PAPER

Health-related quality of life following surgical attenuation of congenital portosystemic shunts *versus* healthy controls

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Objectives: To design a health-related quality of life questionnaire for dogs with congenital portosystemic shunts, use it in a cohort of dogs treated with suture attenuation and compare results with those obtained from a healthy control cohort.

Materials and Methods: Data were collected from the hospital records of dogs treated with suture ligation of an intrahepatic or extrahepatic congenital portosystemic shunt at two referral centres. Owners were asked to complete a questionnaire assessing their dog's health-related quality of life preoperatively (retrospectively) and at the time of follow-up. Owners of control dogs also completed the questionnaire.

Results: One hundred and twenty-eight dogs with congenital portosystemic shunts and 131 control dogs were recruited. Median follow-up time was 64 months (range 19.7 to 157.2). The median long-term health-related quality of life score was excellent for both intrahepatic and extrahepatic shunt cases and similar to that of control dogs. The long-term portosystemic shunt clinical sign scores for both intrahepatic and extrahepatic congenital portosystemic shunt dogs were significantly worse than the those of the control group.

Clinical Significance: Suture attenuation of congenitial portosystemic shunts is associated with an excellent health-related quality of life score at long-term follow-up.

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INTRODUCTION

A congenital portosystemic shunt (CPSS) is an abnormal vascular communication that diverts blood away from the portal circulation into the systemic circulation. The CPSS may be intrahepatic or extrahepatic and results in liver hypoplasia and functional hepatic insufficiency. Surgery to attenuate the shunting vessel, thus redirecting hepatic portal blood flow to the liver, is the preferred treatment (Greenhalgh *et al.* 2014). There are several surgical techniques used to achieve partial or complete attenuation of both intrahepatic and extrahpatic CPSS in dogs including suture attenuation, cellophane banding, ameroid constrictor and coil embolisation (White *et al.* 1998, Youmans & Hunt 1998, Hunt & Hughes 1999, Murphy *et al.* 2001, Winkler *et al.* 2003, Hunt 2004, Kummeling *et al.* 2004, Mehl *et al.* 2007, Falls *et al.* 2013), but few studies compare techniques, resulting in a lack of evidence to recommend one treatment over another (Tivers *et al.* 2012, 2017b).

Additionally, there is a limited number of studies reporting the medium- to long-term follow-up after surgical attenuation

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and those available have varied time frames of follow-up. The current available reports have examined various techniques and different clinical variables to assess the outcome and success; including liver function tests (ammonia, bile acids), imaging to detect persistent shunting (scintigraphy and ultrasound) and owner assessment (Smith *et al*. 1995, White *et al*. 1998, Hunt & Hughes 1999, Hunt 2004, Kummeling *et al*. 2004, Frankel *et al*. 2006, Mehl *et al*. 2007, Falls *et al*. 2013, Greenhalgh *et al*. 2014, Weisse *et al*. 2014, Winkler et al. 2014). Most studies assessing biochemical parameters as an outcome measure do not show a return to normal reference values (Lawrence et al. 1992, Hunt & Hughes 1999, Bristow *et al*. 2017), although those assessing owner opinion on outcome do show an apparent return to a "normal" quality of life (QoL). However, for this latter long-term outcome, most studies use a simple form of owner assessment based on the resolution of clinical signs and whether the dog receives ongoing medical management (Smith *et al*. 1995, Mehl *et al*. 2007, Falls *et al*. 2013, Greenhalgh *et al*. 2014, Weisse *et al*. 2014). Based on the current published literature there appears to be a discrepancy in objective measures of outcome (biochemical changes) *versus* subjective outcome (owner perceived improvement). QoL is an increasingly important outcome measure in both human and veterinary medicine (Fayers *et al*. 1997, Mellanby *et al*. 2003, Freeman *et al*. 2005, Wiseman-Orr *et al*. 2006, Budke *et al*. 2008, German *et al*. 2012) but it is difficult to assess for several reasons. There is no standardised definition, with different studies assessing different aspects under the umbrella term of health-related quality of life (HRQoL) and an extra challenge in veterinary medicine, as for paediatric medicine, is the lack of self-report, meaning the assessment has to be made by a third party. Furthermore, assessment is particularly complicated in dogs with CPSS as it is a congenital condition, so affected dogs are unlikely to have ever been truly "normal," making assessment of whether dogs have made a full recovery, or simply improved, challenging. It is therefore imperative to compare the results of any questionnaire involving CPSS dogs to a population of healthy dogs, so that an accurate, more global evaluation of outcome can be made. The use of a consistent and detailed owner outcome assessment tool, including consideration of QoL in comparison to more detailed analysis of presence or absence of continued clinical signs, and comparing to a control population, would be invaluable as part of the long-term outcome measure in dogs with CPSS.

This study therefore had three main aims:

1. To develop a questionnaire for use in dogs with CPSS that would assess owner-estimated QoL as well as presence or absence of clinical signs;
2. To compare this direct QoL score with a score designed to assess clinical signs in more depth;
3. To compare these results to a control population of healthy dogs to assess the quality of recovery of CPSS dogs following surgical attenuation.

MATERIALS AND METHODS

Recruitment of cases

Medical records were reviewed for all dogs that had undergone surgical attenuation of a single, extrahepatic (EHCPSS) or intrahepatic (IHCPSS) CPSS between January 2000 and December 2012 at two centres (Royal veterinary College (RVC) = centre 1, Utrecht University = centre 2). Attempts were made to contact the owners of these dogs through telephone, email or regular mail. Dogs were included if they had partial or complete suture attenuation, had a minimum of 18 months follow-up postoperatively and were alive at the time of data collection.

Dogs were treated with either complete or partial suture attenuation depending on subjective and objective assessments of intraoperative portal hypertension, as previously described (Kummeling *et al*. 2004, Lee *et al*. 2006, Cariou *et al*. 2009). At centre 1, a polypropylene (Prolene; Ethicon Ltd) ligature (size 2-0 to 3-0) was used to attenuate the shunts (full attenuation where possible), and a second surgery to perform full attenuation was recommended for all dogs that tolerated a partial attenuation at the first surgery. At centre 2, 2-0 polyethylene terephthalate (Ethibond; Johnson & Johnson Medical BV) was used for attenuation in all dogs. Second surgery if a full attenuation had not been achieved was not recommended if dogs had a good clinical response to the first surgery.

Data collected from the medical records included signalment, body condition score, surgery date(s), type of shunt (EHCPSS or IHCPSS), whether complete or partial shunt attenuation was performed, whether a second surgery was performed and, when known, the presence of ongoing shunting in the form of persistent flow through the CPSS or the development of multiple acquired shunts (MAS).

Owners of a control population of healthy dogs were invited to complete the HRQoL questionnaire. Control dogs were selected of the same breed and approximate ages as the CPSS population. Control dogs were recruited by contacting individual UK Kennel club breed societies and telephoning owners to ask them to participate in the study, a small number were recruited *via* centre 1's intranet from pets owned by non-clinical staff.

Questionnaire development

The questionnaire was developed on the basis of previously published veterinary questionnaires (Reid et al. 2013, Levan et al. 2013). A "direct" QOL question was asked using a 10-cm visual analog scale (VAS) from "worst imaginable" to "best imaginable" both before surgery and at long-term follow-up (Appendix S1, Supporting Information). This was measured and converted to give a QoL score out of 100.

For assessment of clinical signs, questions were developed on the basis of widely accepted clinical signs associated with CPSS (Berent & Tobias 2012). For each clinical sign, the frequency was recorded on a categorical scale from "never" to "daily." From these questions a CPSS score was developed, to assess frequency and severity of clinical signs; signs were divided into three classes according to severity, with class 1 answers multiplied by 3, class

Table 1. Classification and scoring of clinical signs to develop a global CPSS score

Class	Clinical sign	Multiplication of original score
1	Seizures	3
2	Head pressing, ataxia, disorientation, aggression, collapse, unresponsiveness, apparent blindness, fatigue/weakness, circling	2
3	Vomiting, diarrhoea, decreased appetite, haematuria, dysuria	1
	Urolithiasis or urethral obstruction	+2 points
	Retarded growth	+4 if present, +2 if owner unsure, 0 for not present

2 by 2 and class 3 by 1. Classes were determined subjectively by the authors, based on expert opinion (see Table 1) and multiplication numbers were determined arbitrarily based on expert opinion and previous work in this field (unpublished data). Consequently, greater CPSS scores represented a more severely clinically affected dog, with the highest score achievable of 110.

There were two parts to the questionnaire with Part 1 (Appendix S2) assessing variables preoperatively and Part 2 at long-term follow-up postoperatively (Appendix S3). The questionnaires also address general behaviour and the dogs willingness to participate in "normal" canine activities including play, exercise and interaction with owners and other dogs. These questions were measured on a VAS scale from "Not at all willing" to "Could not be more willing". In addition, a question on the dog's activity level was asked on a VAS scale from "Not active at all" to "Could not be more active". To capture the effect of CPSS on growth, owners were asked to report whether their dog was considered small or underweight for their breed and age, and whether their body condition had changed since they acquired them. For further questionnaire design see File S1.

The questionnaire was either filled out by the owner while attending a hospital follow-up appointment for a concurrent study at centre 1 (Bristow *et al.* 2017), or mailed or emailed to the owners.

Statistical analysis

Statistical analysis was performed using IBM SPPS Statistics v21. Continuous data were assessed graphically for normality. Mean and standard deviation were reported for normally distributed data and median and 25th to 75th percentiles were reported for non-normally distributed data. IHCPSS and EHCPSS dogs were analysed separately. Differences between the EHCPSS and IHCPSS dogs at long-term follow-up *versus* the control group were compared using the Mann-Whitney U test. Significance was set at $P<0.05$. Statistical analysis was not performed using part 1 of the questionnaire (preoperative results), because of the extended owner recall time.

RESULTS

Demographics

One hundred and twenty-three dogs met the inclusion criteria at centre 1 and 132 at centre 2. Of these, 76 owners (61.8%) returned the questionnaire at centre 1 and 52 (39%) at Centre 2; resulting in 128 study dogs. One hundred and eight dogs had an EHCPSS and 20 an IHCPSS. Median follow-up time was 64 months (range 19.7 to 157.2).

The most commonly represented breed in the EHCPSS group was the Yorkshire terrier (n = 14), followed by the miniature schnauzer (n = 12; Table 2). In the IHCPSS group, golden retrievers (n = 6), followed by Labrador retrievers (n = 3) were the most commonly represented (Table 3). The mean age at follow-up for EHCPSS dogs was 84.9 months (±37.2) and 74.8 months for IHCPSS dogs (±28.7).

One hundred and thirty-one control dogs were recruited (including three dogs *via* centre 1's intranet). In the control group, cross breeds were the most commonly represented (n = 13), followed by bichon frise (n = 9; Table 4). The mean age of the control dogs was 93.5 months (±28.8).

Surgical treatment

Seventy-one of 108 dogs with an EHCPSS (65.7%) had a full attenuation (in one or two surgeries), with 35 dogs (32.4%) having a partial attenuation only (n = 34 with polyethylene terephthalate, n = 1 with polypropylene), and two dogs (2%) diagnosed with MAS; one following partial attenuation (detected at the second surgery), and the second following a full attenuation (both with polypropylene).

Nine of 18 dogs with an IHCPSS (50%) had a complete attenuation (in one or two surgeries, all with polypropylene), with nine dogs (50%) having a partial attenuation (n = 7 with polyethylene terephthalate, n = 2 with polypropylene). Two dogs (10%) developed MAS; one following partial attenuation (detected at

Table 2. EHCPSS dog breeds

Breed	Number
Yorkshire terrier	14
Miniature schnauzer	12
West Highland white terrier	11
Cross breed	11
Maltese terrier	9
Jack Russell terrier	7
Shih-tzu	6
Miniature dachshund	5
Pug	5
12+ breeds	<5/breed

EHCPSS extrahepatic congenital portosystemic shunt

Table 3. IHCPSS dog breeds

Breed	Number
Golden retriever	6
Labrador retriever	3
Cross breed	2
Stabyhoun	2
Bernese mountain dog	1
Cavalier King Charles spaniel	1
Hovawart	1
Weimaraner	1
Rhodesian ridgeback	1
Samoyed	1
Cocker spaniel	1

IHCPSS intrahepatic congenital portosystemic shunt

Table 4. Control dog breeds

Breed	Number
Cross breed	13
Bichon frise	10
West Highland white terrier	9
Labrador retriever	8
Cocker spaniel	8
Yorkshire terrier	7
Samoyed	6
Shih-tzu	6
Golden retriever	5
Lhasa apso	5
Miniature dachshund	5
Welsh Springer spaniel	5
17+ breeds	<5/breed

the second surgery), and the second following a full attenuation (both with polypropylene).

At centre 1, three dogs with MAS were receiving medical management with all three on a low protein diet, one on lactulose and one receiving occasional antibiotics when the owner felt "he was not acting his usual self." One dog that had been treated with a partial attenuation was receiving antibiotics, lactulose and a low protein diet and a second partially attenuated CPSS dog was receiving a low protein diet. A final dog that had been treated by complete attenuation was also on a low protein diet but the owner had decided to continue this after surgery contrary to recommendations.

At centre 2 no dogs were receiving medical management, all lactulose were discontinued immediately after surgery and low protein diet was transitioned to a normal diet over 1 postoperative week.

Questionnaire results

Summaries of the results of the questionnaire for EHCPSS dogs, IHCPSS dogs and control dogs are presented in Tables 5 to 7.

QoL score

The long-term median QoL score of dogs with an IHCPSS was 94 (83 to 97.5), which was not significantly different from the control group at 93 (82 to 98) ($P = 0.782$). The long-term median QoL score of EHCPSS dogs was significantly greater than the control group ($P = 0.015$) at 96 (89 to 100) (Table 5). There was an increase in QoL score in both EHCPSS and IHCPSS dogs from preoperatively to long-term follow-up (Table 5).

CPSS score

The long-term median CPSS score of the IHCPSS [9 (1 to 26)] and EHCPSS [3 (1 to 10)] dogs were significantly worse than that of the control group [1 (0 to 3)], with these differences being statistically siginficant ($P = 0.003$ for IHCPSS and $P<0.001$ for EHCPSS). CPSS score was improved at long-term follow-up in dogs with IHCPSS and EHCPSS compared to that preoperatively, with the median percentage improvement in CPSS score from preoperatively to long-term follow-up 72.4% for dogs with IHCPSS, and 90.5% for dogs with EHCPSS (Table 5).

DISCUSSION

To our knowledge this is the first study to use a HRQoL questionnaire to assess long-term outcome of surgical treatment of CPSS in dogs and to compare these results to a control population.

Design of a HRQoL questionnaire allowed us to compare an overall owner reported health-related outcome in the form of the CPSS score (severity and frequency of clinical signs) with a direct QoL score. Previous studies of dogs treated for CPSS have relied on a brief owner assessment, and one of our aims was to try to develop a more accurate assessment tool that takes into account these two important domains. A need for this more thorough type of evaluation is highlighted in this study by owners reporting the direct QoL to be excellent at long-term follow-up, and comparable to a control population, despite both EHCPSS and IHCPSS groups having significantly worse CPSS scores than those of control dogs at long-term follow-up. Clearly, both the QoL and a CPSS score such as we designed in this study are both necessary to provide complementary information to allow a more accurate overall long-term assessment of owner-derived outcome.

The persistence of a relatively high CPSS score at follow-up, and one statistically higher than a control population, despite an apparent clinical improvement (based on QoL measurement), is a novel finding as it suggests that although surgery for partial or complete attenuation is associated with an improvement in frequency and severity of clinical signs, the majority of dogs undergoing CPSS attenuation do not go back to what is consid-

Table 5. The impact of surgery on the clinical signs of CPSS, QoL and behaviour of intrahepatic and extrahepatic CPSS cases (median and interquartile range)

Variable	Control group (n=131)	IHCPSS (n=20)		EHCPSS (n=108)	
		Presurgery	Postsurgery	Presurgery	Postsurgery
CPSS score	1 (0 to 3)	34 (13 to 49)	9 (1 to 26)*	39 (23.5 to 56)	3 (1 to 10)*
QoL score	93 (82 to 98)	7 (3 to 22)	94 (83 to 97.5)	7 (2 to 29)	96 (89 to 100)*
Activity score	87 (68.5 to 100)	47 (28.5 to 70.5)	87 (53.5 to 94)	43 (19 to 77.5)	86 (63.5 to 98.5)
Willingness to play	93.5 (77 to 99.75)	72.5 (29 to 94.3)	91 (66.3 to 98.5)	47.5 (21 to 76.3)	91 (65.3 to 98)
Willingness to interact with owners	98 (92 to 100)	66 (32.8 to 94.5)	94.5 (79.5 to 99.3)	80 (49.8 to 95)	97 (88 to 100)
Willingness to exercise	97 (81 to 100)	60 (25.5 to 95.5)	95 (68.5 to 97)	48.5 (21.3 to 85.3)	93.5 (72.3 to 99)
Willingness to interact with other dogs	95 (70.3 to 100)	66.5 (29.3 to 95.3)	90.5 (78.3 to 98.5)	47 (10.5 to 87.5)	87 (35.5 to 98)*

CPSS congenital portosystemic shunt, EHCPSS extrahepatic congenital portosystemic shunt, IHCPSS intrahepatic congenital portosystemic shunt, QoL quality of life
*Statistically significant values compared to control group

Table 6. The impact of presurgical treatment (diet and/or medication) on the QoL of intrahepatic and extrahepatic CPSS cases (median and interquartile range)

Variable	IHCPSS	EHCPSS
Willingness to eat special diet	49 (8.5 to 95)	78 (23.8 to 97.3)
Impact of special diet on QoL*	32 (1 to 59)	43 (5 to 91)
Improvement following diet and/or medication	24 (5 to 88)	50 (20 to 83)
Impact of medication on QoL*	4 (0.5 to 28)	2 (0 to 11)

CPSS congenital portosystemic shunt, QoL quality of life
*A higher score denotes a negative owner perception

Table 7. Improvements following surgery and owner perceptions (median and interquartile range)

Variable	IHCPSS	EHCPSS
General improvement following surgery	95 (64 to 99)	98 (90 to 100)
Improvement in body condition	94 (49 to 97)	95 (70 to 98.5)
Satisfaction with response to surgery	96.5 (83 to 98)	99 (95.5 to 100)
Worry over dog's condition*	16 (2.5 to 78.5)	5 (0 to 32.5)

EHCPSS extrahepatic congenital portosystemic shunt, IHCPSS intrahepatic congenital portosystemic shunt
*A higher score denotes a negative owner perception

ered "normal," when compared to a healthy control population. This potentially means that some dogs are being undertreated. If dogs do indeed have persistent subtle clinical signs then individuals may benefit from further treatment. The finding of a lack of return to "normal" fits with studies assessing other outcome measures, for example, serum bile acid concentrations have been shown to not return to within reference intervals in the long-term in the majority of dogs with a complete shunt attenuation (Bristow *et al.* 2017). It is suggested that some dogs have continued microvascular shunting following CPSS surgery due to concurrent microvascular dysplasia or primary portal vein hypoplasia (O'Leary *et al.* 2014). O'Leary *et al.* (2014) proposed a spectrum of disease in dogs with CPSS, which could explain why some of these dogs have not returned to the baseline of "normal" on other tests from previous studies, as well as clinically in our study. People with liver disease can suffer from minimal hepatic encephalopathy (Groeneweg *et al.* 1998, Shawcross *et al.* 2007), so that affected individuals do not show obvious signs of hepatic encephalopathy but do have significant abnormalities in neurophysiological performance and on psychometric testing and this might also occur in dogs.

Further potential causes to be considered are that not all dogs in this study underwent imaging or blood testing to assess if MAS, persistent shunting or other abnormalities were present, and 32% of the EHCPSS cases had a partial attenuation without follow-up to determine whether they had progressed to a full attenutation. Ninty-three percent of these cases were attenuated partially with polyethylene terephthalate and it is therefore probable that some of them had progressed to a full attenuation. Nevertheless some of these 32% of cases could have persistent shunting, thereby accounting for some of the results. Equally, the approximate rate of persistent shunting due to MAS is relatively low for dogs treated with suture ligation (Hottinger *et al.* 1995, White *et al.* 1998, Tivers *et al.* 2017a) and, on balance, this population here reflects standard clinical practice in many hospitals, of a combination of partial and complete attenuation, thereby providing useful information in a large population of surgically treated dogs at follow-up.

Despite the discrepancy in QoL score and CPSS score, encouragingly, our data does also support the suggestion that suture attenuation of a CPSS results in clinical improvement, with an improved CPSS score for both EHCPSS and IHCPSS from preoperatively compared to long-term follow up. Use of this questionnaire prospectively (*i.e.* before and after surgery) will be able to provide statistical analysis on this improvement in the future.

It is important to consider the limitations of owner-based questionnaires, including attention bias, meaning that owners notice and remember "abnormal" episodes more regularly, which could account for some of the difference in CPSS score, recall bias is another potential limitation to owner-based assessment and owners of affected dogs may be more generous in their assessment of QoL compared to owners of "normal" dogs, as they have seen such a dramatic improvement after receiving treatment – as evidenced by the statistically better QoL observed by owners of CPSS dogs. Despite these limitations, HRQoL is becoming increasingly recognised as a very important factor for outcome measurement, with the emerging view in human medicine that it is an essential assessment to consider when measuring treatment success (Garratt *et al.* 2002).

Design of a CPSS score was novel and based on expert opinion as has been the basis of designing questionnaires in other studies (Reid et al. 2013, Freeman et al. 2013). Naturally there will be differing expert opinions as to the impact of different clinical signs on QoL, but this questionnaire was designed as a starting point to begin more in-depth analysis of outcome of CPSS dogs after treatment, leading on to future improvement in this assessment as well as the ability to compare different techniques in the future. As discussed in the introduction, there is a lack of evidence to currently recommend one treatment over another (Tivers *et al.* 2012, 2017b), and we should be striving to improve the evidence, with the use of validated instruments for comparisons. One of the strengths of this study is the availability of long-term information in a large number of dogs, which is often time-consuming and difficult to collect but essential in order to evaluate outcome of a condition and an intervention properly. It is hoped that use of a consistent HRQoL questionnaire tool for CPSS dogs will make this important ongoing task more manageable, easier to compare between different institutions, with a further benefit that it does not require the dog to return for a visit, blood test, sedation or anaesthesia, or imaging investigations.

Conflict of interest

No conflicts of interest have been declared.

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Supporting Information

The following supporting information is available for this article:

File S1. Additional questionnaire design

Appendix S1. Portosystemic shunt quality of life questionnaire: part 1: before surgery

Appendix S2. Portosystemic shunt quality of life questionnaire: Part 2: how is your dog now?

Appendix S3. Quality of life questionnaire