)
3a	Systematic review (with homogeneity) of case-control studies[b]
3b	Individual case-control study
4a	Lower quality prospective cohort/case-control study—concerns regarding definition of comparison groups and/or objective (preferably blinded) nature of assessment and/or consideration of confounding factors and/or adequacy of follow-up
4b	Retrospective cohort/case-control studies
4c	Case series
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Notes: Adapted from Oxford Centre for Evidence Based Medicine and Tivers et al.[6] "Grade 4" of evidence was subdivided in 3 subgroups in order to allow greater differentiation among the evidence available. Abbreviation: RCT, randomized clinical trial.
[a]A cohort study is a study that follows a group of patients over a period of time and investigates the effect of a treatment or risk factor.
[b]A case-control study is 1 that examines the effect of a risk factor on the outcome for a group of patients with a disease compared to that of a matched control group without the disease.

IHPSS population was >5% of each particular outcome, that outcome was not evaluated. Additionally, each study was evaluated for type of shunt morphology (ie, portocaval, portoazygos, and portophrenic).

2.6 | Overall risk of bias assessment

The overall risk of bias for the studies was evaluated based on the Cochrane "risk of bias" tool.[12] Each of the following components was categorized as having a "low," "moderate," "high," or "unclear" risk of bias: random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete data, selective reporting, and other sources of bias. Subsequently, the overall risk of bias for each article was determined (categorized as "low," "low to moderate," "moderate," "moderate to high," or "high." For group 4 studies, the overall risk of bias assessment was not applicable and they were categorized as studies with an overall "high" risk of bias.

2.7 | Assessment of outcome measures

2.7.1 | Classification

For each report included in this review, the medical management, surgical, or interventional technique or both was identified and statistically assessed (survival, clinical, and surgical or interventional outcome percentages; 95% CI and forest plots) by the main author (G.S.) and

1 coauthor (N.D.) working independently. When disagreement occurred, the other coauthors (M.C., H.R., and F.M.) were consulted to resolve the controversy. The term "thin film band" will be used throughout this review when referring to cellophane, to materials alleged to be cellophane, or to other thin films. The term "ligation" was applied to both partial ligation and complete ligation throughout this review. Studies were assessed based on:

1. "Perioperative outcome" (ie, characterized by survival from the moment of anesthetic induction until 1 week after surgery).
2. "Clinical outcome" (ie, characterized by presence, persistence, or severity of postoperative clinical signs as assessed either by a clinician or by the owner at final follow-up).
3. "Surgical or interventional outcome" (ie, characterized by closure state of the cEHPSS and the development of acquired portosystemic shunts [APSS] as assessed by portovenography, CTA, portal scintigraphy, abdominal ultrasonography, MRA, or revision surgery).

For studies in which survival and outcomes of individual dogs could not be deduced, median or mean survival times were used. If solely medical management was chosen, only clinical outcome at follow-up or median or mean survival times were assessed. "Medical clinical outcome" was defined as presence, persistence, or severity of clinical signs as assessed either by a clinician or by the owner at final follow-up time.

A classification system was developed to report clinical (C0-3) and surgical or interventional (S0-2) outcomes of the different techniques (Table 2):

In patients categorized as S1, surgery was successful in closing the cEHPSS without concomitant development of APSS; patients categorized as S2 were considered a surgical or interventional failure, independently of the C status. Patients categorized as C1 or C2 were considered clinical successes whereas patients categorized as C3 were

considered clinical failures, independently of S status. In a patient categorized as C3S1 (clinical failure despite surgical or interventional success), it cannot be excluded that the clinical abnormalities were secondary to other concomitant pathologies, unrelated to cEHPSS disease.

Medically treated dogs were only assessed based on C classification.

When solely "outcome" is mentioned, it relates to the combined subjective analysis of all 3 outcomes (perioperative, clinical, and surgical or interventional).

2.7.2 | Prevalence and 95% CI of outcome success

The perioperative, clinical, and surgical or interventional outcomes were calculated by dividing the number of successful cases in each study by the total number of cases reported in that study. The 95% CI, using Wilson score interval, was calculated for each of the 3 measured success variables assessed.[13] For each of the studies included, the follow-up time was reported so as to make the assessment more objective.

2.7.3 | Statistical analysis

To compare different techniques, a NMA was performed.[14] This methodology (NMA) was chosen over a simple direct comparison among techniques. For example: a study comparing techniques A and B, showing technique A as 2 times more efficacious than B, and another study comparing techniques A and C, showing A as 4 times more efficacious than C. By indirect comparison, one could conclude that treatment B is twice as effective as C. The use of this approach can induce error by failing to incorporate uncertainty about the within-trial direct estimates (eg, the samples size in each comparison group) and use of the NMA model has the advantage of allowing comparison among techniques in a single analysis, using either direct or

TABLE 2 Classification system developed to report on clinical (C0-C3) and surgical or interventional (S0-S2) outcome of the different techniques

	S0	S1	S2
C0	NA	**No clinically information reported** *Closed cEHPSS and no APSS present at imaging technique*	**No clinically information reported** *Patent cEHPSS and/or presence of APSS at imaging technique*
C1	**Clinically normal dog receiving no medical treatment** *No surgical/interventional information reported*	**Clinically normal dog receiving no medical treatment** *Closed cEHPSS and no APSS present at imaging technique*	**Clinically normal dog receiving no medical treatment** *Patent cEHPSS and/or presence of APSS at imaging technique*
C2	**Clinically normal dog or minimal clinical signs (eg, occasional lethargy or diarrhea) on medical treatment** *No surgical/interventional information reported*	**Clinically normal dog or minimal clinical signs (eg, occasional lethargy or diarrhea) on medical treatment** *Closed cEHPSS and no APSS present at imaging technique*	**Clinically normal dog or minimal clinical signs on medical treatment for cEHPSS** *Patent cEHPSS and/or presence of APSS at imaging technique*
C3	**Clinically abnormal dog with clinical signs compatible with a cEHPSS** *No surgical/interventional information reported*	**Clinically abnormal dog with clinical signs compatible with a cEHPSS** *Closed cEHPSS and no APSS present at imaging technique*	**Clinically abnormal dog with clinical signs compatible with a cEHPSS** *Patent cEHPSS and/or presence of APSS at imaging technique*

Note: "Bold" signifies the meaning of the "C" classification, and "italic" signifies the meaning of "S" classification.

indirect evidence while accounting for lack of randomization at study level. Direct evidence is defined as evidence obtained directly from studies comparing at least 2 treatment modalities, (eg, techniques A and B). Indirect evidence is obtained using ≥1 common comparators (eg, in the absence of studies comparing techniques A and B, techniques A and B can be compared indirectly if both have been compared with treatment C). Mixed evidence is defined as the combination of direct and indirect evidence.[15,16]

An NMA comparing perioperative, clinical, and surgical or interventional outcome for different techniques was performed. Network graphs were provided for visualization of the geometry of the network. A league table was generated to present the results of both direct estimate comparisons and network meta-analysis estimates (NME) and a forest plot was generated to compare the assessed treatment modalities to ameroid constrictor.[14] A treatment ranking for each outcome was provided based on P-score. All NMA analyses were performed in R-package "netmeta" using frequentist methods (version 0.9-8).[17] The odds ratio (OR), using the random effects model, was estimated to indicate higher or lower odds for successful outcome in 1 group of dogs compared to a relevant comparison group. The random effects model was selected because it assumes that the observed estimates of treatment effect may vary across studies because of actual differences in treatment effect and sample heterogeneity in each study. When τ^2 is estimated to be zero in the pairwise treatment comparisons, the model is reduced to the fixed effects model. Heterogeneity among studies was calculated using the Chi-square test and was considered significant when $P \le .1$. The fraction of variance because of heterogeneity (I^2 value) was assessed using GRADE guidelines with "no more than 40%," "30 to 60%," "50 to 90%," and "75 to 100%" considered as "low," "moderate," "substantial," and "considerable" heterogeneity, respectively. The term τ^2 is the variance of the effect size parameters across the study population and indicates the variance of the true effects size. The τ^2 value was reported between 0 and 1, with T^2 close to 0 indicating no heterogeneity. Inconsistency of the network was assessed by comparing direct and indirect estimates. P-score was used for ranking the different techniques, with higher P-score meaning a better treatment effect. When network assessment was not possible for an outcome (perioperative, clinical and surgical or interventional), direct meta-analysis outcomes were compared among different surgical or interventional techniques and among different cEHPSS morphologies treated using the same technique. For this, a similar approach, as in previous meta-analyses, was conducted to identify statistical differences among studies that included comparable cases regarding outcomes.[11] Review Manager 5.3 software was used for the dichotomous comparisons.

3 | RESULTS

3.1 | Assessment of quality of evidence

By October 20, 2018, the search strategy identified 645 unique citations, 631 from the electronic searches of PubMed and Web of Science and manual searches from the publication's reference lists and

14 from manual searching of major conference proceedings. Two-hundred twenty-four papers fulfilled stage 1 screening criteria, of which 48 (published between 1979 and 2018) also fulfilled stage 2 selection criteria and were selected for review (Figure 1). Based on grading of the level of evidence, 6 studies were included in subgroup 4b,[18-23] 35 in subgroup 4c,[2-5,24-54] and 7 in grade 5.[55-61]

Overall, the 48 selected papers reported 6 different surgical or interventional techniques and several different medical treatments. Within each paper, ≥1 treatment techniques were evaluated. In 8 studies reporting "ligation," where it was possible to distinguish between cases that had complete or partial ligation,[21,23,26,32,40,42,47,54] statistical analysis was performed to compare outcome between the 2 ligation techniques.

3.2 | Study groups size

A combined total of 1417 dogs affected by cEHPSS were reported in the 48 studies. Eleven studies evaluated very small numbers of dogs (<10 dogs).[3,5,18,24,29,35,53,55,58,61,62] Fourteen studies evaluated small numbers of dogs (10-19 dogs).[2,4,20,26,28,31,34,39-41,44,47,56,57] Fifteen studies evaluated moderate numbers of dogs (20-50 dogs).[19,22,23,27,30,32,41,42,45,46,50-52,54,59] Eight studies evaluated large numbers of dogs (>50 dogs).[21,36-38,48,49,60,63]

3.3 | Subject enrollment quality

Forty-six studies were clearly characterized (including 100% cEHPSS), with 2 studies being of mixed characterization (≤5% IHPSS).[27,57] Congenital extrahepatic portosystemic shunts were described with regard to their termination in 1001 dogs, caudal vena cava (n = 747), azygos vein (n = 232), or phrenic vein (n = 26).

3.4 | Overall risk of bias

Most of the trials had high or unclear risk of bias for all components. In 15 studies,[3,18,19,21,23,26,28,32,37,38,41,45,49,54,63] the number of initially enrolled dogs was higher than the final number of dogs with reported survival or outcomes. Reasons for incomplete follow-up included failure to contact the owners after surgery or lack of postsurgical or interventional evaluations, euthanasia, or other unidentified reasons. Seven studies were congress abstracts.[55-61]

3.5 | Individual assessment of different treatment options

3.5.1 | Medical management (Supporting Information S2)

Three studies evaluated the efficacy of medical management for cEHPSS, giving a combined sample of 13 dogs,[3,28,34] with a median follow-up time of 2.3 to 57.5 months. Medical management consisted of a combination of therapeutic diet, antibiotics, and lactulose. All 3 components varied among studies and even within the same study.
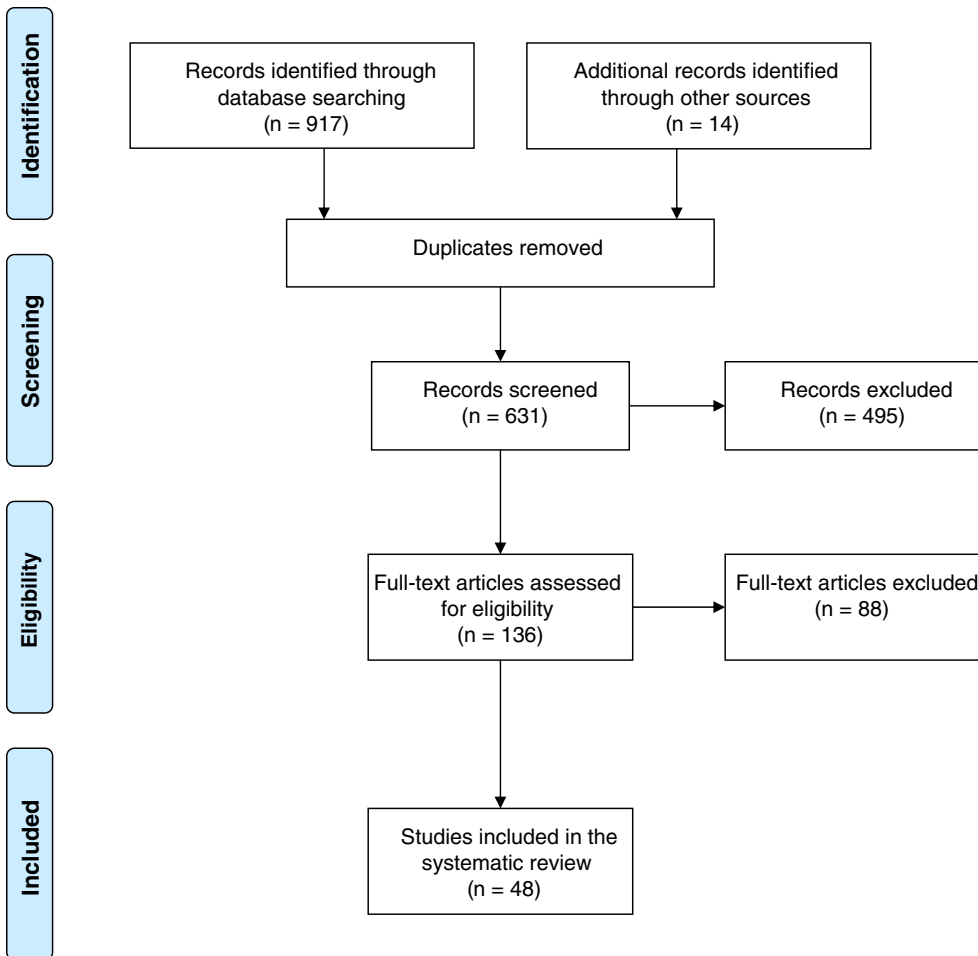
1870 | Journal of Veterinary Internal Medicine ACVIM   SERRANO ET AL.

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Identification

Records identified through
database searching
(n = 917)

Additional records identified
through other sources
(n = 14)

Screening

Duplicates removed

Records screened
(n = 631)

Records excluded
(n = 495)

Eligibility

Full-text articles assessed
for eligibility
(n = 136)

Full-text articles excluded
(n = 88)

Included

Studies included in the
systematic review
(n = 48)

FIGURE 1 Flow diagram for inclusion of studies in the combined systematic review and meta-analysis. *Source*: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed1000097

3.5.2 | Ligation (Supporting Information S3)

Twenty-five studies[21-32,34,36,38-40,42,43,46,47,54,58,61-63] evaluated the efficacy of ligation as treatment for cEHPSS, giving a total number of 553 dogs. Perioperative outcome was reported in all studies except 2[30,31] and was available in 514 of the 553 dogs, with 463 surviving the perioperative period (90.1%). Clinical outcome was described in 19 studies.[21,23,26-32,34,38-40,43,46,47,54,58,61] From the initial 553 dogs, information about clinical outcome was available in 342 dogs with clinical outcome being successful in 255 dogs (74.6%; C1, C2). Median follow-up time varied between 1 and 27.5 months. Surgical or interventional outcome was available in 5 studies.[29,30,39,40,47] Information about surgical or interventional outcome was available in 58 dogs with surgical or interventional outcome being successful in 38 dogs (65.5%; S1).

In 13[21-23,26,30-32,34,40,42,47,54,59] of the 25 studies that described ligation of the cEHPSS, it was possible to evaluate partial ligation as surgical or interventional treatment in 186 dogs. Perioperative outcome could be determined in all studies except 5,[30-32,34,47] and was described in 113 of the 186 dogs with 99 dogs having successful outcome (87.6%). Clinical outcome was available for all studies except 2[22,42] and was described in 122 of 186 dogs, with clinical outcome being successful in 99 dogs (81.1%; C1, C2). Median follow-up time varied between 1 and 50.4 months. Surgical or interventional

outcome was available in 3 studies[30,40,47] and described 29 dogs with 17 having successful outcome (58.6%; S1).

In 11[21-23,26,31,32,34,40,42,47,54] of the 25 studies that described ligation of the cEHPSS, it was possible to evaluate complete ligation as surgical or interventional treatment in 75 dogs. Perioperative outcome could be determined in all studies except 4,[31,32,34,47] and was described in 47 of 75 dogs, with 43 dogs having successful outcome (91.5%). Clinical outcome was available for all studies except 2[22,42] and was described in 52 of 75 dogs, with clinical outcome being successful in 50 dogs (96.1%; C1, C2). Median follow-up time varied between 1 and 54 months. Surgical or interventional outcome was available in 2 studies[40,47] and was available in only 7 dogs with all 7 having successful outcome (100%; S1).

3.5.3 | Ameroid constrictor (Supporting Information S4)

Thirteen studies[4,18-23,48-50,57,58,60] evaluated ameroid constrictor as treatment for cEHPSS, giving a total number of 507 dogs. Perioperative outcome was reported in all studies. From the initial 507 dogs that underwent the procedure, 479 dogs survived the perioperative phase (94.5%). Clinical outcome was described in 8 studies[19-21,23,49,50,57,58] and

described 203 dogs with 192 dogs having successful outcome (94.6%; C1, C2). Median follow-up time varied between 9 and 54 months. Surgical or interventional outcome was available in 5 studies[4,18,19,23,50] and described 61 dogs with 50 dogs having successful outcome (82.0%).

3.5.4 | Thin film banding (Supporting Information S5)

Eleven studies[2,18-20,37,41,44,45,51,52,55] evaluated thin film banding as surgical or interventional attenuation for cEHPSS giving a total number of 269 dogs. Perioperative outcome was reported in all studies. From the initial 269 dogs that underwent the procedure, 260 dogs survived the perioperative period (96.7%). Clinical outcome was available in 6 studies[2,19,20,37,41,44] and described in 139 dogs, with successful outcome in 136 (97.8%; C1, C2). Median follow-up time varied between 2 and 36 months. Surgical or interventional outcome was available in 7 studies[2,18,19,44,51,52,55] and described 90 dogs with 51 dogs having successful outcome (56.7%).

3.5.5 | Coil embolization (Supporting Information S6)

Four studies[35,56,59,60] evaluated coil embolization as treatment for single cEHPSS, giving a total number of 63 dogs. Perioperative outcome was reported in all studies. From the initial 63 dogs that underwent the procedure, 52 dogs survived the perioperative period (82.5%). Clinical outcome was available for 2 studies[35,59] and described 24 dogs with all having successful outcome (100%; C1, C2). Median follow-up time varied between 3 and 12 months. Surgical or interventional outcome was available in 2 studies[56,59] and described in 29 dogs with 22 dogs having successful outcome (75.9%).
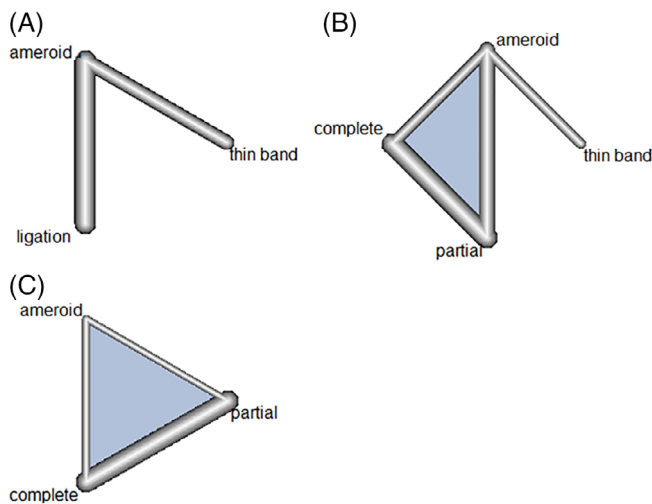

FIGURE 2 A, Network graph of the perioperative outcome; B, perioperative outcome with ligation divided in complete and partial ligation; and C, clinical outcome with ligation divided in complete and partial ligation. The nodes in the graph represent the different treatments. The line between treatment shows that there is at least 1 study comparing these 2 treatments. The thickness of the line is proportional to the inverse SE of the direct treatment comparison

TABLE 3 League table presenting network meta-analysis estimates (lower triangle) and direct estimates (upper triangle) for perioperative and clinical outcome

Perioperative outcome

	Ameroid	Ligation	Thin film band
Ameroid	Ameroid	1.6 (0.30-8.61)	0.41 (0.04-4.36)
Ligation	1.6 (0.30-8.61)	Ligation	NA
Thin film band	0.41 (0.04-4.3)	0.26 (0.01-4.65)	Thin film band

Perioperative outcome (with ligation divided in partial and complete)

	Ameroid	Complete ligation	Partial ligation	Thin film band
Ameroid	Ameroid	2.13 (0.43-10.53)	0.74 (0.21-2.64)	0.26 (0.02-4.47)
Complete ligation	0.71 (0.08-6.33)	Complete ligation	0.75 (0.21-2.64)	NA
Partial ligation	2.1 (0.34-12.86)	1.56 (0.33-7.43)	Partial ligation	NA
Thin film band	0.41 (0.04-4.36)	0.75 (0.21-2.63)	0.20 (0.01-3.86)	Thin film band

Clinical outcome

	Ameroid	Ligation	Thin film band
Ameroid	Ameroid	1.16 (0.11-11.84)	1.63 (0.25-10.57)
Ligation	0.6 (0.08-4.28)	Ligation	3.48 (0.76-15.94)
Thin film band	1.8 (0.3-10.79)	3.04 (0.67-13.83)	Thin film band

Notes: Comparisons between treatments should be read from left to right, and their odds ratio is in the cell in common between the column defining treatment and the row defining treatment. Odds ratio less than 1 favor the column defining treatment for the network estimates and the row defining treatment for the direct estimates. No statistically significant differences were noted.
Abbreviation: NA, not available.

1872 | **Journal of Veterinary Internal Medicine** ACVIM
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SERRANO ET AL.

3.5.6 | Amplatzer vascular plug (Supporting Information S7)

One study[5] evaluated the efficacy of the Amplatzer vascular plug as treatment for single cEHPSS in 6 dogs. From the initial 6 dogs in which the Amplatzer occlusion was possible, all survived the perioperative period (100%). Clinical outcome was available for the 6 dogs and was successful in all 6 (100%). All dogs were followed for at least 1 month. Surgical or interventional outcome could not be assessed, because no postoperative imaging was performed in any of the dogs.

3.5.7 | Polyacrylic acid-silicone gradual occlusion device (Supporting Information S8)

One study[53] evaluated the efficacy of a polyacrylic acid-silicone gradual occlusion device (PAS-OD) as treatment for single cEHPSS in 6 dogs. All 6 dogs survived the perioperative period (100%). Clinical outcome was available for the 6 dogs and was successful in all 6 (100%; C1, C2). All dogs were followed for 2 months. Surgical or interventional outcome was available in all 6 dogs with 4 dogs having successful outcome.

3.6 | Meta-analysis

3.6.1 | Perioperative outcome

Ligation versus ameroid constrictor versus thin film band

An NMA for the perioperative outcome variable was performed to compare multiple treatments: ligation, ameroid constrictor, and thin film
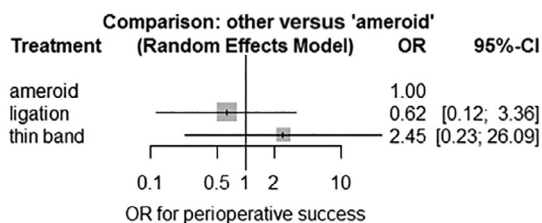

FIGURE 3 Forest plot comparing perioperative outcome of ligation and thin film band in regard to ameroid constrictor. No statistically significant differences were noted. CI, confidence interval; OR, odds ratio

band. Adequate data to calculate OR for the NMA was available in 4 studies.[19-22] A graph of the network perioperative outcome was generated (Figure 2). A league table was generated to present the results of both direct comparisons and NME (Table 3). Ameroid-ligation NME was based on 100% direct evidence. Ligation-thin film band NME was 100% based on indirect evidence. No statistically significant differences were found in any treatment comparison by either direct or indirect comparison. A forest plot comparing ameroid constrictor with the remaining techniques is presented in Figure 3. No statistical difference in perioperative outcome was found among dogs treated by thin film banding, ameroid constrictor placement, or ligation (Table 4). No heterogeneity or network inconsistency was observed ($T^2 = 0$; $I^2 = 0\%$).

Partial ligation versus complete ligation versus ameroid constrictor versus thin film band

An NMA for the perioperative outcome variable was performed to compare multiple treatments: partial and complete ligation, ameroid constrictor, and thin film band. Adequate data to calculate OR for the NMA was provided by 6 studies.[19-22,26,40] A graph of the network perioperative outcome was generated (Figure 2). A league table was generated to present the results of both direct comparisons and NME (Table 3). Direct and indirect comparisons of outcomes were similar for all treatment comparisons, except for the comparison between ameroid constrictor and complete ligation. In the comparison ameroid constrictor-complete ligation, the proportion of direct evidence contributing to the NME was 69%. The remaining 31% came from indirect evidence. Direct comparison between the 2 techniques identified increased odds for success in the complete ligation group, but indirect comparison indicated increased odds for success in the ameroid constrictor group. For the comparison between complete ligation-thin film band and partial ligation-thin film band, no direct evidence was available (no papers compared both techniques) and the NME were based on indirect evidence. Direct comparisons accounted for 95.3% of the ameroid constrictor-partial ligation comparison, 99.2% of complete-partial ligation and 100% of ameroid constrictor-thin film band. No statistically significant differences were found in any treatment by either direct or indirect comparison. Because of overlap between CIs, no statistical superiority of 1 treatment over another could be determined. A forest plot comparing ameroid constrictor with the remaining techniques is presented in Figure 4.

TABLE 4 Treatment ranking regarding comparison of perioperative and clinical outcome among treatments

Perioperative outcome			Perioperative outcome (with ligation divided in partial and complete)			Clinical outcome (with ligation divided in partial and complete)		
Ranking	Technique	P-score	Ranking	Technique	P-score	Ranking	Technique	P-score
1	Thin film band	.80	1	Thin film band	.82	1	Complete ligation	.81
2	Ameroid	.47	2	Ameroid	.58	2	Ameroid	.52
3	Ligation	.23	3	Partial ligation	.38	3	Partial ligation	.17
			4	Complete ligation	.23			

Notes: Bigger *P*-scores indicate a better treatment effect. Rankings near 1 suggest better treatment effect. No statistically significant differences were noted.

No significant difference was found among perioperative outcomes in dogs treated by thin film banding, ameroid constrictor placement, or partial or complete ligation (Table 4). No heterogeneity or network inconsistency was observed ($T^2 = 0$; $I^2 = 0\%$).

3.6.2 | Clinical outcome

Complete ligation versus partial ligation versus ameroid constrictor
An NMA for the clinical outcome variable was performed to compare multiple treatments: complete ligation, partial ligation, and ameroid constrictor. Adequate data to calculate OR for the NMA was provided by 3 studies.[21,23,32] A graph of the network clinical outcome was generated (Figure 2). A league table was generated to present the results of both direct comparisons and NME (Table 3). Direct and indirect comparisons of outcomes were similar to all treatment comparisons except for ameroid constrictor-complete ligation. In the ameroid constrictor-complete ligation comparison, the proportion of direct evidence contributing to the NME was 72%. The remaining 28% came
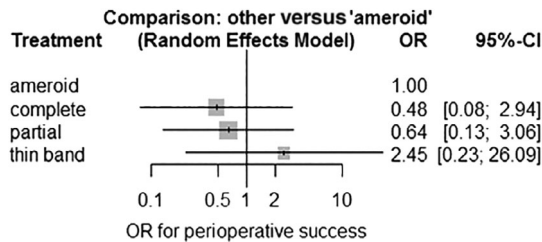

Comparison: other versus 'ameroid'

Treatment	(Random Effects Model)	OR	95%-CI
ameroid		1.00	
complete		0.48	[0.08; 2.94]
partial		0.64	[0.13; 3.06]
thin band		2.45	[0.23; 26.09]

OR for perioperative success

FIGURE 4 Forest plot comparing perioperative outcome of complete ligation, partial ligation and thin film band in regard to ameroid constrictor. No statistically significant differences were noted. CI, confidence interval; OR, Odds ratio

Comparison: other versus 'ameroid'

Treatment	(Random Effects Model)	OR	95%-CI
ameroid		1.00	
complete		1.54	[0.18; 12.93]
partial		0.51	[0.07; 3.61]

OR for clinical success

FIGURE 5 Forest plot comparing clinical outcome of complete ligation, partial ligation and thin film band in regard to ameroid constrictor. No statistically significant differences were noted. CI, confidence interval; OR, Odds ratio
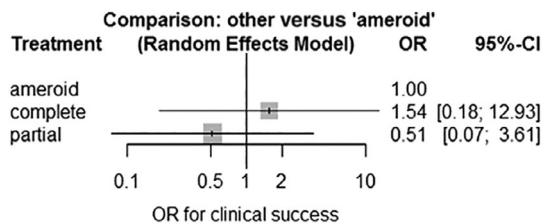
from indirect evidence. Direct comparison between the 2 techniques identified increased odds for successful treatment in the ameroid constrictor group, but indirect comparison identified increased odds for successful treatment in the complete ligation group. Direct comparisons accounted for 90.9% of the ameroid constrictor-partial ligation comparison and 98.9% of the complete-partial ligation comparison. No statistical significant differences were found in any treatment comparison by either direct or indirect comparison. A forest plot comparing ameroid constrictor with the remaining techniques is presented in Figure 5. Because of overlap between CIs, no statistical superiority of 1 treatment over another could be identified.

No significant difference was found in clinical outcome among dogs treated by thin film banding, ameroid constrictor placement, or partial ligation (Table 4). Low heterogeneity and network inconsistency was observed ($T^2 = 0.3012$; $I^2 = 12.7\%$).

Ameroid constrictor versus ligation
Adequate information to calculate OR for clinical outcome comparing placement of an ameroid constrictor by ligation (complete or partial) was provided in 2 studies.[21,23] The joint estimated OR was 1.37 (95% CI, 0.05-37.93), favoring the ameroid constrictor technique, but this finding was not statistically significant ($P = .85$). Moderate heterogeneity was shown between studies (Chi-square = 2.66, $P = .10$, $I^2 = 62\%$; Figure 6).

3.6.3 | Surgical outcome

Partial versus complete ligation
Adequate information to calculate OR for surgical or interventional outcome was provided in 2 studies.[40,47] The joint estimated OR was 0.37 (95% CI, 0.04-3.82), favoring the complete ligation technique ($P = .41$), but this finding was not statistically significant. Low heterogeneity was shown between studies (Chi-square = 0.07, $P = .79$, $I^2 = 0\%$; Figure 7).

Ameroid constrictor versus thin film banding
Adequate information to calculate OR for surgical or interventional outcome was provided in 2 studies.[18,19] The common estimated OR was 36.58 (95% CI, 3.29-407.10), showing a statistically significant association ($P = .003$) between the 2 techniques, with increased odds of success using the ameroid technique. Low heterogeneity was shown between studies (Chi-square = 0.03, $P = .86$, $I^2 = 0\%$; Figure 8).

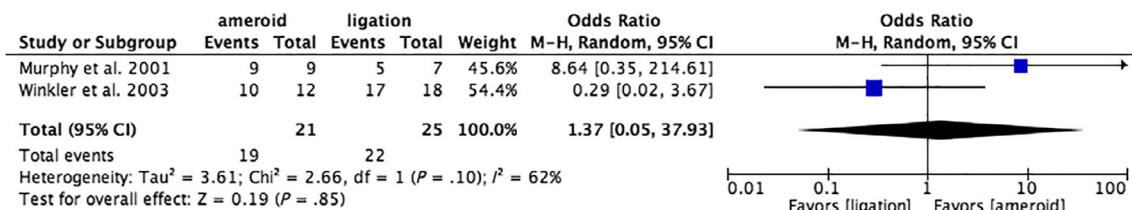Insufficient data were available to directly compare other treatment modalities.

Study or Subgroup	ameroid Events	ameroid Total	ligation Events	ligation Total	Weight	Odds Ratio M-H, Random, 95% CI
Murphy et al. 2001	9	9	5	7	45.6%	8.64 [0.35, 214.61]
Winkler et al. 2003	10	12	17	18	54.4%	0.29 [0.02, 3.67]
Total (95% CI)		21		25	100.0%	1.37 [0.05, 37.93]
Total events	19		22			

Heterogeneity: Tau^2 = 3.61; Chi^2 = 2.66, df = 1 ($P = .10$); $I^2 = 62\%$
Test for overall effect: Z = 0.19 ($P = .85$)

FIGURE 6 Forest plot comparing clinical outcome in ameroid constrictor versus ligation. Odds ratio (95% confidence interval [CI]) of clinical success between the 2 techniques. No statistically significant differences were noted
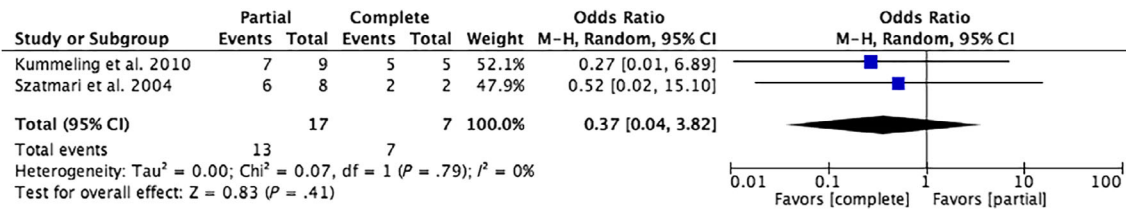
Study or Subgroup	Partial Events	Total	Complete Events	Total	Weight	Odds Ratio M–H, Random, 95% CI
Kummeling et al. 2010	7	9	5	5	52.1%	0.27 [0.01, 6.89]
Szatmari et al. 2004	6	8	2	2	47.9%	0.52 [0.02, 15.10]
Total (95% CI)		17		7	100.0%	0.37 [0.04, 3.82]
Total events	13		7			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = .79); I² = 0%
Test for overall effect: Z = 0.83 (P = .41)

Odds Ratio M–H, Random, 95% CI
0.01 0.1 1 10 100
Favors [complete] Favors [partial]

FIGURE 7 Forest plot comparing surgical outcome in partial versus complete ligation. Odds ratio (95% confidence interval [CI]) of surgical success between the 2 techniques. No statistically significant differences were noted
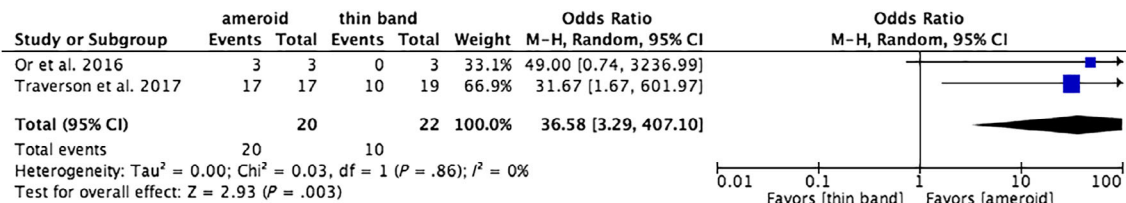
Study or Subgroup	ameroid Events	Total	thin band Events	Total	Weight	Odds Ratio M–H, Random, 95% CI
Or et al. 2016	3	3	0	3	33.1%	49.00 [0.74, 3236.99]
Traverson et al. 2017	17	17	10	19	66.9%	31.67 [1.67, 601.97]
Total (95% CI)		20		22	100.0%	36.58 [3.29, 407.10]
Total events	20		10			

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = .86); I² = 0%
Test for overall effect: Z = 2.93 (P = .003)

Odds Ratio M–H, Random, 95% CI
0.01 0.1 1 10 100
Favors [thin band] Favors [ameroid]

FIGURE 8 Forest plot comparing surgical outcome in ameroid constrictor versus thin film band. Odds ratio (95% confidence interval [CI]) of surgical success between the 2 techniques. The common estimated OR was 36.58 (95% CI, 3.29-407.10), showing a statistically significant association (P = .003) between the 2 techniques, with increased odds of successful cases in the ameroid technique

Assessment of surgical technique for cEHPSS morphology

The small number of cases, different follow-up times, and absence of imaging techniques confirming cEHPSS closure made outcome assessment unreliable and therefore it was not reported.

4 | DISCUSSION

To our knowledge, this study is the first to systematically review and provide meta-analysis for the treatment of cEHPSS in dogs. An evidence-based review was published in 2012, and found weak evidence for the treatment of extrahepatic portosystemic shunts.[6] Although 7 years separate the manuscripts and more papers could be included, the major conclusion remains, mainly the low-quality evidence of the papers. However, information gained by this meta-analysis may help veterinary clinicians when designing and communicating a treatment plan for dogs with cEHPSS. This combined systematic review and NMA differs from the previously published report by including studies in which >95% of the cases included were cEHPSS and adding 22 studies not previously included,[18-20,24,25,29,35,36,43,48-53,55-61] including 2 non-English language publications.[20,25] Inevitably, the quality of the systematic review, and thus the accuracy of the evidence-based information to be gained, is strongly influenced by the amount, quality and content of the included papers. To assess the treatment of cEHPSS, 48 studies were identified including 1417 dogs with cEHPSS. However, most studies were case series and thus provided weak evidence. During data retrieval, on only a single occasion was a different classification of "successful" versus "unsuccessful" surgical outcome given by the authors. This difference occurred in a paper assessing 2 different imaging techniques to assess shunt closure, which have different sensitivities.[52] After discussion, a consensus was obtained. Otherwise, no difference in patient

classification occurred between authors. The comparisons between techniques (meta-analysis) were based on retrospective studies in 5 of 6 instances. Although inclusion of these retrospective studies could increase the risk of bias, case series can make a useful contribution in increasing the evidence base and strengthening the credibility of a review of an emerging health technology.[64] Calculation of heterogeneity (I²) provides an estimate of the proportion of variability in a meta-analysis that is because of the differences among included trials, rather by sampling error. Our comparisons included a small number of trials, which can make calculation of I² unreliable in our meta-analysis.[65,66] Also, wide variation in follow-up times was observed within and among studies and, in many reports, clinical outcome was based solely upon the owners' subjective evaluation of their dogs' condition after treatment without using standardized questionnaires or quality-of-life scoring systems. The development and use of such standardized quality-of-life questionnaires therefore is recommended.[67] Also, publication bias can be a limitation of this systematic review and NMA, with the possibility of nonpublication of negative results not being excluded. Studies designed to report complications after surgery were not included in an attempt to decrease this publication bias, because these studies report only specific clinical signs and fail to report all complications (eg, reporting postsurgery neurologic complications while failing to report gastrointestinal or urinary signs). Abstracts of specialist conferences were included in the systematic review but not in the meta-analysis. These publications can add important information about cEHPSS treatment, but because these manuscripts are not peer-reviewed, might consist of low-quality evidence and might have high bias, data interpretation must be done carefully. Statistical comparison and individual study assessment among treatment techniques were performed, based on perioperative outcome (survival in the perioperative period up to 7 days after the procedure), clinical outcome (quality of life), and surgical or interventional outcome (closure of the

original cEHPSS without development of APSS). Percentage of successful cases was used as an indicator of perioperative, clinical, and surgical or interventional outcome. The addition of the 95% CI allowed us to balance the percentage of success, by taking into account the number of cases reported in each study.

Theoretically, placement of an ameroid constrictor, thin film banding, or coils will lead to gradual cEHPSS attenuation.[4,68,69] When looking directly at the results of individual studies, thin film band seemed to be the technique that provided the best perioperative outcome, closely followed by ameroid constrictor (Supporting Information S2-S8), whereas coil embolization led to a less favorable perioperative outcome. However, the number of cases assessed after coil embolization was 4 and 6 times smaller than that after ameroid constrictor placement and thin film banding, respectively, rendering comparison less accurate. From a statistical point of view, no differences were found among techniques for perioperative outcome, and further studies assessing the perioperative outcomes of different techniques are necessary before 1 technique should be considered superior to another. Factors other than surgical technique may influence survival. For example, the choice and dosages of anesthetics often differed among studies (or were not specified). Likewise, more or less intraoperative attenuation can be exerted when applying a thin film band around the shunting vessel.[41] Furthermore, surgical skill and expertise with the technique could have had an impact on morbidity and mortality, with the possibility that the level of perioperative surveillance and critical care may have varied among institutions, influencing the management of perioperative morbidities. For these reasons, a random effect model was chosen as a statistical model. Regardless of these factors, it is generally believed that gradual reduction of the shunt diameter rather than acute shunt occlusion allows the liver to adapt to increased portal blood flow, limiting the risk of acute fatal portal hypertension.[2,4] Nevertheless, it is still possible that ameroid constrictors lead to kinking and possibly peracute occlusion of the shunting vessel.[4,70]

While looking directly at the results of individual studies, placement of an ameroid constrictor and complete ligation appeared to be the surgical or interventional techniques with strongest evidence of giving a good quality of life, followed by thin film banding and coil embolization (Supporting Information S2-S8). The NMA produced contradictory results for these 2 techniques with increased odds of better clinical outcome for ameroid constrictor in the direct estimate comparison but for complete ligation in the indirect estimate comparison (Table 3). From a statistical point of view, no significant differences among techniques were observed for clinical outcome. This result could be a consequence of the low number of cases and studies included. More and larger studies (in terms of cases included) are needed to address this contradiction. The terms clinical success and surgical or interventional success should not be used interchangeably. Dogs with a patent cEHPSS or with APSS, both considered surgical failures, could have been asymptomatic during the follow-up period and therefore could have been classified as clinical successes. Also, postoperative screening for shunt status by means of medical imaging was not consistently performed in most of the studies. Therefore,

outcome often is judged on clinical success without evaluating surgical or interventional success.

Shunt ligation was by far the best-documented technique in dogs with cEHPSS. Not only have large numbers been described, but relatively long follow-up times also were considered, subjectively suggesting that this technique might lead to higher chances of successful clinical outcome (Supporting Information S2-S8), but the quality of evidence was still weak. However, dogs that underwent cEHPSS attenuation using an ameroid constrictor appeared to have a better subjective overall 95% CI for clinical outcome compared to dogs in which shunts were ligated. Median follow-up periods in dogs that received an ameroid constrictor were considerably shorter than in dogs that underwent cEHPSS ligation, which might have overestimated the superiority of ameroid constrictors over ligation. Thin film banding had 95% CI for outcome equivalent to or even better than that of ameroid constrictor, but smaller numbers of cases were assessed and follow-up times were shorter than for the previously mentioned techniques. Standardization of thin film material is vital.[71] Further studies comparing the clinical outcome of ameroid constrictor, ligation, and thin film band techniques are necessary before a single technique should be considered superior to another. Studies describing coil embolization reported a small number of dogs with short follow-up times. Although the results of coil embolization seem promising, studies of a large cohort of patients are needed to better evaluate this approach. Amplatzer vascular plug embolization only was reported in a single case series of 6 dogs and follow-up was not well documented. The same was true for PAS-OD, with only 6 cases that underwent PAS-OD placement reported. Further studies including higher numbers of dogs are needed before proposing definite recommendations about Amplatzer vascular plug and PAS-OD use.

When looking subjectively at the results of individual studies, complete ligation seemed to result in better clinical outcome than did partial ligation. The lack of a statistically significant difference in outcome between complete and partial ligation was surprising because it is widely assumed that complete cEHPSS occlusion provides the highest likelihood of a good long-term quality of life.[72] However, the lack of statistical significance between complete and partial ligation might be explained by variations in follow-up times between groups. In 1 study,[21] dogs with complete ligation were followed for a median of 58 months, whereas dogs that underwent partial ligation were only followed for a median of 18 months. For the sake of this meta-analysis, clinical outcome was deduced from the data available at 18 months for both ligation groups. It has been reported that clinical signs related to cEHPSS patency started to reoccur only after a mean follow-up of 36.2 months (SD = 21.6 months) after partial shunt ligation.[30] Therefore, it can be hypothesized that if the partial ligation group would have had an equally long follow-up period (58 months), the differences in clinical success between the 2 approaches might have been more pronounced. Intraoperatively, it is common to attempt complete ligation of the cEHPSS, reserving partial ligation for cases in which complete ligation was deemed impossible based on observation of splanchnic viscera, systemic arterial pressure, central venous pressure, mesenteric venous pressure, interpretation of portovenography after temporary ligation, or a combination of these.[73,74] In some institutions, in cases that tolerate only

partial ligation, a second surgery is performed some months later to completely occlude the cEHPSS. Because we included only the results of the first procedure, we might have underestimated the overall outcome success of the ligation technique. A multi-phase or 2-step ligation surgery might culminate in complete ligation at the last procedure, but also might increase perioperative morbidity and financial cost for the owner. We included only the first surgery that cEHPSS patients underwent, in order to have the most objective criteria to compare all of the techniques.

It seems logical that postoperative medical support might positively influence clinical outcome.[48] However, the subgroups of surgically treated dogs with cEHPSS that would benefit the most remain unclear. Articles often did not mention if additional medical management was provided and, even if it was, treatment often was not standardized. The most common medical management used currently is combination treatment, usually with a therapeutic diet, antibiotics, and lactulose, but it is currently unknown whether all components of this combination treatment are of added value.

The surgical or interventional outcome in dogs with cEHPSS only can be assessed if medical imaging is performed during follow-up. Serum bile acid concentrations were used in some studies as a measure of cEHPSS closure, but it is not uncommon for dogs with closed cEHPSS and no evidence of APSS to have bile acid concentrations that did not return to normal months after successful surgery.[44,50,51,75,76] For this reason, bile acid concentrations were not evaluated in our systematic review and meta-analysis. Different imaging techniques, radiologist experience in performing and interpreting imaging studies and the attenuation devices themselves can hamper the classification of surgical or interventional outcome as successful or unsuccessful. In only one-third of the studies included in our systematic review and meta-analysis was postoperative medical imaging routinely performed. Additionally, the medical imaging technique used to assess cEHPSS patency or APSS development varied within and among the studies.

Furthermore, the time of imaging postsurgery or intervention was not standardized, with some dogs having imaging techniques as early as 2 months after the procedure whereas imaging was delayed up to 7 months in other dogs.[51,56,75] Applying thin film banding around the shunting vessel can cause complete occlusion within 8 weeks,[2] but shunts with larger diameters may take longer to occlude.[41] Differences in timing of imaging can influence the classification of the cEHPSS as being patent or closed.

Comparison of surgical or interventional outcome between ameroid constrictor and thin film band indicated a statistically significant superiority of ameroid constrictor in causing shunt occlusion. No statistically significant difference between thin film band and ligation was noted. The subjective assessment of results (Supporting Information S2-S8) of individual studies with regard to surgical or interventional outcome for the different techniques seemed to indicate the superiority of ameroid constrictor and ligation techniques over thin film banding. Thin film banding had a subjectively lower surgical or interventional success percentage with wide 95% CI when compared with ligation. However, the total numbers of cases on which these observations were based were rather small,

overall resulting in wide 95% CIs. Biochemical assessment of commonly used thin film bands of different origins showed little to no irritant components capable of inducing local inflammation necessary for adequate shunt closure.[77] Surprisingly, the composition of most of the commercially available thin film bands was not truly cellophane.[71] These findings might explain the inconsistent efficacy of thin film banding for cEHPSS closure.

In 1 of the studies[18] in which comparison between ameroid constrictor and thin film band was possible, none of the 3 thin film band cases experienced cEHPSS closure 3 months after surgery. In that study, all thin film bands were placed in the thoracic cavity to attenuate portoazygos shunts. The authors hypothesized that thin film band behavior might be inferior in the thorax compared to in the abdomen.[18] Future randomized prospective studies are needed to compare surgical outcome after ameroid constrictor with different types of thin film banding. Coil embolization was performed and evaluated only in a few of cases, indicating a subjective surgical or interventional success percentage similar to the above-mentioned techniques and also with a wide 95% CI (Supporting Information S6).

Studies comparing surgical or interventional versus medical management of cEHPSS as a sole treatment of cEHPSS and the effect of different protein sources on treatment of congenital portosystemic shunts have been published,[7,78] but they could not be included in the current systematic review and meta-analysis because they did not meet the inclusion criteria (not defining if cEHPSS or IHPSS and mixing cEHPSS and IHPSS outcomes). The few included papers evaluating medical management reported small numbers of cEHPSS cases with short follow-up times, resulting in a wide 95% CI (Supporting Information S2). Long-term clinical outcome after different surgical techniques for management of congenital portosystemic shunts was clearly superior to outcome after medical management only.[7] This difference could not yet be appreciated at a median follow-up time of 579 days, but only became evident when the median follow-up time was 1936 days. The shorter follow-up times reported in most of the studies included in the current systematic review and meta-analysis were therefore insufficient to identify all cases of clinical relapse. Another important fact to consider when comparing medical versus surgical treatment is that long-term medical management usually is reserved for cases in which the owner cannot afford the cost of surgical or interventional procedures, the anesthetic risk to perform surgery is considered too high, the shunt morphology is challenging, or the dog only shows mild clinical signs.[8] These factors probably introduce considerable bias when it comes to comparison of solely medically managed cases versus those that were additionally treated using surgical or interventional techniques.

A comparison of perioperative, clinical, and surgical or interventional outcomes for different cEHPSS morphologies (portocaval versus portoazygos) was attempted. However, an objective recommendation for or against specific treatment modalities for specific cEHPSS morphologies was impossible, because of the small number of cases, variable follow-up times, and absence of imaging techniques to confirm cEHPSS closure, APSS development or both. Larger studies, including standardized postoperative imaging techniques, are needed because different

cEHPSS morphologies might have different responses to treatment techniques.[18]

5 | CONCLUSION

No technique was shown to be conclusively superior to any of the others. Based on our systematic review and meta-analysis, dogs with cEHPSS will benefit most from placement of an ameroid constrictor over thin film band to achieve good surgical outcome. The strength of this conclusion is, however, limited because of the low quality of evidence given the absence of unbiased, large, randomized, prospective studies available for dogs with cEHPSS. The general evidence quality is low because most studies were in grade 4c—case series (35/48), 6 were grade 4b, and 7 were grade 5. Direct and indirect estimates in some NMA comparisons were not consistent and all other comparisons among treatment modalities identified no significant differences. In order to make objective and strong evidence-based recommendations for veterinary practitioners, well-designed, large-scale studies comparing different surgical or interventional and medical management options for dogs with cEHPSS are needed. Future studies ideally should include advanced imaging techniques for unambiguous cEHPSS morphology classification and for postoperative assessment of cEHPSS patency or APSS development. The ideal timing for postsurgical or interventional imaging should be defined and standardized. Imaging techniques must be compared for their ability to evaluate cEHPSS closure and detection of APSS, so as to establish a gold standard postoperative imaging protocol. Finally, future studies should evaluate clinical outcome on a long-term basis, using standardized questionnaires or validated quality-of-life scoring systems.[67]

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.