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Renal Amyloidosis in Dogs: A Retrospective Study of 91 Cases with Comparison of the Disease between Shar-Pei and Non-Shar-Pei Dogs

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Background: Renal amyloidosis (RA) is a progressive and fatal renal disease.

Hypothesis: Clinical and pathologic manifestations of RA differ between Chinese Shar-Pei (CSPs) and non-Shar-Pei (NSPs) dogs.

Animals: 91 client-owned dogs.

Methods: Retrospective review of medical records of dogs with a histological diagnosis of RA. Clinical and clinicopathologic data, hospitalization, complications, and outcome were compared between CSPs and NSPs.

Results: Comorbid diseases were present in 64% of all dogs. CSPs were significantly younger compared to NSPs (median, 4.8 years; range: 3.6–17 versus median: 9.0 years; range: 2.4–11.1; $P < .0001$). The frequency of hypoalbuminemia, the most common biochemical abnormality, was higher in NSPs compared to CSPs (100% versus 64.7%, respectively; $P < .001$). Median serum creatinine concentration at presentation was 5.5 mg/dL, and was 3-fold higher in CSPs compared to NSPs ($P = .005$). Increased urine protein : creatinine ratio was present in 96% of all dogs. Nephrotic syndrome was present in 10% of NSPs but not in CSPs. Glomerular amyloid deposition, present in both CSPs (78.6%) and NSPs (95.6%) was most commonly diffuse, global, and severe. Renal medullar amyloidosis was more common in CSPs (100%) compared to NSPs (49.0%, $P = .002$), as was extrarenal amyloid deposition. The median survival time of all dogs was 5 days (range: 0–443 days). Serum creatinine concentration was significantly and negatively associated with survival ($P = .025$).

Conclusions and Clinical Relevance: The clinical and pathologic manifestations of amyloidosis differ between CSPs and NSPs. The survival time observed herein was unexpectedly low, and argues for early surveillance and management of the underlying predisposing conditions.

Key words: Canine; Chronic kidney disease; Survival; Amyloid; Familial Shar-Pei fever; Thromboembolism.

Amyloidosis is a heterogeneous group of diseases, characterized by extracellular deposition of insoluble, fibrillary proteins with a specific β-pleated sheet conformation, generally termed amyloid.[1] Several distinct amyloid proteins that originate from distinctive precursors have been described in human beings and animals, and differ in their primary structure and function.[2] Despite diversity in their origins, all amyloid proteins possess similar structural, physical and chemical properties, including the formation of X-ray diffraction patterns characteristic of β-sheet aggregates, uniform fibril morphology and fibril formation patterns, and specific staining with Congo red and thioflavin T.[3]

Abbreviations:

ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CKD	chronic kidney disease
CSP	Chinese Shar-Pei
FSF	familial Shar-Pei fever
GGT	gamma-glutamyl transpeptidase
HDL	high-density lipoprotein
NSP	non-Shar-Pei
RA	renal amyloidosis
SAA	serum amyloid A
UPC	urine protein to creatinine ratio

Amyloid deposits can be localized, organ-limited, or generalized and can affect any tissue or organ type.[2] Three distinct systemic amyloidosis types, immunoglobulin-associated (primary), reactive (secondary), and senile (heredofamilial), have been classified in human patients.[4] Canine and feline amyloidosis, including familial amyloidosis in the Chinese Shar Pei (CSP) and Abyssinian cat, are mostly considered the reactive, or secondary, amyloidosis type.[5] In reactive amyloidosis, deposits are composed of the protein amyloid A, an amino-terminal fragment of serum amyloid A (SAA), an acute phase protein, produced during inflammation, as part of the acute phase response. Reactive amyloidosis frequently is idiopathic, but may be associated with chronic inflammation, infection, or neoplasia.[6]

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In dogs, the kidney is the most frequent, and often the sole site of amyloid deposition. Clinical, laboratory and pathological findings of reactive amyloidosis often are associated with progressive chronic kidney disease (CKD) as the primary clinical feature.[7] Renal amyloidosis (RA) in dogs primarily exhibits glomerular involvement, and the cortical and medullary interstitium are less frequently involved.[7] An exception to this pattern occurs in CSPs, in which renal medullary lesions are reported to predominate.[8] Amyloid deposition in dogs also has been reported in a variety of extra-renal organs including the spleen, liver, adrenal gland, pancreas, gastric and intestinal submucosa, myocardium, thyroid, prostate and lymph nodes.[1,8]

Familial Shar-Pei fever (FSF) is a hereditary disorder, occurring in up to 23% of CSPs.[9] It is considered similar to human familial Mediterranean fever and characterized by recurrent episodes of fever of unknown origin, with concurrent swollen, painful hocks, swelling of the muzzle, abdominal pain, diarrhea, and anorexia. It has been proposed that FSF predisposes CSPs to systemic reactive amyloidosis,[10] similarly to human familial Mediterranean fever patients.[11,12]

The aims of this study were (1) to characterize the historical, physical, laboratory, histopathology findings, secondary complications, and survival in a large dog population with RA, (2) to evaluate risk factors for death in RA, and (3) to compare the features of RA between the CSP and non-Shar-Pei dogs (NSPs).

Materials and Methods

Selection of Cases and Collection of Data

The medical records of dogs presented to the Veterinary Teaching Hospitals of the Hebrew University, Jerusalem, Israel between 1998 and 2007 and of the University of California, Davis between 1986 and 2005 were reviewed retrospectively for dogs with a histological diagnosis of RA, based on light microscopic examination of renal tissue, obtained by renal biopsy or at necropsy.

Data obtained from the medical records included signalment, history, clinical signs, laboratory test results, secondary complications, gross and microscopic pathology findings, duration of hospitalization, and outcome. Survival time was calculated as the number of days from diagnosis to death or euthanasia. The diagnosis of FSF was based on at least 2 episodes of fever of unknown origin with concurrent swelling of at least 1 joint.

Laboratory Tests

All clinicopathologic data were collected at first presentation for a variety of problems and the dogs were ultimately diagnosed with amyloidosis. CBC[a] and serum biochemistry analyses[b] were performed in the hospitals' diagnostic laboratories. Serum electrolyte concentrations were measured in heparinized whole blood or plasma using ion-specific electrode electrolyte analyzers.[c] Blood samples for coagulation tests, including prothrombin time, activated partial thromboplastin time, fibrinogen concentration, and antithrombin activity, were collected in 3.2% trisodium-citrate tubes, centrifuged within 30 minutes of collection, and plasma analyzed immediately.[d,e] Antithrombin activity was measured as percent activity compared to pooled canine reference plasma.

Urine samples for routine urinalysis were collected by cystocentesis or catheterization. Urine specific gravity was determined using standard clinical refractometers. Urine chemistry analysis was performed using dipstick methodology. Urine protein-to-creatinine (UPC) ratio was measured in samples in which urine sediment was inactive and was determined by automated pyrogallol red-molibdate direct colorimetric method and Jaffe's method for urine protein and for urine creatinine concentration, respectively, using wet chemistry autoanalyzers.[b]

Microscopic examinations of renal biopsy and necropsy specimens were performed at the Departments of Pathology, Kimron Veterinary Institute, Bet Dagan, Israel, and the William R. Pritchard Veterinary Medical Teaching Hospital, UC Davis, using the same guidelines. The microscopic diagnosis of amyloidosis in all cases was confirmed using light microscopy, by the presence of birefringent deposits in Congo red-stained sections, viewed under polarized light, and in some cases, also by fluorescence of the deposits, under ultraviolet light of thioflavin T-stained sections.

Statistical Analysis

Statistical analyses were performed using statistical software.[f] Normality of data distribution was assessed using Shapiro-Wilk's test. Continuous variables were compared between CSPs and NSPs using 2-sample *t*- and Mann-Whitney *U*-tests, for normally and non-normally distributed data, respectively.

The proportion of clinical signs and other categorical variables were expressed as a percentage of all dogs, CSPs, and NSPs. These were compared between groups using Fisher's exact test. Correlations between variables were assessed using Pearson's or Spearman's rank correlation tests, as appropriate. Kaplan-Meier analysis was used to assess survival time and the log-rank test was used to compare survival between CSPs and NSPs. A Cox's regression model was used to analyze the effects of different continuous variables on survival. For all tests applied, $P \leq .05$ was considered statistically significant.

Results

Signalment

Ninety-one dogs were included in the study, of which 42 were males (23 castrated) and 49 females (34 spayed). There were 18 CSPs (10 males and 8 females) and 73 NSPs (32 males and 41 females). The median age at the time of diagnosis of amyloidosis in CSPs (4.5 years; range: 3.6–17) was significantly lower compared to NSPs (median, 9.0 years; range: 2.4–10.0, $P < .0001$). Body weight was recorded in 61 dogs, with a median of 20.0 kg (range: 2.9–49.0). The NSPs included the following breeds: mixed (33%), Cocker Spaniel (12%), Golden Retriever (5.3%), Dachshund (5.3%), Irish Setter, German Shepherd, Rough Collie (4% each), and Keeshound, Great Dane, Rottweiler, Poodle, and Beagle (2.7% each).

History and Clinical Signs

The most common clinical signs at presentation in the whole study population included anorexia (n = 51, 56%), vomiting (n = 45, 50%), lethargy (n = 32, 35%), polyuria, and polydipsia (n = 26, 29%), weight loss (n = 23, 25%), cachexia (n = 19, 21%), and leth-

Table 1. Historical and clinical findings at presentation in 91 dogs with renal amyloidosis.

Clinical sign	All dogs (n = 91) n (%)	Non-Shar-Peis (n = 73) n (%)	Shar-Peis (n = 18) n (%)
Anorexia	51 (56.0)	38 (52.1)	13 (72.2)
Vomiting	45 (49.5)	34 (46.6)	11 (61.1)
Lethargy	32 (35.2)	25 (34.2)	7 (38.9)
Polyuria/polydipsia	26 (28.6)	22 (30.1)	4 (22.2)
Weight loss	23 (25.3)	16 (21.9)	7 (38.9)
Cachexia	19 (20.9)	11 (15.1)	8 (44.4)
Lethargy	16 (17.6)	10 (13.7)	6 (33.3)
Hematochezia	13 (14.3)	10 (13.7)	3 (16.7)
Skin lesions	12 (13.2)	9 (12.3)	3 (16.7)
Dehydration	12 (13.2)	9 (12.3)	3 (16.7)
Pale mucous membranes	11 (12.1)	6 (8.2)	5 (27.8)
Ascites	10 (11.0)	9 (12.3)	1 (5.6)
Fever	10 (11.0)	5 (6.8)	5 (27.8)
Melena	9 (9.9)	6 (8.2)	3 (16.7)
Nephrotic syndrome[a]	9 (9.9)	9 (12.3)	0 (0.0)
Edema	9 (9.9)	7 (9.6)	2 (11.1)
Paraparesis	7 (7.7)	6 (8.2)	1 (5.6)
Urinary incontinence*	5 (5.5)	1 (1.4)	4 (22.2)
Icterus	4 (4.4)	2 (2.7)	2 (11.1)

[a]Nephrotic syndrome was defined by presence of concurrent proteinuria, hypoalbuminemia, hypercholesterolemia, and ascites or edema; *significant difference ($P \leq .05$) between groups.

argy (n = 16, 18%). There were no significant differences in proportions of clinical signs between CSPs compared to NSPs, with exception of urinary incontinence, which was significantly more common in CSPs (Table 1).

A history of chronic comorbid disease, including neoplastic and inflammatory (infectious and noninfectious) conditions, was present in 64% of all dogs, 70% of the NSPs, and 56% of the CSPs (Table 2). Infectious diseases were significantly ($P = .002$) more common in NSPs compared to CSPs (58% versus 17%, respectively). Familial Shar-Pei fever was described in 8 (44%) CSPs. Concurrent bacterial cystitis at presentation was recorded in 16/91 dogs (18%), with no statistical difference in its proportion between males and females.

Hematology and Coagulation Findings

The most common hematologic abnormalities in the whole study population included nonregenerative anemia (58%) and leukocytosis (61%) (Table 3), with no significant differences between CSPs and NSPs. Median prothrombin and activated partial thromboplastin times were within reference intervals, with no differences between groups. Antithrombin activity was measured in 23 dogs (median: 59%; range: 22–120%), of which 16 (70%), had hypoantithrombinemia, which was the most common hemostatic abnormality recorded in this study. Its proportion was higher in NSPs compared to CSPs (78% versus 40%, respectively, $P = .016$). Antithrombin activity was positively and significantly correlated with serum albumin concentration ($r = 0.8$, $P < .001$). Serum albumin con-

Table 2. Diseases diagnosed before presentation in 91 dogs with renal amyloidosis.[a]

Historical diseases (before presentation)	All dogs (n = 91) n (%)	Non-Shar-Peis (n = 73) n (%)	Shar-Peis (n = 18) n (%)	*P* Value
Familial Shar-Pei fever	8 (8.8%)	NA	8 (44.4%)	NA
Recurrent pancreatitis	5 (5.5%)	4 (5.5%)	1 (5.6%)	1.0
Chronic arthritis	9 (9.9%)	8 (11%)	1 (5.6%)	.68
Chronic bronchitis	2 (2.2%)	2 (2.7%)	0 (0.0%)	1.0
All inflammatory diseases*	24 (26.4%)	14 (19.2%)	10 (55.6%)	.005
Skin diseases[b]	15 (16.5%)	12 (16.4%)	3 (16.7%)	1.0
Urinary tract infection	16 (17.6%)	16 (21.9%)	0 (0.0%)	.03
Recurrent pneumonia	6 (6.6%)	6 (8.2%)	0 (0.0%)	.59
Otitis externa	4 (4.4%)	4 (5.5%)	0 (0.0%)	.58
Endocarditis	2 (2.2%)	2 (2.7%)	0 (0.0%)	1.0
Heartworm disease	2 (2.2%)	2 (2.7%)	0 (0.0%)	1.0
All infectious diseases*	45 (49.5%)	42 (57.5%)	3 (16.7%)	.002
IMHA[c]	2 (2.2%)	2 (2.8%)	0 (0.0%)	1.0
Mammary tumors	3 (3.3%)	3 (4.1%)	0 (0.0%)	1.0
Testicular tumors	3 (3.3%)	3 (4.1%)	0 (0.0%)	1.0
Hepatic tumors	3 (3.3%)	3 (4.1%)	0 (0.0%)	1.0
Pulmonary tumors	3 (3.3%)	3 (4.1%)	0 (0.0%)	1.0
Thyroid tumors	3 (3.3%)	2 (2.7%)	1 (5.6%)	.49
Pheochromocytoma	2 (2.2%)	2 (2.7%)	0 (0.0%)	1.0
All tumors	17 (18.7%)	16 (21.9%)	1 (5.6%)	.18
All historical diseases	58 (63.7%)	51 (69.9%)	10 (55.6%)	.25

NA, not applicable. [a]Some dogs had more than 1 historical disease; [b]including pyoderma, seborrhea, alopecia; [c]immune mediated hemolytic anemia; *significant difference ($P \leq .05$) between groups.

Table 3. Hematologic findings in dogs with renal amyloidosis.

	Non-Shar-Peis (n = 73)				Shar-Peis (n = 18)				
Analyte	n	Median (Range)	<RI n (%)	≥ RI n (%)	n	Median (Range)	<RI n (%)	≥ RI n (%)	RI
Red blood cells ($\times 10^6/mm^3$)	42	5.3 (3.3–7.7)	25 (59.5)	0 (0.0)	14	6.0 (2.7–8.0)	6 (42.9)	0 (0.0)	10–24
Hemoglobin (g/dL)	41	12.8 (9.1–17.1)	15 (36.6)	0 (0.0)	14	11.8 (6.8–17.1)	7 (50.0)	0 (0.0)	145–154
Hematocrit (%)	41	36.5 (25.7–50.1)	23 (56.0)	0 (0.0)	16	32.8 (17–49.2)	10 (62.5)	0 (0.0)	3.6–5.3
Mean corpuscular volume (fl)*	42	69.1 (59.2–78.4)	1 (2.3)	1 (2.3)	15	58.8 (51.0–65.0)	5 (33.3)	0 (0.0)	108–118
Mean corpuscular hemoglobin (pg)*	42	24.4 (20.1–28.4)	0 (0.0)	21 (50.0)	14	20.2 (16.8–24.8)	5 (35.7)	1 (7.1)	16–26
MCHC (g/dL)	42	35.2 (30.2–38.5)	1 (2.4)	17 (40.5)	15	34.0 (29.8–40.0)	2 (13.3)	4 (26.7)	9.7–11.5
White blood cell ($\times 10^3/mm^3$)	42	16.5 (7.0–39.0)	0 (0.0)	25 (59.5)	15	24.4 (7.6–67.5)	0 (0.0)	10 (66.7)	3–6.2
Neutrophils ($\times 10^3/mm^3$)	34	13.0 (0.0–34.3)	0 (0.0)	24 (70.6)	6	12.3 (6.9–52.7)	0 (0.0)	4 (66.7)	0.3–1.4
Lymphocytes ($\times 10^3/mm^3$)	34	1.03 (0.2–3.5)	17 (50.0)	0 (0.0)	6	1.4 (0–3.4)	2 (33.3)	0 (0.0)	1–4
Monocytes ($\times 10^3/mm^3$)	34	0.8 (0.1–3.5)	1 (2.9)	13 (38.2)	6	0.8 (0–13.5)	1 (16.7)	2 (33.3)	64–123
Eosinophils ($\times 10^3/mm^3$)	34	0.15 (0.0–1.2)	0 (0.0)	0 (0.0)	6	0.2 (0–1.1)	0 (0.0)	0 (0.0)	5.4–7.6
Basophils ($\times 10^3/mm^3$)	34	0.0 (0.0–0.03)	0 (0.0)	0 (0.0)	6	0.0 (0.0–0.0)	0 (0.0)	0 (0.0)	3–4.4
Platelets ($\times 10^3/mm^3$)	40	410 (80–992)	4 (10.0)	5 (12.5)	15	424 (53–1136)	2 (13.3)	2 (13.3)	1.8–3.9
Prothrombin time (s)	22	8.4 (6.5–12.5)	0 (0.0)	8 (36.4)	7	8.2 (7–11.5)	0 (0.0)	2 (28.6)	6–8.4
aPTT (s)	22	15.5 (10.7–26.2)	3 (13.6)	7 (31.8)	7	14.1 (12.4–26.8)	0 (0.0)	2 (28.6)	11–17.4
Fibrinogen (mg/dL)	32	538 (100–1300)	1 (3.1)	19 (59.3)	5	476 (100–685)	1 (20.0)	4 (80.0)	200–400
Antithrombin activity (%)	18	61.2 (22–112)	14 (77.8)	0 (0.0)	5	89.6 (53–120)	2 (40.0)	0 (0.0)	80–120

RI, reference interval; MCHC, mean corpuscular hemoglobin concentration; aPTT, activated partial thromboplastin time.
*Significant ($P \leq .05$) difference between the medians of the dog groups.

centration < 2 g/dL was recorded in 14/15 hypoantithrombinemic dogs (93%).

Serum Biochemistry Findings

Serum biochemistry results are presented in Table 4. Median serum albumin and total protein concentrations and the albumin-to-globulin (A/G) ratio were significantly lower in NSPs compared to CSPs. Forty-nine dogs (53.8%) had serum albumin concentration < 2 g/dL, of which 41 dogs were NSPs and 8 were CSPs. Eight dogs, all of which were NSPs (8.8%), had serum albumin concentration < 1 g/dL. Hypoalbuminemia was the most common biochemical abnormality, recorded in 92% (67/73) of all dogs. Hypoalbuminemia was significantly more common in NSPs compared to CSPs (100% versus 65%, respectively; OR = 21.3, $CI_{95\%}$: 3.2–140.3, $P < .001$). Evidence of nephrotic syndrome, (ie, concurrent proteinuria, hypoalbuminemia, hypercholesterolemia, and ascites or edema) was present in 10% of NSPs, but not in the CSPs. Median serum albumin concentration in dogs presenting with nephrotic syndrome was lower compared to those without nephrotic syndrome (0.95 g/dL versus 1.6 g/dL, $P < .001$). There was no significant correlation between serum albumin and cholesterol concentrations.

Azotemia was present in approximately 90% of the dogs (Table 4), with no significant difference in its proportion between groups. Median serum creatinine concentration in all dogs was 5.5 mg/dL, and was significantly (3-fold) higher in CSPs compared to NSPs ($P = .005$). Median blood urea nitrogen concentration of all dogs was 87 mg/dL, with no difference between groups (Table 4).

Median serum hepatobiliary enzyme (ALT, AST, ALP, and GGT) activities in all dogs and in NSPs were within reference interval, but were significantly higher in CSPs compared to NSPs (Table 4). In addition, the proportions of dogs with increased serum ALT, AST and ALP activity was significantly higher in CSPs compared to NSPs (OR = 7.3, $CI_{95\%}$: 2.0–27.3, $P = .002$; OR = 4.0, $CI_{95\%}$: 1.01–15.5, $P = .05$, and OR = 5.7, $CI_{95\%}$: 1.5–22.2, $P = .01$, respectively). Median serum total bilirubin concentration was within reference interval in the whole study population and in NSPs, but was significantly higher in CSPs compared to NSPs (Table 4). In addition, hyperbilirubinemia was significantly more common in CSPs (75%) compared to NSPs (37%) (OR = 6.6, $CI_{95\%}$: 1.5–30.1, $P = .008$). Median total serum calcium concentration was significantly higher in CSPs compared to NSPs ($P = .043$, Table 4). Hypocalcemia was documented in 66% of all study dogs, and was significantly more common in NSPs compared to CSPs (73% versus 39%, respectively, OR = 4.11, $CI_{95\%}$: 1.2–14.1, $P = .026$).

Urinalysis Findings

Median urine specific gravity of the whole study population was 1.015 (range: 1.005–1.048), with no difference between groups. Proteinuria (urine dipstick protein ≥ 1 +) was detected in 94% of all dogs (97% of NSPs and 93% of CSPs) with median concentration of 3 + (300–1000 mg/dL) in these study populations. The UPC ratio was > 0.5 in 96% of all dogs (97% of NSPs and 93% of CSPs) with no group difference. It was > 2 in 44/48 dogs (92%), 32/34 NSPs (94%) and 12/14 CSPs (86%), and was higher in NSPs compared

Table 4. Serum biochemistry findings and proportion of serum biochemistry abnormalities in dogs with renal amyloidosis.

	Non-Shar-Peis (n = 73)				Shar-Peis (n = 18)				
Analyte	N	Median (Range)	<RI n (%)	≥ RI n (%)	n	Median (Range)	<RI n (%)	≥ RI n (%)	RI
Anion gap (mEq/L)	38	21 (4–38)	1 (2.6)	10 (26.3)	5	21 (16–25)	0 (0.0)	1 (20.0)	10–24
Sodium (mEq/L)	49	146 (128–161)	20 (40.8)	3 (6.1)	15	138 (120–169)	7 (46.7)	2 (13.3)	145–154
Potassium (mEq/L)	49	5.1 (1.3–9.3)	5 (10.2)	13 (26.5)	15	5.0 (3.5–6.8)	1 (6.7)	5 (33.3)	3.6–5.3
Chloride (mEq/L)	43	112 (89–129)	9 (20.9)	8 (18.6)	11	110 (92.6–139)	3 (27.3)	1 (9.1)	108–118
Total CO_2 (mmol/L)	44	17.7 (7–32)	17 (38.6)	3 (6.8)	10	20 (14–30)	2 (20)	1 (10)	16–26
Calcium*† (mg/dL)	48	9 (5.6–11.4)	35 (72.9)	0 (0.00)	13	10 (8–11.5)	5 (38.5)	0 (0.00)	9.7–11.5
Phosphorus (mg/dL)	51	11.9 (3.6–36.6)	0 (0.0)	37 (72.5)	13	11.1 (4.4–18.8)	0 (0.00)	9 (69.2)	3.0–6.2
Creatinine* (mg/dL)	60	3.7 (0.6–23.5)	0 (0.0)	52 (86.7)	17	10.6 (1–27.7)	0 (0.00)	16 (94.1)	0.3–1.4
Blood urea nitrogen (mg/dL)	58	97.7 (8–301)	0 (0.0)	53 (91.4)	16	114 (15.6–203)	0 (0.00)	14 (87.5)	5–20
Glucose (mg/dL)	45	107 (34–324)	5 (11.1)	7 (15.6)	10	109 (40–185)	1 (10)	4 (40.0)	64–123
Total protein* (g/dL)	51	4.9 (2.6–7.3)	32 (62.7)	0 (0.00)	14	6.0 (4–8.4)	5 (35.7)	2 (14.3)	5.4–7.6
Albumin* (g/dL)	56	1.6 (0.5–3.1)	56 (100)†	0 (0.00)	17	2.4 (1–3.8)	11 (64.7)†	0 (0.00)	3.0–4.4
Globulin (g/dL)	50	3.3 (1.7–5.4)	1 (2)	15 (30.0)	14	3.4 (2.3–4.9)	0 (0.0)	3 (21.4)	1.8–3.9
Albumin-to globulin ratio*	50	0.5 (0.2–0.8)	38 (76.0)†	0 (0.00)	14	0.7 (0.3–1.3)	3 (21.4)†	1 (7.1)	0.6–1.2
Alanine aminotransferase (U/L)	45	80 (5–692)	11 (24.4)	10 (22.2)†	13	120 (15–359)	0 (0.00)	9 (69.2)†	19–67
Aspartate aminotransferase* (U/L)	41	54 (12–220)	3 (7.3)	17 (41.5)†	12	174 (2–453)	2 (16.7)	9 (75.0)†	19–42
Alkaline phosphatase* (U/L)	43	359 (11–5170)	2 (4.7)	15 (34.9)†	13	796 (35–3750)	0 (0.00)	10 (76.9)†	21–170
Total bilirubin* (mg/dL)	46	0.4 (0–5.5)	0 (0.00)	17 (36.9)†	12	1.9 (0–9.7)	0 (0.00)	9 (75)†	0.0–0.2
Cholesterol (mg/dL)	47	347 (83–598)	1 (2.1)	21 (44.7)	14	364 (253–724)	0 (0.00)	4 (28.6)	135–361
Amylase (U/L)	4	3141 (487–10136)	0 (0.0)	1 (25.0)	10	1834 (2–5950)	1 (10.0)	6 (60.0)	225–1270
Creatine kinase (U/L)	3	314 (153–854)	0 (0.0)	2 (66.7)	10	520 (1–12496)	1 (10.0)	8 (80.0)	13–250
γ-glutamyltransferase* (U/L)	4	3.6 (1.2–4.9)	0 (0.0)	0 (0.00)	9	12.5 (0.8–464)	0 (0.0)	3 (33.3)	0–19
Triglycerides (mg/dL)	2	102 (65–139)	0 (0.0)	1 (50.0)	8	111 (50–179)	0 (0.0)	4 (50.0)	15–100
Free magnesium (mmol/L)	6	0.6 (0.5–0.7)	6 (100)	0 (0.0)	4	0.5 (0.3–2.7)	3 (75.0)	1 (25.0)	1.4–2.5
Free calcium (mmol/L)	13	1.1 (0.7–1.9)	1 (7.7)	1 (7.7)	7	1.1 (0.6–1.2)	1 (14.3)	0 (0.00)	0.8–1.4

RI, reference interval

*Significant ($P \leq .05$) difference between the median of the dog groups; †Significant ($P \leq .05$) difference of the proportions of abnormalities between groups.

to CSPs but not significantly (15.4 versus 9.9, $P = .07$). The UPC ratio was negatively and significantly correlated with concentration of serum albumin ($r = -0.75$, $P < .001$) and total protein ($r = -0.58$, $P < .001$) and plasma antithrombin activity ($r = -0.56$, $P = .02$).

Histopathology Findings

Renal histopathology data were available in 83/91 dogs (14 CSPs and 69 NSPs). Complete postmortem examination was performed on 63 dogs, and histopathology was available in 60 dogs (11 CSPs and 49 NSPs). The remaining dogs were diagnosed with RA based on an antemortem renal biopsy (28 dogs), in 5 of which histopathologic descriptions were missing from the medical records. Glomerular amyloid deposition, most commonly described as diffuse, global, and severe, was more common in NSPs (95.6%) than CSPs (78.6%) but not significantly ($P = .06$, Table 5). Renal medullary amyloid deposition also was severe and diffuse and observed significantly more commonly in CSPs (100%) compared to NSPs (49.0%, $P = .002$). Secondary tubulointerstitial and glomerular changes were documented in 81% of all dogs, 81% of NSPs, and 79% of CSPs.

Amyloid deposition in extrarenal organs was more common in CSPs compared to NSPs (73% versus 29%, $P = .006$), and affected organs included the pancreas, spleen, liver, gastrointestinal tract, adrenal and thyroid glands, testicles, myocardium, lungs, and central nervous system (Table 6). Amyloid deposition in the thyroid, testicles, and central nervous system each was recorded in a single NSP, in the myocardium in 4 NSPs, and in the adrenal and thyroid glands in a single CSP each. Hepatic and pancreatic amyloidosis was documented more frequently in CSPs compared to NSPs (Table 6).

Complications

Thromboembolism. Thromboembolism was detected postmortem in 13/62 of all dogs (21%), 12/51 of NSPs

Table 5. Renal histopathology findings in 83 dogs with renal amyloidosis.[a]

Change or Abnormality	All Dogs (n = 83) n (%)	NSPs (n = 69) n (%)	CSPs (n = 14) n (%)
Primary lesions			
Glomerular			
Severe diffuse glomerular amyloidosis	66 (79.5)	55 (79.7)	11 (78.6)
Moderate multifocal glomerular amyloidosis	8 (9.6)	8 (11.6)	0 (0)
Mild focal glomerular amyloidosis	3 (3.7)	3 (4.3)	0 (0)
Total number of glomerular involvement	77 (92.8)	66 (95.6)	11 (78.6)
Medullary[b]			
Severe diffuse medullar amyloidosis*	21 (35.0)	13 (26.5)	8 (72.7)
Moderate multifocal medullar amyloidosis	9 (15.0)	7 (14.3)	2 (18.2)
Mild focal medullar amyloidosis	5 (8.3)	4 (8.2)	1 (9.1)
Total number of medullar involvement*	35 (58.3)	24 (49.0)	11 (100)
Secondary lesions[c]			
Interstitial			
Interstitial fibrosis	30 (36.1)	22 (31.9)	8 (57.1)
Interstitial edema	3 (3.6)	2 (2.9)	1 (7.1)
Lymphoplasmacytic nephritis	37 (44.6)	30 (43.5)	7 (50.0)
Tubular			
Tubular atrophy	6 (7.2)	3 (4.3)	3 (21.4)
Tubular necrosis	7 (8.4)	7 (10.1)	0 (0)
Tubular degeneration	8 (9.6)	8 (11.6)	0 (0)
Soft tissue mineralization	7 (8.4)	7 (10.1)	0 (0)
Tubular ectasia and hyaline casts	36 (43.4)	32 (46.4)	4 (28.6)
Glomerular			
Thickened bowman capsule	18 (21.7)	16 (23.2)	2 (14.3)
Thickened basement membrane	5 (6.0)	4 (5.8)	1 (7.1)
Glomerular tufts adhesions	9 (10.8)	8 (11.6)	1 (7.1)
Total number of cases with secondary lesions	67 (80.7)	56 (81.1)	11 (78.6)

NSPs, Non-Shar-Peis; CSPs, Chinese Shar-Peis.

[a]In 29 dogs the diagnosis was based on kidney percutaneous kidney biopsy whereas in the remaining dogs the diagnosis was based post mortem examination.

[b]In some cases the diagnosis was based on antemortem renal biopsy and did not contain medulla. Information regarding the medulla was available for 60 dogs (49 NSPs and 11 CSPs)

[c]The proportions of secondary changes may represent an underestimation of their true occurrence; thus statistical comparisons of these lesions between groups were not performed.

*Significant ($P \leq .05$) difference between groups.

Table 6. Postmortem examination findings in 60 dogs with renal amyloidosis: location and occurrence of extrarenal amyloid deposition.

Location of Amyloid Deposition	All Dogs (n = 60) n (%)	NSPs (n = 49) n (%)	CSPs (n = 11) n (%)	*P* Value
Pancreas*	4 (6.7)	1 (2.0)	3 (27.3)	.002
Spleen	15 (25.0)	12 (24.5)	3 (27.3)	.85
Liver*	10 (16.7)	5 (10.2)	5 (45.5)	.005
Gastrointestinal tract	4 (6.7)	3 (6.1)	1 (9.1)	.72
Lung*	1 (1.7)	0 (0.0)	1 (9.1)	.03
All extrarenal organs*	22 (36.7)	14 (28.6)	8 (72.7)	.006

NSPs, Non-Shar-Peis; CSPs, Chinese Shar-Peis.

*Significant ($P \leq .05$) difference between groups.

(24%) and 1/12 CSPs (8%). Thromboembolism was documented in the pulmonary arteries (in 8 NSPs and 1 CSP), aortic bifurcation (3 NSPs and 1 CSP) and in coronary, intrarenal, splenic and mesenteric arteries, vena cava and jugular vein, and hind limb veins (each in a single NSP).

Blood Pressure and Hypertension. Blood pressure (BP) measurements were available in 17 dogs. Systolic BP > 150 mmHg was recorded in 9/15 (60%) of all dogs, 6/10 NSPs (60%), and 3/5 CSPs (60%), with no group differences. Mean systolic BP in all dogs, NSPs and CSPs, was 166 mmHg (SD 51), 182 mmHg (SD 43), and 155 mmHg (SD 36), respectively, with no group differences.

Survival. Survival data were available in 90/91 dogs. The time to death or euthanasia was available in 72/91 dogs (12 CSPs and 60 NSPs). The 30-day survival was 20% (18 dogs). Of the nonsurvivors, 56 dogs (78%) were euthanized, whereas 16 dogs (22%) died naturally. The median survival times of all dogs, NSPs, and CSPs were 5 days (range: 0–443 days), 5 days (range: 0–443 days), and 2 days (range: 0–368 days),

respectively, with no significant differences among groups. The survival time did not differ between dogs in which the diagnosis of RA was based on an antemortem percutaneous biopsy and those in which the diagnosis was based on postmortem examination. The association of different analytes (eg, serum albumin, creatinine, cholesterol, total protein concentrations, and UPC) with survival was investigated, and only serum creatinine concentration had a significant negative association with survival ($P = .025$).

Discussion

This study characterizes the clinical signs, clinicopathologic findings, clinical complications, and outcome of dogs with RA in a large cohort, and compares these findings between NSPs and CSPs. Retrospective surveys of canine RA in general, and specifically in CSPs, had limited numbers of dogs, and a direct comparison of RA between CSPs and NSPs has not been made in a single study.[1,7,8]

Renal amyloidosis is recognized most commonly in middle-aged to older dogs. In the present study, CSPs were significantly younger compared to NSPs, in agreement with previous reports.[1] The relatively early disease presentation in CSPs supports the breed's genetic predisposition for RA. An autosomal recessive trait predisposing CSPs to RA has been suggested previously.[1,7,10]

Predisposing conditions are suggested to precede the occurrence of reactive amyloidosis by induction of SAA production. The proportion of prior, presumably predisposing, inflammatory and neoplastic diseases recorded in CSPs tended to be lower compared to NSPs, further supporting their hypothesized genetic predisposition for RA that plays a role in the pathogenesis of the disease. The overall diagnosis of comorbid diseases in the present study (64%) is higher compared to previous reports (53% and 23%).[1,7] Comorbid diseases were mostly (80%) chronic inflammatory conditions (infectious and noninfectious), whereas neoplasia accounted for the remaining ones (20%), predominantly mammary gland neoplasia. Chronic inflammatory and neoplastic conditions induce hepatic SAA production, predisposing to secondary (reactive) amyloidosis.[2,13] Retrospective studies, however, cannot prove a cause and effect relationship, and this association warrants further investigation. Familial Shar-Pei fever was the most common historical predisposing disease in the CSPs, further supporting the hypothesis that FSF is a genetically based, heredofamilial inflammatory disease in this breed.[9] This disease is characterized by chronically occurring, intermittent, short illness episodes, which often resolve spontaneously. Thus, its clinical signs might have been overlooked by dog owners, or may have been deemed irrelevant at presentation, and therefore unreported, and hence the proportion of FSF presently reported might be an underestimate of its true occurrence in CSPs.

The most common clinical signs observed in this study were anorexia, vomiting, lethargy, polyuria, polydipsia, weight loss, lethargy, and cachexia, all of which are nonspecific and consistent with CKD. Clinical signs of nephrotic syndrome were unexpectedly uncommon, especially so in light of the profound proteinuria caused by RA, and were recorded in only 10% of the dogs. However, a similar proportion (15%) was reported previously in canine glomerulonephritis.[14] In those dogs with nephrotic syndrome, median serum albumin concentration was < 1 g/dL, suggesting that this clinical manifestation occurs only with severe hypoalbuminemia. Interestingly, nephrotic syndrome was not recorded in CSPs, likely attributable to their predominantly medullary, rather than glomerular, amyloid deposition, resulting in less severe proteinuria compared to NSPs.[8]

The high proportion of leukocytosis in the study (61%) is likely associated with the high occurrence of predisposing inflammatory and neoplastic diseases (64%) in both groups. In CSPs, the leukocytosis is likely associated with the high proportion of FSF. In human familial Mediterranean fever, a similar condition, approximately 66% of the patients present with leukocytosis, even between fever episodes, and their acute phase protein concentrations are chronically increased.[15] In addition, leukocytosis also might have resulted from inflammation, secondary to extrarenal organ amyloid deposition, which was more commonly detected in CSPs compared to NSPs.

Hypoproteinemia was recorded previously in approximately 70% of dogs with RA.[1,7] Hypoalbuminemia was universally identified in this study, and was the main cause of hypoproteinemia and decreased A/G ratio. Correspondingly, proteinuria and increased UPC ratio were the most common urinary abnormalities detected, resulting from glomerular amyloid deposition and persistent urinary albumin loss. Proteinuria was less severe and less common in CSPs compared to NSPs, probably attributable to the lower proportion and severity of glomerular involvement observed in the former,[8] and likely also attributable to the lower glomerular filtration rate in CSPs. The significant, negative correlation between the UPC ratio and serum albumin concentration suggests that albumin is the major protein lost in the urine, although confirmatory tests such as urine albumin-to-protein ratio or urine protein electrophoresis were not performed. Concurrent inflammation likely also contributed to the development of hypoalbuminemia, as albumin is a negative acute phase protein.[16] In addition, decreased hepatic albumin production might have played a role in the pathogenesis of hypoalbuminemia in cases of hepatic amyloidosis, which was more common in CSPs compared to NSPs. Hypoalbuminemia, more severe in NSPs, probably accounted for the higher proportion of hypocalcemia and the lower median serum total calcium concentration in this group.

Azotemia was the second most common serum biochemistry abnormality in this study, most likely caused by primary renal injury, although a prerenal component also might have been present in dogs with dehydration. Median serum creatinine concentration was significantly higher in CSPs compared to NSPs, sug-

gesting that renal impairment was more advanced in CSPs at presentation. Renal amylodiosis and azotemia in CSPs develop at a relatively younger age compared to NSPs, potentially resulting in a more severe azotemia at the time of diagnosis. Some CSPs may have been presented later in their disease course because of a presumptive diagnosis of amyloidosis by their referring veterinarians and the lack of a specific treatment.

Despite the significant difference in serum creatinine concentration between CSPs and NSPs, there was no significant difference in BUN concentration between these groups. There are several potential explanations for these observations, but because there were no differences between groups in the occurrence of anorexia, gastrointestinal bleeding and dehydration, a reason for the relatively low BUN concentration in the CSPs could be decreased urea generation rate caused by liver impairment. The latter was commonly observed in CSPs, as reflected by the high occurrence of hyperbilirubinemia (75%) and hepatic amyloid deposition.

The higher median serum activity of hepatobiliary enzymes and total bilirubin concentration and the higher proportion of hepatobiliary abnormalities in CSPs also suggest that systemic amyloidosis commonly affects the liver in this breed. This is consistent with previous observations of amyloidosis in Abyssinian cats and CSPs, documenting wide tissue distribution of amyloid deposition, including the liver.[8,17]

Hypercholesterolemia was detected in a 33% of our dogs, with no group difference. Conversely, in previous studies of canine RA, hypercholesterolemia was the most common biochemical abnormality reported.[1,7,8] This inconsistency likely relates to the lower proportion of nephrotic syndrome in our dogs. Hypercholesterolemia in canine RA is associated with high concentrations of SAA, which is primarily transported in the circulation in association with HDL (HDL_{SAA}). The physiologic relevance of this complex remains controversial. SAA may play a role in cholesterol removal from inflammation or sites of tissue destruction, or in commandeering HDL during the acute phase reaction, thereby delivering phospholipids and cholesterol to cells involved in tissue repair.[18]

Isosthenuria was observed in approximately half of the dogs, compatible with presence of CKD, and in agreement with previous reports of canine RA.[1,7,19] Interestingly, polyuria and polydipsia were reported by dog owners in only 29% of the cases, possibly because owners of dogs with chronic, slowly progressing, sustained CKD become accustomed to their pet's high daily water consumption and their polyuria, thereby perceiving these as normal. Low urine specific gravity decreases the urine dipstick sensitivity for detection of proteinuria,[20] exemplifying the need to use more accurate, quantitative methods to measure proteinuria, such as UPC ratio, urine albumin-to-creatinine ratio or species specific urine microalbumin quantification. Nevertheless, proteinuria invariably was present in both CSPs and NSPs, with significantly higher magnitude in NSPs, likely attributable to more severe and frequent glomerular involvement. In addition, judging from the magnitude of azotemia, affected CSPs likely have lower glomerular filtration rate compared to NSPs, and consequently less glomerular surface area from which serum protein can be lost. The consistent occurrence of proteinuria seen in CSPs in the present study is higher compared to that in previous studies (25–43%), but is consistent with the presence of glomerular amyloid deposition, recorded in 79% of our CSPs. Although 16/91 of the present dogs had documented cystitis, the UPC ratio was measured only in animals with inactive urine sediment, and thus, urinary tract infection likely did not contribute to the high UPC ratio. In addition, 92% of the study dogs had UPC ratio > 2, consistent with glomerular origin of most urinary protein.[21]

Hypoantithrombinemia was observed in 70% of the dogs in which antithrombin was measured, likely caused by urinary loss, consumption (ie, disseminated intravascular coagulation), and potentially caused by decreased production in those dogs with severe hepatic amyloidosis. Attributable to the similar molecular size of antithrombin and albumin, urinary antithrombinuria is to be expected with renal albuminuria. Although urinary antithrombin was not measured, excessive antithrombinuria likely was present, because plasma antithrombin activity and serum albumin concentration were significantly and positively correlated, and both were significantly and negatively correlated with the UPC ratio. In the present study, 14/16 hypoantithrombinemic dogs had serum albumin < 2 g/dL, in agreement with previous findings, suggesting that dogs with serum albumin concentration < 2 g/dL are at risk for hypoantithrombinemia and consequent thromboembolism.[22]

Hyperfibrinogenemia was commonly observed, in agreement with previous reports of canine glomerular disease.[22] Because fibrinogen is a positive acute phase protein, hyperfibrinogenemia suggests ongoing inflammation.[23] It was more common in CSPs, supporting presence of chronic, active, persistent inflammation. Concurrent hyperfibrinogenemia and hypoantithrombinemia likely predisposed these dogs to thrombosis. The proportion of thromboembolism (21%) is higher compared to that in previous studies of canine RA (14%).[1] The pathogenesis of the hypercoagulable state in RA is multifactorial and includes urinary antithrombin loss, increased platelet thromboxane production (resulting in increased platelet aggregation), and hyperfibrinogenemia, with potential increase in fibrin complex formation.[24] In human amyloidosis patients, the tendency for thromboembolism is aggravated further by increased concentrations of α_2-antiplasmin, procoagulant cytokines, coagulation factors V, VII, VIII, and X (all of which increase during an acute phase response) and von Willebrand's factor, increased plasma viscosity, decreased plasminogen and protein S concentrations, decreased plasma volume and blood flow, and presence of endothelial injury and infections.[24,25] The present results support the role of hypoantithrombinemia and hyperfibrinogenemia in the pathogenesis of thromboembolism in canine RA.

Thromboembolism is a life-threatening complication of RA. The proportion of thromboembolism in our study possibly underestimates its true prevalence in canine RA. Therefore, careful hemostatic monitoring should be employed in dogs with RA, particularly in those with concurrent marked proteinuria and hypoalbuminemia (serum albumin < 2 g/dL). Hemostatic monitoring should include assessment of coagulation (eg, PT aPTT and fibrinogen), anticoagulants (eg, antithrombin) and fibrinolysis (eg, D-dimers). Based on previous observations, when severe hypoantithrombinemia is present (<60%), treatment with anticoagulants (eg, low molecular weight heparin) and low dose aspirin should be strongly considered.[26]

The median time to death or euthanasia was 5 days in all dogs and in NSPs and only 2 days in CSPs, which are considerably shorter compared to previous studies of canine amyloidosis.[22] Severe renal failure at presentation was the most common cause of death, reflected by the fact that serum creatinine concentration was the only laboratory analyte at presentation that was significantly associated with the outcome, in agreement with previous reports of canine glomerular disease.[22] Nevertheless, true outcomes are difficult to document with a high proportion of dogs subjected to euthanasia.

The higher proportion of renal medullary amyloid deposition, observed in CSPs is in agreement with previous reports.[8] However, the consistent presence of severe, diffuse glomerular amyloid deposition in the CSPs is in contrast with previous observations.[8] It is tenable to speculate that in CSPs, amyloid deposition occurs initially in the renal medulla, and with disease progression, its deposition extends to the glomeruli, as a relatively late manifestation. In contrast, in NSPs, glomerular amyloid deposition likely occurs initially, and other renal sites are affected later, with disease progression. This hypothesis is supported by the more severe protein-losing nephropathy as well as the higher magnitude of hypoalbuminemia and higher occurrence of nephrotic syndrome observed in NSPs. Similarly, differences in renal amyloid distribution between CSPs and NSPs likely account for the differences in laboratory abnormalities between these groups, namely more severe azotemia and milder proteinuria in CSPs. These pathologic and laboratory abnormality differences in RA between CSP and NSP breeds suggest that intrinsic differences in the pathogenesis of RA among breeds might exist.

Tubulointerstitial and glomerular changes (eg, fibrosis) have been uncommonly described in canine RA, suggesting that postglomerular perfusion is mostly preserved, despite ongoing glomerular amyloid deposition,[8] in contrast with observations in familial amyloidosis of Abyssinian cats.[17] In the present study, secondary tubulointerstitial and glomerular changes were common in both CSPs and NSPs, but were more severe in NSPs, whereas extrarenal amyloidosis (especially hepatic and pancreatic) was more common in CSPs, in agreement with previous findings in familial amyloidosis.[8,17] Central nervous system amyloid deposits were a unique finding in this study.

This study has several limitations. First, histopathologic examinations were conducted by different pathologists, thereby introducing variability, as the interpretation of histopathologic specimens is subjective. Second, there is no way to retrospectively assure that each renal biopsy was evaluated similarly, including close inspection of all parts of the renal biopsy specimen (ie, glomeruli, tubules, and interstitium), and thus some lesions might have been missed or underreported. These limitations likely are inconsequential because most renal biopsies were examined at 1 institution (UC Davis), whereas the rest all were examined by a single pathologist (HUVTH), using guidelines established by the 1st institution (UC Davis). Third, in 28 dogs the diagnosis of RA was based on a percutaneous biopsy rather than complete necropsy. Thus, tissues collected from dogs during necropsy may bias toward more severe lesions, whereas percutaneous antemortem biopsies may be biased toward inclusion of earlier glomerular lesions. Finally, some of the laboratory parameters were available only in small number of dogs, thereby decreasing the statistical power of comparisons that were based on these measures.

In conclusion, CSPs develop RA at a relatively younger age compared to NSPs, and present with more severe azotemia and milder proteinuria. Medullary renal amyloid deposition is more common in CSPs compared to NSPs, whereas the latter more commonly present with glomerular amyloid deposition. However, glomerular involvement also is common in CSPs. CSPs have a wider tissue amyloid deposits distribution compared to NSPs, mostly hepatic and pancreatic. Creatinine concentration at presentation was a significant prognostic indicator and was positively associated with death or euthanasia.

Footnotes

[a] Abacus or Arcus, Daitron, Wien, Austria; Coulter ZBI, Coulter Corp, Miami, FL; Baker 2000, BioChem ImmunoSystems, Allentwon, PA, USA; Advia 120, Bayer Diagnostics, Tarrytown, NY

[b] Cobas-Mira, Roche, Rottkreutz, Switzerland, Coulter Electronics Inc, Hialeah, FL; Technicon SMA 12/60, Technicon, Tarrytown, NY; Roche Hitachi 717, 917 Chemistry Analyzers, Roche Diagnostics, Indianapolis, IN

[c] OmniC, Roche, Germany

[d] ACL-200, Instrumentation Laoratories, Milano, Italy, KC1-micro, Amelung, Lemgo, Germany; Roche Hitachi 912 Chemistry Analyzer, Roche Diagnostics, Indianapolis, IN

[e] Fibrometer, BD Diagnostic Systems (BBL), Sparks, MD

[f] NCSS 6.0.22 software, NCSS, Kaysville, UT

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