Long-term outcome and prognostic indicators of symptomatic treatment in dogs and cats with CPSS: a retrospective study.

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Contents

Abstract

To evaluate long term outcome and prognostic indicators for medically treated dogs and cats with a congenital portosystemic shunt, case records of 78 dogs and 10 cats referred to the Department of Clinical Science of Companion Animals, University of Utrecht, between September 2003 and February 2015 were reviewed. Thirty-seven questionnaires were used to assess quality of life in dogs before and during treatment. Age, breed, sex, hematological and serum biochemistry findings corresponded mainly with previous literature. Clinical signs consisted of the usual signs, although the incidence of polyuria and polydipsia in dogs in our study is higher than reported before. Estimated median survival time (EMST) for dogs was 41,5 months. No significant different EMST's were found between patients with extrahepatic or intrahepatic shunts, or between treatment with only an adjusted diet or an adjusted diet combined with lactulose. EMST for cats was found to be 3,5 months, although with a wide range. Clinical signs with a significant decrease in frequency during treatment were head pressing, circling, ataxia, general weakness or tiredness, vomiting and hematuria. Besides, dogs were considered to be more active, and a significant improvement in quality of life scored by the owners was found. Leukocytosis was identified as a prognostic indicator for prolonged survival. Surgical attenuation of the shunt remains treatment of first choice, though our study demonstrated that symptomatic treatment results in reasonable survival times and quality of life for most canine patients.

Introduction

Portosystemic shunts are vascular anomalies, allowing portal blood to bypass the hepatic parenchyma and directly enter the systemic circulation.[1, 2] Portosystemic shunts can be acquired, due to portal hypertension, or be a congenital anomaly. Congenital portosystemic shunts (CPSS), both intrahepatic (IHPSS) and extrahepatic (EHPSS), are the result of inappropriate closure of fetal vasculature, leading to a single CPSS in most of the times, although multiple CPSS have been found as well.[1, 3] CPSS is more frequently seen in dogs, but can also occur in cats. In large-breed dogs significantly more IHPSS are seen, while affected small-breed dogs and cats more often suffer from EHPSS.[4] Ammonia, an important substance that accumulates in the systemic circulation in patients with CPSS because of the bypass, is largely responsible for the development of hepatic encephalopathy (HE), although other accumulating substances such as aromatic amino acids and bile acids contribute to HE as well.[4] Besides the neurological signs of HE, symptoms of the gastrointestinal system and lower urinary tract are frequently present.[2, 5, 6] These lower urinary tract signs are the result of ammonium urates.[7] Diagnostic workup should contain biochemistry, hematology and urinalysis. Plasma ammonia is a feasible measurement, with great sensitivity but even a better specificity to detect PSS.[6, 8] The final diagnosis of CPSS will be established with imaging techniques, such as ultrasonography, scintigraphy, computed tomographic angiography and magnetic resonance angiography or direct demonstration with explorative laparotomy.[1, 9]

Surgical intervention is frequently recommended and many methods for surgical shunt occlusion have been investigated.[1, 6] Unfortunately, surgery is not always possible due to anatomical or financial reasons.[2] Medical management is used to control the clinical signs by reducing the transport of factors absorbed from the gastrointestinal tract to the systemic circulation. This conservative therapy does not alter the portal blood flow like surgery does.[1] Medical management mainly includes a specific diet, which contain an adapted share of proteins. Medical management also might include disaccharides, such as lactulose, and antimicrobial treatment to reduce ammonia uptake in the gastrointestinal tract. Additionally, anticonvulsant medication and antacids are mentioned as part of the medical treatment in specific cases. [1, 2, 6, 9, 10] Few studies discuss the long-term follow-up of medically managed patients.[2, 10] The aim of this study is to determine the long-term outcome, both survival time and quality of life, and prognostic factors in dogs and cats with CPSS that only received medical treatment. These results might help veterinarians to inform owners better about expectations and prognosis of medical treatment of dogs and cats with CPSS.

Materials and Methods

Animals

Case records of all dogs and cats with CPSS referred to the Department of Clinical Science of Companion Animals (DCSCA), University of Utrecht, the Netherlands, between September 2003 and February 2015 were reviewed. Only those cases in which the diagnosis CPSS was confirmed by ultrasound or computed tomography were selected. Data about signalment, medical history, age at diagnosis, shunt type and diameter, and hematological and serum biochemistry findings were obtained.

Follow-Up

Owners were contacted by telephone to determine survival time and presumed cause of death if applicable. Referring veterinarians were contacted if the owners could not be reached. Owners were asked to confirm that their animal had received or still received medical treatment instead of surgery and what the current or last treatment consisted of. Permission was asked to send them a questionnaire about the different symptoms, frequency and quality of life before and during the symptomatic treatment, given that their pet received treatment for at least one month (Appendix I). Based on the follow-up information, the subjects were assigned to a treatment group. Specific treatment was determined for 65/78 dogs and 8/10 cats. Two main groups were created, being 'adjusted diet' and 'adjusted diet in combination with lactulose', and animals were assigned to the adjusted diet group if they received last, or were still receiving an adjusted diet for at least one month at time of follow-up. They were assigned to the adjusted diet with lactulose group if they received any amount of lactulose besides an adjusted diet, for at least one month at time of follow-up. An adjusted diet is specified as a diet lower in protein then the diet they would have received if CPSS had not been diagnosed. The vast majority of the dogs received 'hepatic' from Royal Canin ®. Other commercial diets fed were 'l/d' from Hill's®, a kidney diet, a senior diet and a lamb and rice diet. Four owners mentioned they gave home cooked meals low in protein. Not for all dogs the specific diet and brand could be determined. Other medication mentioned to control symptoms due to CPSS in dogs were metronidazole, antacids, corticosteroids, anti-diuretic hormone and diuretics to control ascites due to hypoalbuminemia. Additional medication prescribed for cats with CPSS was gabapentine to diminish seizures (n=1).

Evaluated variables

The analyzed variables are history, signalment, type and size of CPSS, hematologic and serum biochemistry markers, clinical signs before and during treatment, experiences of treatment by the owners and survival time. Only hematological and biochemistry results obtained at the University veterinary diagnostic laboratory (UVDL) on the same date as diagnosis was confirmed, or within the same primary hospitalization period, were used.

Statistical analysis

Statistical analysis was performed by use of commercially available software packages (IBM SPSS Statistics version 22, IBM Corporation). Survival analysis was based on a Kaplan-Meier curve. Survival time had been defined as the time between confirmed diagnosis and death or euthanasia. Patients that died of CPSS-related causes were counted as events. If the cause of death was considered unrelated, patients were censored, just like those who were still alive at time of follow-up. Significant differences between Kaplan-Meier curves were tested by a Log rank test. Data about frequency of clinical signs and quality of life are summarized in crosstabs with a kappa coefficient. A Wilcoxon rank

sum test for paired data was performed to compare the frequency of clinical signs and scored quality of life before and during treatment. For comparison of the two treatment groups, a Mann Whitney U test was performed on the improvement in both groups. Prognostic indicators for survival time were analyzed with Cox regression models. Values of $p<0,05$ were considered significant.

Results

Animals

The data base search resulted in 303 dogs and 26 cats with CPSS. 97 Dogs and 11 cats were treated symptomatically only. In 8/97 dogs an initial attempt was made to surgically ligate the shunt, but attenuation proved to be unachievable during the procedure and symptomatic treatment was continued. One dog was euthanized by the referring veterinarian one day after diagnosis because no response on treatment was seen. As medical treatment had been tried in this case, it was selected. Two dogs were euthanized at the time of diagnosis and were not selected because no symptomatic treatment was tried. At follow-up, 78/97 dogs and 10/11 cats were confirmed not to have been operated because of their shunt, and were finally included in the study. The breeds and their shunt types of the encountered dogs and cats are represented in Table 1A and 1B respectively.

Table 1A. Shunt type and breed distribution of the selected dogs (n=78).

Breeds with EHPSS	**N**	**Breeds with IHPSS**	**N**
Yorkshire Terriër	6	Bernese Mountain Dog	4
Cairn Terriër	5	Nova Scotia Duck Tolling Retriever	4
Chihuahua	5	Cross breed	2
Miniature Schnauzer	5	Doberman Pinscher	2
Jack Russel Terriër	4	Golden Retriever	2
Shih Tzu	4	Labrador Retriever	2
Maltese Dog	3	Borzoi	1
Cross breed	2	Basset Hound	1
Dachshund	2	Belgian Shepherd Dog	1
Labrador Retriever	2	Cavalier King Charles Spaniël	1
Cavalier King Charles Spaniël	1	Chihuaha	1
English Springer Spaniël	1	English Cocker Spaniël	1
Golden Retriever	1	French Bulldog	1
Keeshond large	1	Grand Basset Griffon Vendéen	1
Lhasa Apso	1	Jack Russel Terriër	1
Miniature Poodle	1	Maltese Dog	1
Norfolk Terriër	1	Rhodesian Ridgeback	1
Pug	1	Scottish Terriër	1
Schapendoes	1	Weimaraner	1
West Highland White Terriër	1		

Table 1B. Shunt type and breed distribution of the selected cats (n=10).

Breeds with EHPSS	**N**	**Breeds with IHPSS**	**N**
Domestic shorthair	3	Cross breed	1
British shorthair	1	Domestic shorthair	1
Persian	1	Maine Coon	1
Ragdoll	1	Turkish Angora	1

Dogs - Fourty-eight dogs were diagnosed with EHPSS, and 29 dogs with IHPSS. In one dog, only CPSS was diagnosed but the exact location of the shunting could not be established. More EHPSS were seen in the smaller breeds (<10 kg), 42 against 6 EHPSS in larger breeds (>10 kg). In contrast, 22 large breed dogs were diagnosed with IHPSS, whereas IHPSS was diagnosed in 7 small breed dogs. Median age at diagnosis of CPSS in dogs is 11 months (range 2-133 months) (Table 2A). No sex predisposition was suspected.

Cats - Six cats were diagnosed with an EHPSS, while 4 suffered from IHPSS. The median age at diagnosis for cats is 6 months (range 3,5-104 months) (Table 2B). Seven cats were male, and 3 cats were female.

Table 2A. Age at diagnosis in dogs (n=78).

Age at diagnosis	**N**
< 6 months	24
6-12 months	18
1-2 years	7
2-5 years	11
> 5 years	18

Table 2B. Age at diagnosis in cats (n=10).

Age at diagnosis	**N**
< 6 months	5
6-12 months	3
1-2 years	1
2-5 years	0
> 5 years	1

Clinical signs

Dogs - Clinical signs were mostly intermittent and consisted of signs of the central nervous system (head pressing, circling, ataxia, apparent blindness, sopor and confusion), gastrointestinal signs (vomiting, diarrhea, low body condition and excessive salivation) and signs of lower urinary tract disease caused by urolithiasis, sometimes confirmed as ammonium urates. Other signs present were retarded growth, polyuria and polydipsia (pu/pd) and pale mucous membranes due to anemia. All of the previous signs were often accompanied by depression and/or anorexia and the majority of dogs showed signs of more than one organ system. Two dogs did not show any signs alarming to the owners. One of them was a puppy of 2 months old, which was suspected of CPSS because of an abnormal serum ammonia level during nest screening. The CPSS of the other dog without any clinical signs was discovered after a pre-anesthetic blood examination showed altered liver values. An overview of clinical signs is listed in Table 3.

Cats - All cats had shown neurological signs at least once. Out of the 10 cats, 5 suffered also from gastrointestinal signs, 4/10 from retarded growth, 2/10 had pu/pd and only one cat showed signs of lower urinary tract disease.

Table 3. Clinical signs before or at time of diagnosis in dogs with CPSS (n=78).

Clinical signs	**N**	**Percentage**
Neurological signs	52	67 %
Pu/pd	37	47 %
Gastrointestinal signs	25	32 %
Urinary tract disease *with confirmed ammonium urates*	17 *11*	22 % *14%*
Retarded growth	13	17 %
Pale mucous membranes	3	4 %
No clinical signs present	2	3 %
Unknown	1	1 %

Hematological and serum biochemistry findings

Dogs - In serum biochemistry parameters, preprandial bile acids were most frequently increased, followed by ALT, plasma ammonia levels and ALP. Total protein, albumin and blood urea nitrogen (BUN) were decreased in 23/29, 25/31 and 9/14 dogs, respectively. (Table 4A) Hematologic markers showed an anemia in 13/17 dogs and a leukocytosis was seen in 11/15 dogs. In the coagulation profile is seen that the PT and APTT are prolonged in 4/14 and in 9/14 dogs respectively (Table 4B).

Cats - Plasma ammonia levels were determined in 7 cats at time of diagnosis, with a median value of 286 µmol/L. Bile acids were available for 4 cats with a median of 63,5 µmol/L. Other parameters were only available for 3 cats or less at time of diagnosis confirmation.

Table 4A. Biochemistry findings in dogs with CPSS.

Parameter	**n**	**Median (range)**	**Reference range**	**Decreased**	**Increased**
NH3 (µmol/L)	62	131,5 (24-286)	24-45	0/79	54/62 (87%)
NH3 20 (µmol/L)	7	286 (277-286)			
NH3 40 (µmol/L)	6	286 (286)			
Bileacids (µmol/L)	48	91 (3-390)	< 10	NA	45/48 (94%)
ALP (U/L)	27	108 (28-608)	< 73	NA	20/27 (74%)
ALT (U/L)	23	203 (32-471)	< 54	NA	21/23 (91%)
BUN (mmol/L)	14	1,6 (0,8-3,3)	2,1-8,4 (fasted)	9/14 (64%)	0/14 (0%)
Total protein (g/L)	29	47 (25-66)	55-72	23/29 (79%)	0/29 (0%)
Albumine (g/L)	31	22 (9-29)	26-37	25/31 (81%)	0/31 (0%)

Table 4B. Hematological findings in dogs with CPSS.

Parameter	n	Median (Range)	Reference interval	Decreased	Increased
HT (L/L)	17	0,34 (0,27-0,48)	0,42-0,61	13/17 (76%)	0/17 (0%)
MCV (fl)	11	58,7 (49,0-66,2)	63,5-72,9	10/11 (91%)	0/11 (0%)
MCHC (mmol/L)	11	21,8 (19,8-22,6)	20,5-22,4	2/11 (18%)	1/11 (9%)
MCH (fmol)	11	1,26 (1,05-1,44)	1,37-1,57	10/11 (91%)	0/11 (0%)
Reticulocytes (%)	3	1,2 (0,6-2,2)	<1,5	NA	1/3 (33%)
CHr (fmol)	3	1,32 (1,27-1,32)	1,43-1,71	3/3 (100%)	0/3 (0%)
WBC (10^9/L)	15	16,4 (8,7-34,6)	4,5-14,6	0/15 (0%)	11/15 (73%)
Neutrophils (10^9/L)	15	10,2 (5,9-26,0)	2,9-11,0	0/15 (0%)	6/15 (40%)
Bands (10^9/L)	14	0 (0-1,9)	0,0-0,3	NA	3/14 (21%)
Blasts (10^9/L)	14	0 (0-0,3)	0	NA	1/14 (7%)
Metamyelocytes (10^9/L)	6	0 (0-0,5)	0	NA	1/6 (17%)
Lymphocytes (10^9/L)	15	4,2 (1,5-8,7)	0,8-4,7	0/15 (0%)	4/15 (27%)
Monocytes (10^9/L)	14	0,8 (0,2-3,5)	0,0-0,9	NA	4/14 (29%)
Eosinophils (10^9/L)	14	0,6 (0-2,7)	0,0-1,6	NA	1/14 (7%)
Basophils (10^9/L)	14	0 (0-0,2)	0,0-0,1	NA	2/14 (14%)
Normoblasts (/100 leucocytes)	14	0 (0)	*No reference*	NA	NA
Platelet (10^9/L)	11	227 (143-392)	144-603	1/11 (9%)	0/11 (0%)
PT (sec)	14	8,95 (6,8-12,0)	6,7-9,5	0/14 (0%)	4/14 (29%)
APTT (sec)	14	17,9 (11,0-23,1	10,0-17,2	0/14 (0%)	9/14 (64%)
Fibrinogen (g/L)	14	2 (1,1-3,2)	1,0-2,8	0/14 (0%)	3/14 (21%)
MPC (g/L)	4	247,5 (240-295)	162-261	0/4 (0%)	1/4 (25%)
MPM (pg)	4	2,195 (2,05-2,91)	1,42-2,46	0/4 (0%)	1/4 (25%)
MPV (fl)	4	9,5 (8,5-14,7)	6,8-13,4	0/4 (0%)	1/4 (25%)

Quantity of life

Dogs - Survival times after diagnosis were estimated for the entire group, type of shunt and the different treatment groups (Figure 1.A-C). The estimated median survival time (EMST) after diagnosis is 41,5 months (range 0 to 91 months). Two dogs did not receive an adjusted diet, one of them was treated with lactulose only. They were not included in one of the treatment groups. Neither the shunt types (p=0,12), nor the treatment groups (p=0,08) differed significantly in EMST.

Prognostic indicators were analyzed with a Cox regression model. Variables screened are age at diagnosis, gender, shunt diameter, neurological signs, gastrointestinal signs, lower urinary tract signs, pu/pd, retarded growth, ammonia>100, ammonia>200, bile acids>100, increased ALP, hypoproteinemia, hypoalbuminemia, decreased BUN, anemia, leukocytosis, increased fibrinogen and prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT). Only leukocytosis was significant (p=0,050), and was associated with a longer survival time.

Cats - EMST for cats is 3,5 months (range 0,5 to 104 months) (Figure 1.D). Because of the small number of cats, comparison for treatment and shunt type was not performed.

Quality of life

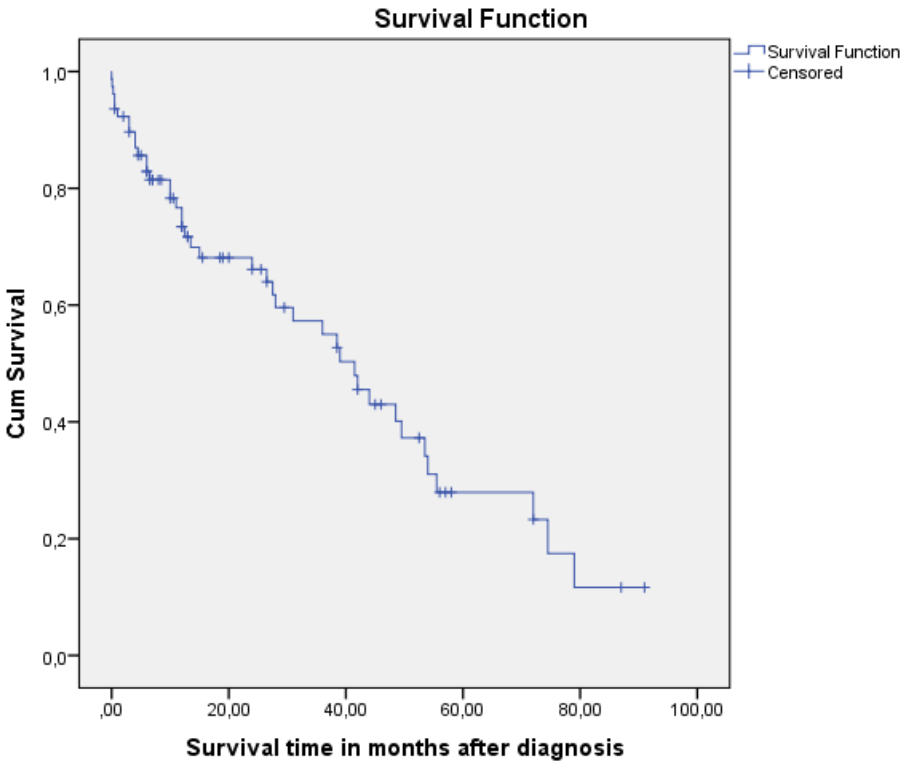
Dogs – Questionnaires were send to 56 dog owners, of which 37 returned the questionnaire. Data about frequency of clinical signs before and during treatment, and quality of life are summarized in crosstabs with a kappa coefficient (Appendix II). Several clinical signs occurred significantly less during treatment, being circling (p=0,03), ataxia (p=0,03), general weakness or tiredness (p=0,00), vomiting (p=0,00) and hematuria (p=0,02). Also, the dogs showed to be significantly more active than before treatment (p=0,03). Although not all clinical signs were reduced significantly, overall quality of life was scored better during treatment than before treatment (p=0,00). Clinical signs in which no significant decrease in frequency was seen, were seizures (p=0,56), head pressing (p=0,054), disorientation (p=0,92), aggression (p=0,63), fainting (p=1,0), mental absence (p=0,26), blindness (p=0,28), diarrhea (p=0,20), diminished appetite (p=0,33), dysuria (p=0,89), ptyalism (p=0,38) and pu/pd (p=0,52).

The returned questionnaires could also be grouped in the different treatment groups, resulting in 18 forms for only adjusted diet and 19 for adjusted diet with lactulose. Only one of the symptoms, hematuria, differed significantly between the groups, showing more improvement of hematuria in dogs receiving only an adjusted diet (p=0,01).

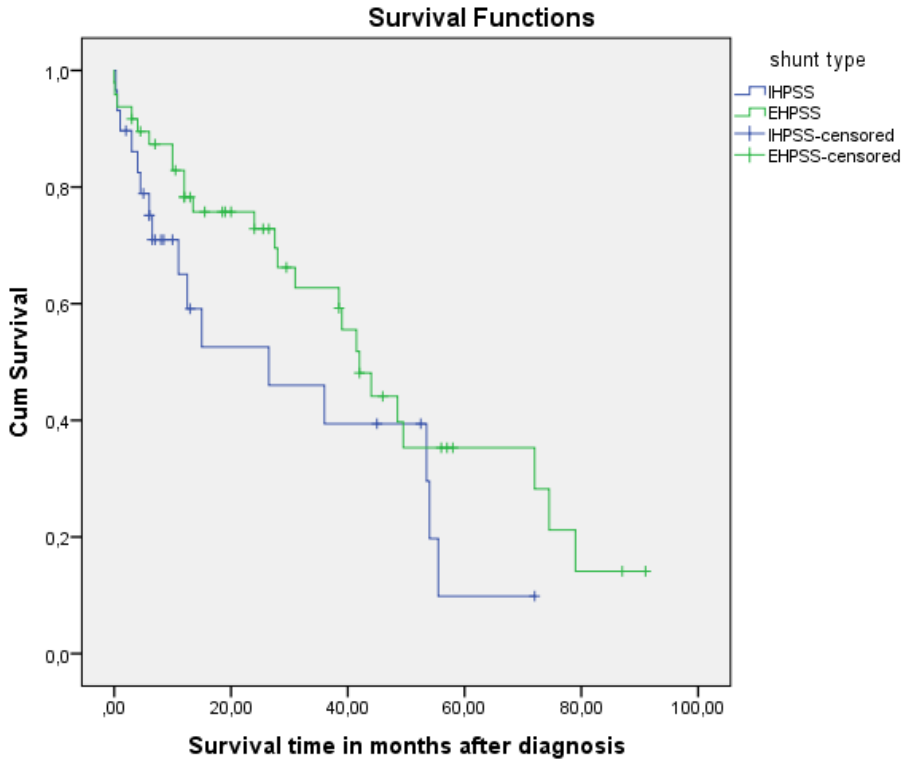
Cats – Questionnaires were send to 10 cat owners, of which 3 returned the questionnaire. Quality of life could not be properly assessed for cats because of this small number.

Figure 1. Kaplan-Meier curves for the survival times of A) the entire 78 dogs, B) shunt type (IHPSS vs. EHPSS), C) treatment groups (adjusted diet vs. adjusted diet with lactulose) and D) cats, n=10.

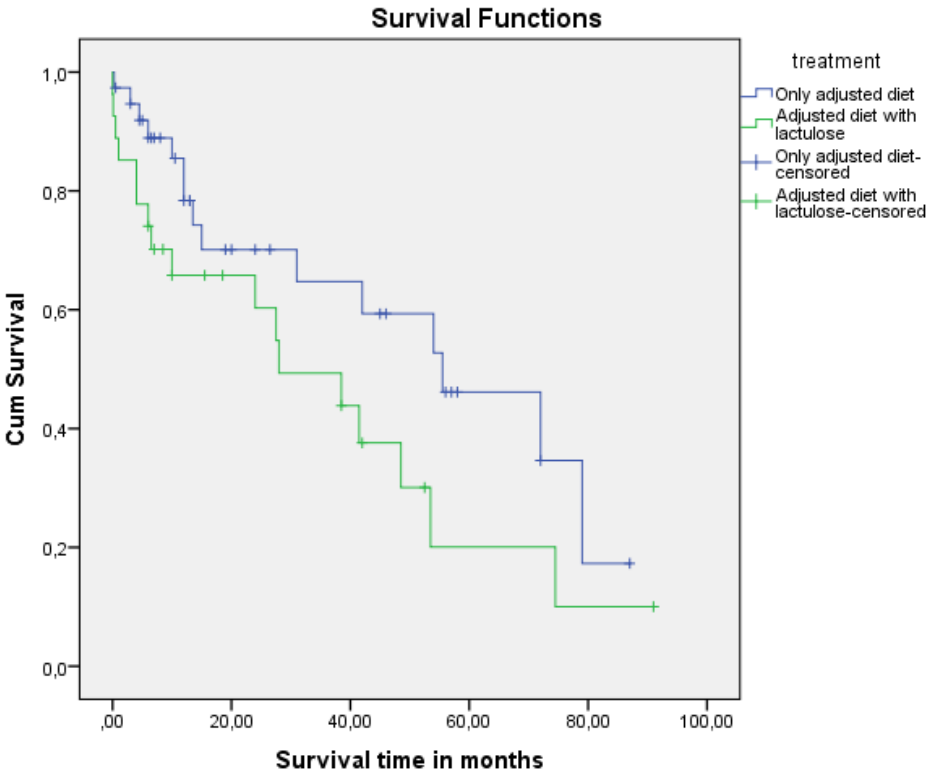
A)



B)



C)


Survival Functions
treatment
Only adjusted diet
Adjusted diet with lactulose
Only adjusted diet-censored
Adjusted diet with lactulose-censored
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40,00
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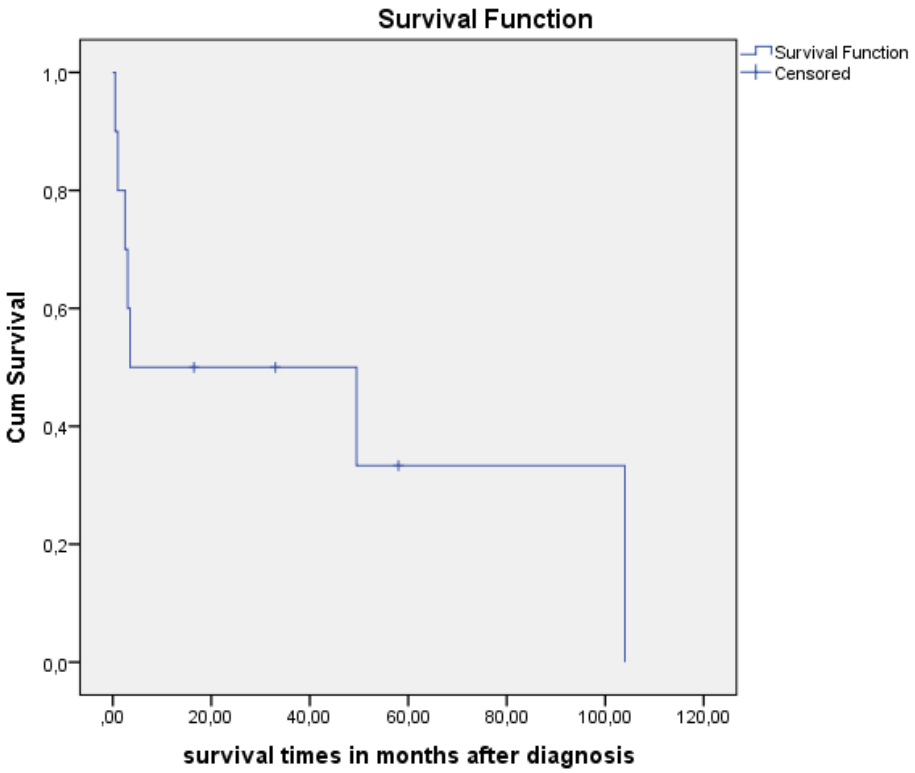
Survival time in months

D)


Survival Function
Survival Function
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120,00
survival times in months after diagnosis

Discussion

This retrospective study aimed to determine survival time, quality of life and prognostic indicators for dogs and cats with congenital PSS that were symptomatically treated only. Studies about the evaluation of the non-surgical treatment of dogs are sparse[2, 10], and in cats even no studies have been reported as far as the authors are aware of.

Because only patients with CPSS treated medically, confirmed by the owners, participated in this study, the group is biased for several factors. If animals were older than 5 years when diagnosed, surgery was advised against at the DCSCA[11], although a recent publication found no different results between surgery at young and old age.[10] So animals older than 5 years of age at time of diagnosis, would be overrepresented in our study, compared to the overall group of CPSS patients. It could be possible that the type of shunt and/or diameter are responsible for this late onset of clinical signs, leading to a different distribution of shunt type, IHPSS vs. EHPSS, in our study. Also, IHPSS are generally more difficult to ligate, so these can be overrepresented in this group.[12] This study found an IHPSS incidence of 37% in dogs while other studies found an incidence of 13-33%.[6, 13] Because of these factors, no comparison was made with the normal hospital population. Breed distribution is in line with previous reported findings demonstrating more EHPSS in small breeds and more IHPSS in large breed dogs.[4, 6] Also in common with previous literature, no sex predilection was found in dogs with CPSS.[2]

The number of cats with CPSS is much smaller. In accordance with other publications, 8/10 cats were younger than 1 year of age, whereas the majority of dogs at time of diagnosis is <2 years of age.[14] Most cat breeds encountered are also described in other articles, but the Turkish Angora and Main Coon are not.[6, 14, 15] It has been reported that cats with CPSS are more common with EHPSS.[6] Of the 10 cats in this study, 6 had an EHPSS and 4 cats had an IHPSS, but due to the small number, no further analysis was performed.

Most common clinical signs before or at time of diagnosis were of neurological origin, and as in other reports, gastrointestinal signs, lower urinary tract disease and retarded growth were seen but less often.[2, 6, 14] Although pu/pd has been reported as well in dogs with CPSS [6, 14, 16], no numbers of dogs affected were given. This study shows that pu/pd may be a more frequent symptom than the chronic gastrointestinal signs or lower urinary tract disease in dogs as 47% had pu/pd. Lower urinary tract disease due to urolithiasis is reported to occur in 20-75% of dogs with CPSS.[6, 7, 17] In our study 22% of the dogs had signs of recurrent cystitis or urolithiasis. In most dogs that did not show any signs of the urinary tract, no urinalysis was performed. If during ultrasonography both urolithiasis as the CPSS were detected, urinalysis was not always executed in the dogs in our study. So, this 22% could be higher if urinalysis of all dogs had been performed. Three dogs had pale mucous membranes at the physical examination, only one of them was known with melena. Pale mucous membranes are not frequently reported as clinical signs, though hematologic findings often show a mild to moderate anemia.[2, 6, 17]

All cats demonstrated neurological signs, and half of them showed gastrointestinal signs as well. Especially ptyalism is more often seen in cast than in dogs and could explain the difference in occurrence of gastrointestinal signs between them.[5] The largest contrast between dogs and cats besides neurologic signs however, is the occurrence of pu/pd as only two of the cats in this study had pu/pd.

Study entry was defined as the date on which CPSS was confirmed. Some referring veterinarians started symptomatic therapy before confirmation of CPSS. This could lead to altered blood results at time of diagnosis confirmation compared with the initial values at the referring veterinarian. Similar

to a previous study, more dogs with CPSS had increased fasted bile acids than increased fasted ammonia levels, so these findings could support their conclusion that the sensitivity of increased fasted bile acids is slightly higher than that of fasted ammonia.[2, 8] Other often increased values were ALT and ALP, with the same frequency of 75% or more as found in previous studies. It has been reported that these increases are mild or mild to moderate (2-to 3-fold)[6, 17], but the range found in this study is wider with both increases of ALP and ALT up to more than 8-fold. It must be considered though that elevated ALP levels could be due to the young age of some of the dogs as the bone isoenzyme can be responsible for this elevation in dogs below six months of age.[2, 17] Total protein, albumin and BUN are frequently decreased in dogs with CPSS. Hypoproteinemia and hypoalbuminemia occur in about 50% in dogs with CPSS[6, 17], whereas in our study an incidence of around 80% was found for both parameters. This difference could be explained by the fact that dogs with hypoalbuminemia are less frequently treated surgically as this is a negative predictor for outcome after surgery.[18] Decreased BUN is reported in 40-70% of the dogs, which is in accordance of the findings of our research. Hematological findings such as a mild to moderate microcytic anemia in 60-75% of the cases and leukocytosis are confirmed in this study as well.[6, 17] Dogs with CPSS are also known to have a decreased platelet count and a prolonged PT and APTT in their coagulation profile compared to healthy dogs.[19] In this study PT and APTT were prolonged in some of the dogs, 4/14 and 9/14 respectively, platelet count however, was decreased in only 1/11 dogs. The low number of dogs in which coagulation profiles were determined could be due to the fact that these dogs were not treated surgically.

Though biochemical and/or hematological findings at time of diagnosis were reported in only 7 of the cats, all had high fasted ammonia levels, with a median of 286, and 4/4 cats had increased fasted bile acids. These parameters could fit with previous results, but a previous study found that in 1/6 cats fasted ammonia levels are not elevated.[20] Other parameters were measured in only 3/10 cats or less, and are therefore difficult to interpret.

Follow up for determining quantity and quality of life before and during treatment was performed by telephone. Therefore, answers are based on the owners' perceptions and recalls. The questionnaires for examining the quality of life by scoring the presence and frequency of clinical symptoms before and after treatment, were send after starting treatment, or in some cases, even after the animal had already died. This could lead to recall bias. Because answers were given by the owners, not an objective measurement was made, but this method has been used in other studies as well.[2, 10] The owners however, know their pet best, and know what normal or strange behavior is for their dog or cat. They are the ones to request euthanasia when they consider it time, so their assessment of the quality of life of their pet is important. With their assessment, they could influence survival time as almost every patient in our study is euthanized instead of dying from the disease. As the disease has a fluctuating course with intermittent clinical signs, it is possible that patients were euthanized within such a temporary deterioration, while clinical signs could have improved or be resolved in a short period of time. If a long asymptomatic period was ahead, it could be argued that survival time of such a patient is underestimated. Therefore, it is essential to consider the fluctuating nature of clinical signs, so survival times do not become underestimated.

This study found an EMST of 41,5 months (range 0 to 91 months) for dogs with CPSS treated only medically. The wide spread of age at diagnosis in this study should be considered to interpret this EMST. As 18/78 dogs were older than 5 years of age at diagnosis, an age above 8 years is conceivable. On the other hand, for young dogs at time of diagnosis, 41,5 months could be disappointing. Only two other studies have reported survival times for these dogs. Watson and Herrtage followed 23 dogs, from which 14 had been euthanized. For the euthanized dogs a median survival time of 6 months was reported. Nine dogs were still alive at the end of that study resulting in a median period between diagnosis and end of the study was 51 months (range 36 to 96 months).[2] Greenhalgh et al. found an EMST of 27,4 months for 24 dogs that died or had been euthanized during

the study and the 3 remaining dogs were lost at 5,5 to 96,7 months of follow up.[10] These studies clearly used fewer animals, though the ranges of survival times of all three studies are similar. EMST's in both studies were divided for euthanized patients and patients who were still alive, so not one EMST was given. Greenhalgh et al. compared the survival rate between dogs with CPSS treated medically versus dogs treated surgically and found a significantly greater survival rate in the surgical group.[10] Although an EMST of 41,5 months for medically treated dogs is reasonable, to prolong overall survival time longest, surgical attenuation of the shunt would be required. These previous two studies did not find a significant difference in EMST for shunt type, but one of them did find a significant lower median age at the end of the study for dogs with IHPSS, though no difference was found in age at diagnosis between IHPSS and EHPSS. Because these groups were smaller, differences could have been missed. However, this research with 78 dogs also did not find a significant difference in EMST between dogs with IHPSS and EHPSS.

A more difficult comparison is between treatment regimes. The vast majority of the group received only a special diet or a special diet combined with lactulose, this diet being the Hepatic® by Royal Canin. Only very few participants fed their pet another commercial or home cooked diet lowered in protein, so no attempts were made to compare these different diets. Patients receiving lactulose, could receive very diverse dosages, as only the usage is taken into account for assignment to this group. Some of the subjects had switched between treatment groups over time. They were grouped in the treatment they received last or still had been receiving, given that this was for at least one month of duration. All dogs in this study received their last treatment longer than this month however. Altogether, each treatment group has some variation within, but the major compounds within the groups are alike. No significant difference between EMST's were found, although diet and lactulose tended to have a shorter EMST. There could be reasoned that dogs which were clinically worse, received lactulose with the adjusted diet in contrast to dogs that were clinically not so bad receiving only adjusted diet. As this study covers 11 years, multiple preferences in using or not using lactulose were seen however. In this study, no data was obtained about the influence of metronidazole in symptomatic treatment, because this is not usually prescribed for this indication at the DCSCA. Only one dog was treated with metronidazole at a regular basis of one week a year.

A Cox regression model identified leukocytosis to affect survival time. Dogs with a leukocytosis are suggested to have a significant longer survival time. It has been suggested that leukocytosis in patients with CPSS may be associated with the translocation of intestinal bacteria into the portal blood, and with the portal blood bypassing the liver, subsequent entering of these bacteria into the systemic circulation.[17] The presence of leukocytosis would protect the animal against these bacteria, what might result in a longer survival time. Previous studies about medical treatment of CPSS in dogs did not evaluate the effect of the white blood cell count on survival. No other prognostic indicators were identified in this study, just like the results of Greenhalgh et al.[10] The significant positive correlation between age at diagnosis and survival time and the correlation between BUN and survival time reported earlier[2], are not confirmed in our study with a larger group of dogs.

EMST for cats with CPSS is 3,5 months, much shorter than it is for dogs. The range is wide however, from 0,5 to 104 months, and three of the cats being still alive at the end of this study with survival times after diagnosis varying from 16,5 months to 58 months. This 3,5 months might therefore be underestimated, nevertheless EMST for cats would be shorter than it is for dogs, what has not been reported yet.

To assess quality of life during symptomatic treatment, questionnaires were used to evaluate clinical signs and satisfaction of the owner with symptomatic treatment. Neurological signs, gastrointestinal sigs and lower urinary tract disease are the major three problems reported in dogs with CPSS.[5, 6] In all of these three groups, one or more symptoms were significantly reduced during treatment, being the

neurological symptoms circling and ataxia, gastrointestinal sign vomiting and the urinary tract sign macroscopic hematuria. Also, general weakness and/or tiredness were significantly reduced during treatment and the dogs were significantly more active. Moreover, according to the owners, quality of life is significantly better during symptomatic treatment. Though this questionnaire was developed carefully, it did not have an option about not having any symptoms for multiple years during treatment, before reoccurrence of clinical signs. A few owners reported this situation. This might have resulted in an underestimation of the decrease of certain clinical signs, as they occurred only after multiple years again, but at the end were scored as monthly, weekly or daily. Another feature missing in the questionnaire was ascites. Although not seen often due to CPSS, it has been reported.[2] One dog was euthanized because of reoccurring ascites during treatment. Ascites could be the result of severe hypoalbuminemia due to the impaired liver function. Also, liver diets contain less proteins, so protein and albumin levels in the blood can decrease because of the enduring low intake .[2] The commercial diets used nowadays are better balanced in protein however, and none of the other owners reported the occurrence of ascites during treatment in their optional comments.

Quality of life between the treatment groups did not differ significantly, except for the improvement of macroscopic hematuria during treatment. Significant more improvement of hematuria was seen in dogs which only received an adjusted diet. As the usage of lactulose did not result in a significant longer EMST, nor a better quality of life, lactulose is not recommended if a patient is doing clinically well on only an adjusted diet. It could be used temporary to stabilize a patient or when an adjusted diet alone proves to be insufficient however.

Depending on the clinical signs and what bothers the owners, symptomatic treatment could be useful to prolong life with a reasonable quality of life in most dogs. If pu/pd or dysuria is the main problem, success with conservative treatment is less likely and surgical attenuation would be necessary. Eventually, surgical closure of the shunt would remain first choice of treatment for both dogs and cats, but if this is not possible for any reason, conservative treatment would be a reasonable alternative in most canine and in some feline patients with CPSS.

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Appendix

Appendix I. Questionnaire for evaluating quality of life before and during symptomatic treatment of canine and feline patients with CPSS.

Question form about dogs and cats with a livershunt and their quality of life:

Part 1: before treatment

1: How often showed your pet the following symptoms?
(Before a treatment was started by a veterinarian)

Please mark the correct answer with a color or underlining.

a: Seizures (*or epilepsy*)

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?
(With 1 representing not unpleasant at all and 5 severely unpleasant.)

1 2 3 4 5

b: Head pressing *(pressing its head against a wall, or standing very close to a wall without moving)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

c: Circling *(walking around in circles)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

d: Disorientation *(looks like it has lost its way, does not know what to do or where to go)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

e: Aggression *(biting, snapping or growling or for cats hissing, biting or scratching without any reason)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

f: Fainting *(to lose consciousness and drop down)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

g: Unstable gait *(having difficulty to walk normally, walk like a drunk man, falling over)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

h: Absence *(Less or not reacting at all, to the environment, drowsing)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

i: (Apparent) blindness *(walking against obstacles or walls)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

j: Tiredness or weakness *(lies down quickly, does not have enough energy, sleeps a lot)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

k: Vomiting *(throwing up food, bile or gastric juice)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

l: Diarrhoea *(thinner stool)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

m: Bad appetite *(No or less appetite)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

n: Having difficulty with urinating *(pressing while and after urinating and/or pee tiny bits very often)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

o: Blood in the urine *(red pee)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

p:Obvious drooling *(spontaneous salivating)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

q: Drinking a lot *(in combination with a lot more and often urinating)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

2: Did your pet suffer from bladder stones or an obstructed urethra that moved you to visit a veterinarian for diagnosing and treatment?
If so, could you please explain a bit below?

Yes No

3: Did you find your pet too small or too skinny for its age and breed before the treatment?

Yes No In doubt

4: How active is/was your pet?
(With 1 representing not active at all and 5 maximal)

1 2 3 4 5

5: How much would your pet like to:
(With 1 representing not at all and 5 could not be more)

a: play?

1 2 3 4 5

b: interact (contact) with you as the owner?

1 2 3 4 5

c: strain physically?

1 2 3 4 5

d: interact (contact) with other cats (or dogs)?

1 2 3 4 5

6. Did your pet have a surgery in which the shunt was narrowed or closed?

No Yes

If no, what was/were the reason(s) for not choosing surgery?

Low age (not 6 months yet) High age (older than 5 years when diagnosed)

General risk of surgery The surgeon advised not to operate Costs

(Much) improvement after switching to medical treatment and/or diet Otherwise:

If otherwise, could you please specify below:

7a: Did your pet get treated with a medication (lactulose for example) and/or a special diet for the liver? If so, what was used?
(Examples of diets for supporting liver function are 'hepatic' from Royal Canin and 'l/d' from Hills.)

No Diet Lactulose Diet and lactulose

Other medication

If other medication, could you please specify below:

7b. Have any changes occurred in this treatment? (For instance a change in diet, quitting with lactulose or adding the lactulose.)

No Yes

If yes, could you specify what these changes were and when they occurred?

Part 2: During treatment/ on the diet and/or medication

1: If your pet was/is given a special diet, could you indicate if and how much improvement was or is seen?
(With 1 representing no improvement at all and 5 maximal improvement.)

1 2 3 4 5

2: If your pet was given a special diet and/or medication, do you think this had an ADVERSE effect on its quality of life?
(With 1 representing no adverse effect at all and 5 maximal.)

1 2 3 4 5

3: How often showed your pet the following symptoms? (During treatment)

a: Seizures (*or epilepsy*)

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?
(With 1 representing not unpleasant at all and 5 severely unpleasant.)

1 2 3 4 5

b: Head pressing *(pressing its head against a wall, or standing very close to a wall without moving)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

c: Circling *(walking around in circles)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

d: Disorientation *(looks like it has lost its way, does not know what to do or where to go)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

e: Aggression *(biting, snapping or growling without any reason)*

Never Less than once a month Monthly Weekly Daily

How unpleasant was this for your pet?

1 2 3 4 5

f: Fainting *(to lose consciousness and drop down)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

g: Unstable gait *(having difficulty to walk normally, walk like a drunk man, falling over)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

h: Absence *(Less or not reacting at all, to the environment, drowsing)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

i: (Apparent) blindness *(walking against obstacles or walls)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

j: Tiredness or weakness *(lies down quickly, does not have enough energy, sleeps a lot)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

k: Vomiting *(throwing up food, bile or gastric juice)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

l: Diarrhea *(thinner stool)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

m: Bad appetite *(No or less appetite)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

n: Having difficulty with urinating *(pressing while and after urinating and/or pee tiny bits very often)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

o: Blood in the urine *(red pee)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

p:Obvious drooling *(spontaneous salivating)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

q: Drinking a lot *(in combination with a lot more and often urinating)*

Never Less than once a month Monthly Weekly Daily

How unpleasant is/was this for your pet?

1 2 3 4 5

4: Does/did your pet suffer from bladder stones or an obstructed urethra that moved you to visit a veterinarian for diagnosing and treatment?

Yes No

If so, could you please explain a bit below?

5: Did/do you find your pet too small or too skinny for its age and breed during treatment?

Yes No In doubt

6: How active is/was your pet?
(With 1 representing not active at all and 5 maximal)

1 2 3 4 5

7: How much would your pet like to:
(With 1 representing not at all and 5 could not be more)

a: play?

1 2 3 4 5

b: interact (contact) with you as the owner?

1 2 3 4 5

c: strain physically?

1 2 3 4 5

d: interact (contact) with other cats (or dogs)?

1 2 3 4 5

8: Do you think that the body condition score has improved during treatment? (With 1 representing not at all and 5 maximal.)

1 2 3 4 5

Which score did your pet have before treatment (see attachment):

Which score did your pet have during treatment (see attachment):

9: How much overall improvement was seen during treatment?
(1 representing no improvement and 5 maximal)

1 2 3 4 5

10: How content are you with the results of this treatment?
(With 1 representing not content at all and 5 maximal.)

1 2 3 4 5

11: How would you score the quality of life of your pet <u>before</u> treatment? (With 1 representing very bad and 5 excellent.)

1 2 3 4 5

12: How would you score the quality of life of your pet <u>during</u> treatment? (With 1 representing very bad and 5 excellent.)

1 2 3 4 5

13: Do/did you still worry about the health of your pet? (With 1 representing no worries at all and 5 very much.)

1 2 3 4 5

14: If you have further comments, they can be written below:

Thank you very much for your cooperation!

Appendix II. *Cross tables and Cohen's kappa coefficient for frequency of clinical signs before and during treatment.*

Clinical signs	**Number of dogs affected before treatment**	**Less frequently during treatment**	**More frequently during treatment**	**Kappa**
Seizures	8/35	50%	3%	.589
Head pressing	14/33	79%	7%	.285
Circling	14/35	64%	10%	.388
Disorientation	13/35	62%	23%	.267
Aggression	6/35	17%	9%	.648
Fainting	2/35	***50%***	0%	.657
Ataxia	21/34	52%	7%	.463
Mental absence	25/34	52%	21%	.277
(Apparent) blindness	12/35	58%	9%	.398
General tiredness or weakness	29/35	48%	10%	.409
Vomiting	24/35	58%	10%	.366
Diarrhoea	16/34	63%	6%	.442
Less appetite	22/35	45%	23%	.409
Ptyalism	7/35	43%	6%	.535
Dysuria	11/35	45%	16%	.435
Hematuria	13/35	77%	9%	.268
Urolithiasis	7/34	43%	7%	.525
Pu/pd	24/34	29%	16%	.561
Too small or skinny	15/35	27%	12%	.643

Activity	**More or better during treatment**	**Less or worse during treatment**	**Kappa**
General activity	54%	18%	.200
Intention to play	44%	23%	.307
Interaction with owner	44%	11%	.449
Physical strain	42%	27%	.212
Interaction with other dogs	27%	29%	.415
Quality of life	79%	9%	.098

* Too small or skinny according to the owners

Level of agreement is[a]:

- 'Poor' if $\kappa \leq 0.20$
- 'Fair' if $0.21 \leq \kappa \leq 0.40$
- 'Moderate' if $0.41 \leq \kappa \leq 0.60$
- 'Substantial' if $0.61 \leq \kappa \leq 0.80$
- 'Good' if κ exceeds 0.80

[a] Petrie, A. & Watson, P. (2006). *Statistics for Veterinary and Animal Science.* (2nd edition). Oxford: Blackwell publishing.