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Urinary creatinine to serum creatinine ratio and renal failure index in dogs infected with *Babesia canis*

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Abstract

Urinary creatinine to serum creatinine (UCr/SCr) ratio and renal failure index (RFI) are useful indices of renal damage. Both UCr/SCr ratio and RFI are used in differentiation between prerenal azotaemia and acute tubular necrosis. In this work the authors calculated the UCr/SCr ratio and RFI in dogs infected with *Babesia canis* and the values of these indices in azotaemic dogs infected with the parasite. The results of this study showed significantly lower UCr/SCr ratio in dogs infected with *B. canis* than in healthy dogs. Moreover, in azotaemic dogs infected with *B. canis* the UCr/SCr ratio was significantly lower and the RFI was significantly higher than in non-azotaemic dogs infected with *B. canis*. The calculated correlation between RFI and duration of the disease before diagnosis and treatment was high, positive and statistically significant ($r = 0.89$, $p < 0.001$). The results of this study showed that during the course of canine babesiosis caused by *B. canis* in Poland acute tubular necrosis may develop.

Keywords

Acute tubular necrosis, azotaemia, *Babesia canis*, canine babesiosis, renal failure index, urinary creatinine to serum creatinine ratio

Introduction

Babesia canis (formerly: *Babesia canis canis*) is a protozoan blood parasite of dogs. The infection caused by this agent leads to the development of mild to severe clinical signs of canine babesiosis. In Europe the disease may be caused also by infections with other species of the genus *Babesia* (Matijatko *et al*. 2012). However, only *B. canis* has been detected in dogs in Poland (Adaszek and Winiarczyk 2008, Zygner *et al*. 2011). In pathogenesis of canine babesiosis, as in human babesiosis and malaria, the immune response and overproduction of pro-inflammatory cytokines play a crucial role (Jacobson 2006, Gray *et al*. 2010). Fever, vomiting, apathy, pale mucous membranes, and thrombocytopenia are common clinical signs of the disease (Jacobson 2006, Matijatko *et al*. 2012). Phenomena such as systemic inflammatory response and multiple organ dysfunction syndromes develop during the course of the disease. In infected dogs kidney and liver insufficiency, acute pancreatitis, disseminated intravascular coagulation, immune-mediated haemolytic anaemia, and acute respiratory distress syndrome have been observed. Acute renal failure is considered as one of the most prevalent complication of canine babesiosis in Europe (Matijatko *et al*. 2012). This complication leads to decrease of glomerular filtration rate and in consequence causing azotaemia and uraemia (Cowgill and Langston 2011, Venkataraman and Kellum 2007).

Urinary creatinine to serum creatinine (UCr/SCr) ratio and renal failure index (RFI) are useful indices of renal damage. Both UCr/SCr ratio and RFI are used in veterinary and human medicine in the differentiation between prerenal azotaemia and acute tubular necrosis (Hanson *et al*. 2011, Waldrop 2008). Another useful indicator of renal damage is the calculated value of fractional excretion of sodium (Waldrop 2008). This parameter was estimated in canine babesiosis in the previous work suggesting acute tubular necrosis in affected dogs which probably developed from prerenal azotaemia (Zygner *et al*. 2012). The current work is a continuation of previous research on changes in the SUSPPUP (serum sodium/urinary sodium to (serum potassium)^2/urinary potassium) ratio and fractional excretion of strong monovalent electrolytes during the course of canine babesiosis (Zygner *et al*. 2012).

The purposes of this study were to estimate UCr/SCr ratio and RFI in dogs infected with *B. canis* and to estimate the

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values of these indices in azotaemic dogs infected with the parasite.

Materials and Methods

In a previous study (Zygner *et al*. 2012), samples of the blood, serum and urine were collected from 17 dogs with babesiosis (group A) and 12 healthy dogs as a control group (group B). All blood and urine samples were collected before treatment (including fluid therapy) during the first visit in the clinic and were examined immediately after sampling. Serum of one azotaemic dog was haemolytic and the colour of the urine in this dog was dark-brown. The rest of dogs had yellow urine. Group A was subdivided into 2 subgroups: 9 azotaemic dogs (A1) and 8 non-azotaemic dogs (A2). Infection in group A was initially diagnosed by capillary blood smear examination stained with Giemsa and confirmed by the PCR method. The duration of the disease before admission to the clinic amounted to 1 to 7 days (Median = 2 days; 25%–75%: 1–2 days).

Urinary sodium concentration was determined by a clinical chemistry analyser (MEDICA Easy Electrolytes, The Netherlands) according to the manufacturer's instructions (dilution of the urine sample with deionized water in the proportion urine to water 1 to 10). Blood urea and creatinine concentrations in serum samples, and creatinine concentration in urine samples were determined by a clinical chemistry analyser (XL 640, Erba Mannheim, Germany). Dogs with both serum urea and creatinine concentrations above reference intervals were considered as azotaemic (serum urea higher than 1.7 mg/dL, serum creatinine higher than 45 mg/dL).

The results obtained in that study allowed calculation of the UCr/SCr ratio and RFI using the following formulae (Waldrop 2008):

- UCr/SCr = urinary creatinine concentration ÷ serum creatinine concentration,
- RFI = urinary sodium concentration × serum creatinine concentration ÷ urinary creatinine concentration.

The results were analysed using the Statistica 8.0 program. The Mann-Whitney U test was used to compare UCr/SCr ratio and RFI between groups A and B, and between subgroups A1 and A2. Pearson's correlations between the duration of the disease before admission to the clinic and UCr/SCr ratio and RFI in infected dogs were calculated. The value of $p < 0.05$ was considered significant.

Results

Single results of serum and urinary creatinine concentration, urinary sodium concentration, UCr/SCr ratio, RFI and the duration of the disease in 17 dogs infected with *B. canis* are presented in Table I. Comparison of UCr/SCr ratio between group A and B showed statistically significantly lower median in group A (Fig. 1). Comparison of UCr/SCr ratio between subgroup A1 and A2 showed statistically significantly lower median in group A1 (Fig. 2). Correlation between UCr/SCr ratio

Table I. Single results of serum and urinary creatinine concentration, urinary sodium concentration, UCr/SCr ratio, RFI and the duration of the disease in 17 dogs infected with *B. canis*

Subgroup	Dog No.	SCr	UCr	UNa	UCr/SCr	RFI	Dur. Dis.
A1	1	9.5	160	33.2	16.84	1.97	2
	2	5.1	25.6	167.9	5.02	33.45	4
	3	1.8	22.5	91.3	12.5	7.3	1
	4	1.8	127.7	65.5	70.94	0.92	1
	5	20	70	143.4	3.5	40.97	7
	6	2.8	75	39.5	26.79	1.47	1
	7	5.2	25.2	152	4.85	31.36	4
	8	2.1	275	27.1	130.95	0.21	1
	9	2.5	30	122.2	12	10.18	4
A2	10	1	60	18.8	60	0.31	2
	11	1.2	281	57.5	234.17	0.24	1
	12	1.35	245	122.2	181.48	0.67	2
	13	1	265	17.5	265	0.07	1
	14	1	528	108	528	0.2	1
	15	1.1	502	106	456.36	0.23	1
	16	1.4	251	127.1	179.29	0.71	2
	17	1	40	96.6	40	2.41	2

+A1 – subgroup of azotaemic dogs infected with *B. canis*, A2 – subgroup of non-azotaemic dogs infected with *B. canis*, Dog No. – dog's number, SCr – serum creatinine concentration (mg/dL), UCr – urinary creatinine concentration (mg/dL), UNa – urinary sodium concentration (mEq/L), UCr/SCr – urinary creatinine to serum creatinine (UCr/SCr) ratio, RFI – renal failure index, Dur. Dis. – duration of the disease (days).

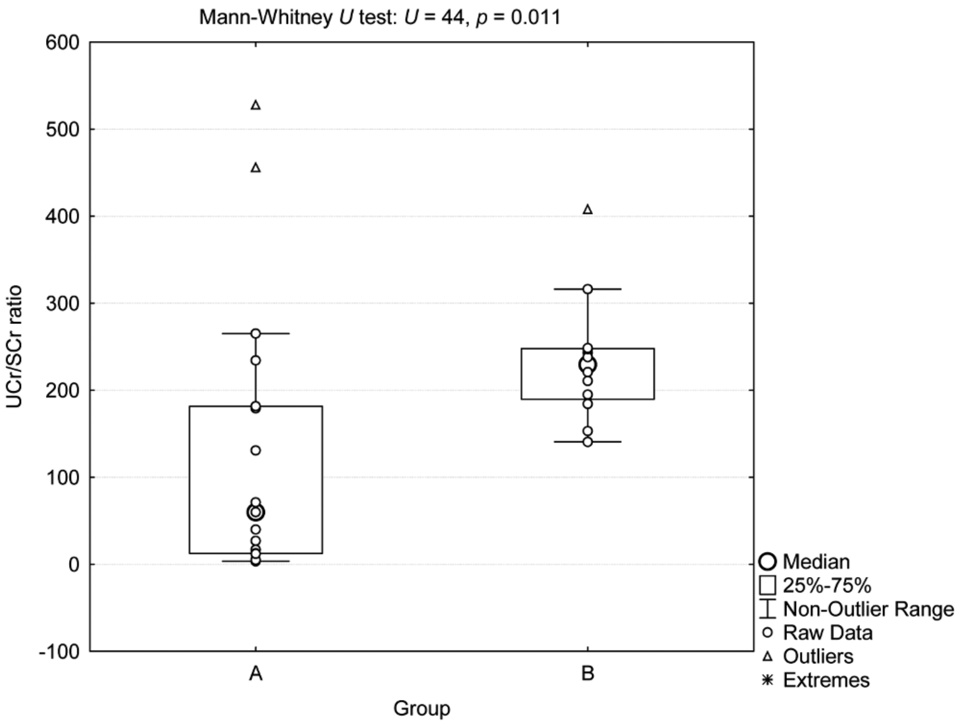

Fig. 1. Comparison of UCr/SCr ratio between 17 dogs infected with *B. canis* (group A) and 12 healthy dogs (group B)

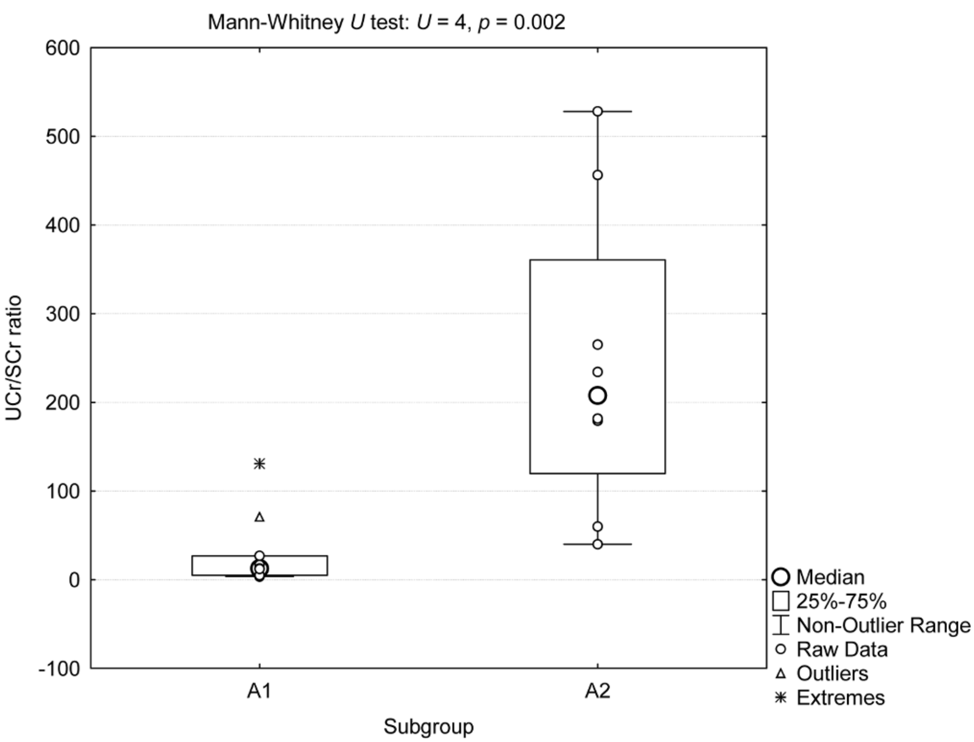

Fig. 2. Comparison of UCr/SCr ratio between 9 azotaemic dogs infected with *B. canis* (subgroup A1) and 8 non-azotaemic dogs infected with *B. canis* (subgroup A2)

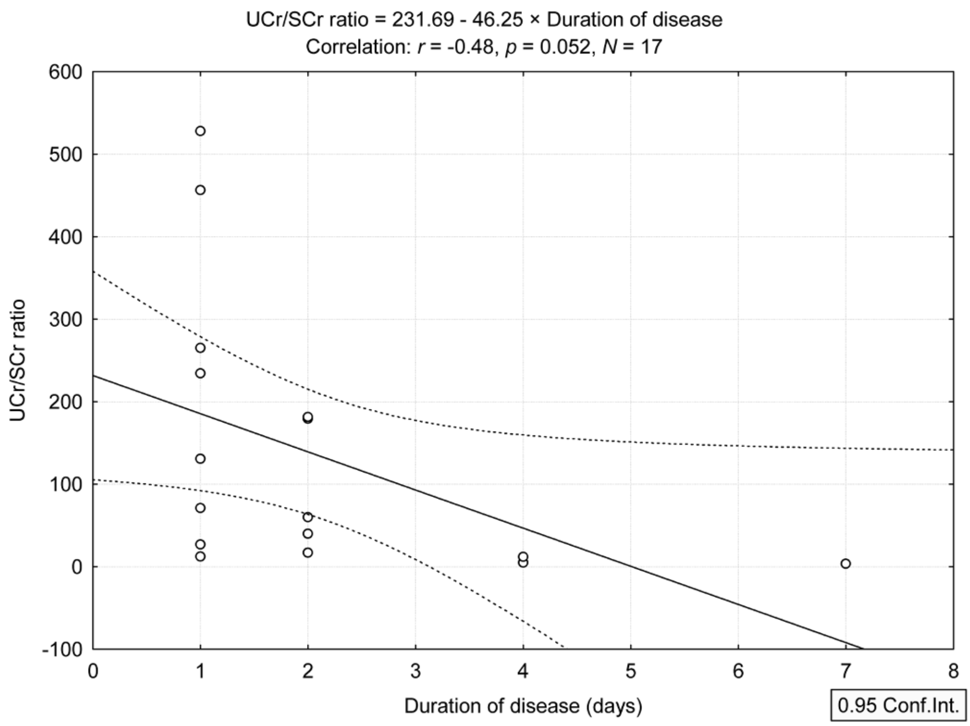

Fig. 3. Correlation between UCr/SCr ratio and duration of the disease in 17 dogs infected with *B. canis* (0.95 Conf.Int. – 95% Confidence Interval, r – Pearson's correlation coefficient, p – a value of p, N – number of dogs). The function of the correlation formula: UCr/SCr ratio = 231.69 – 46.25 × Duration of disease

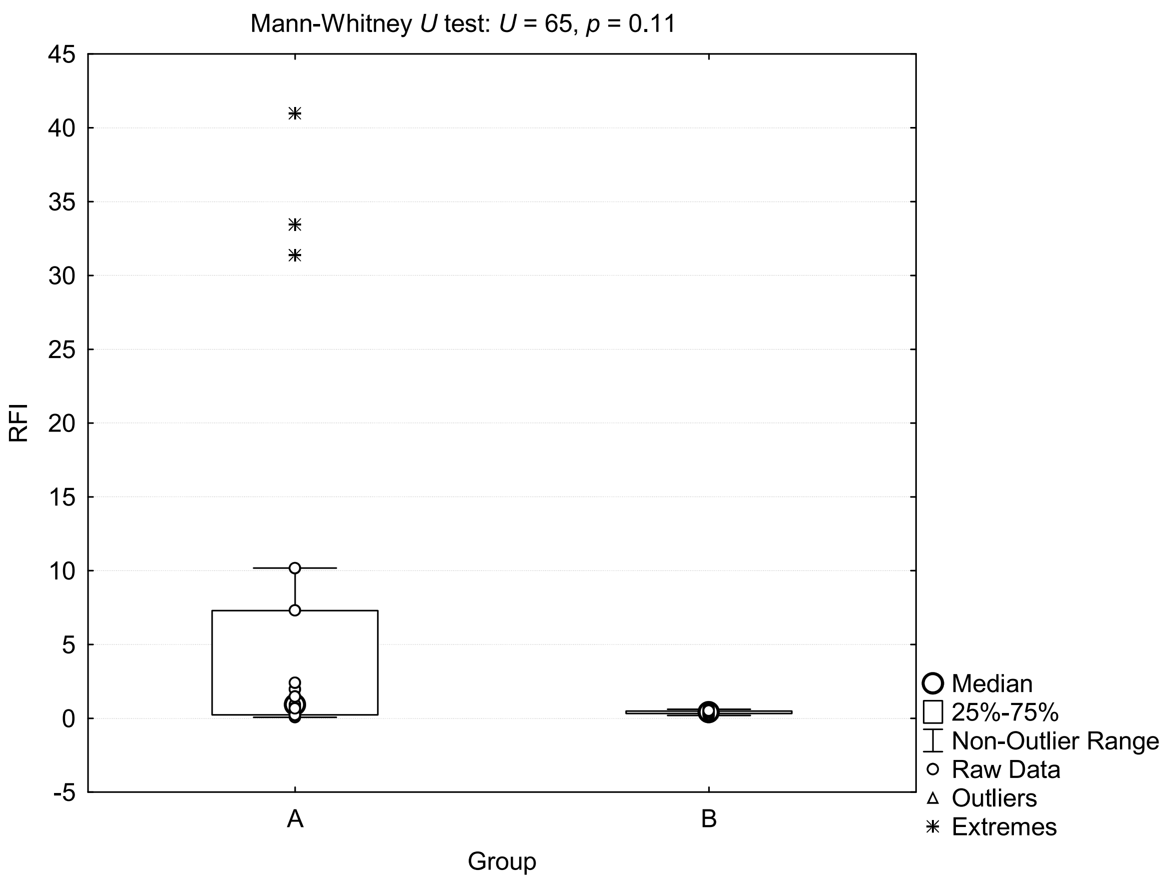

Fig. 4. Comparison of RFI between 17 dogs infected with *B. canis* (group A) and 12 healthy dogs (group B)

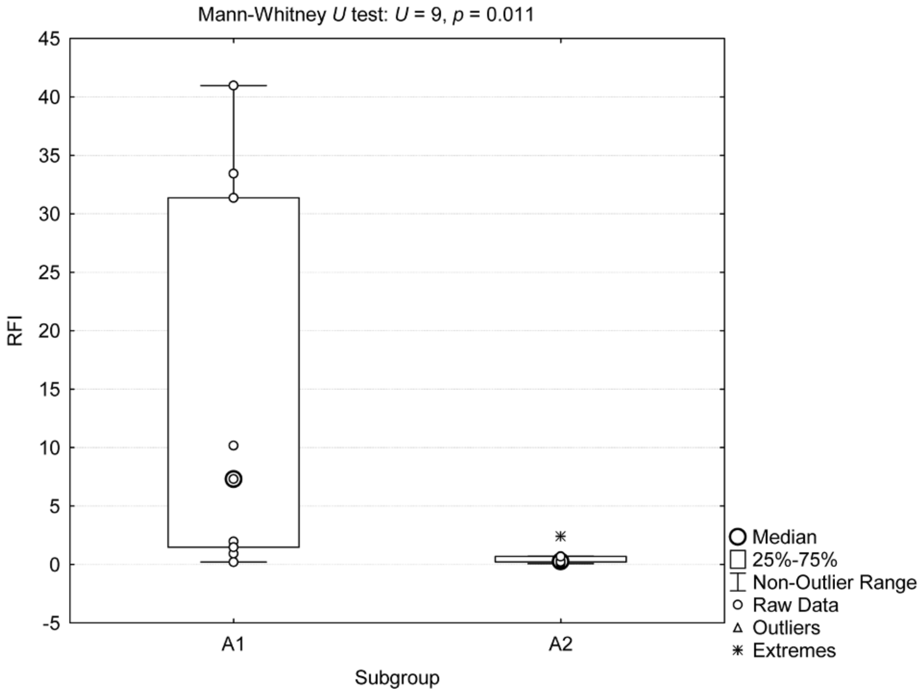

Fig. 5. Comparison of RFI between 9 azotaemic dogs infected with *B. canis* (subgroup A1) and 8 non-azotaemic dogs infected with *B. canis* (subgroup A2)

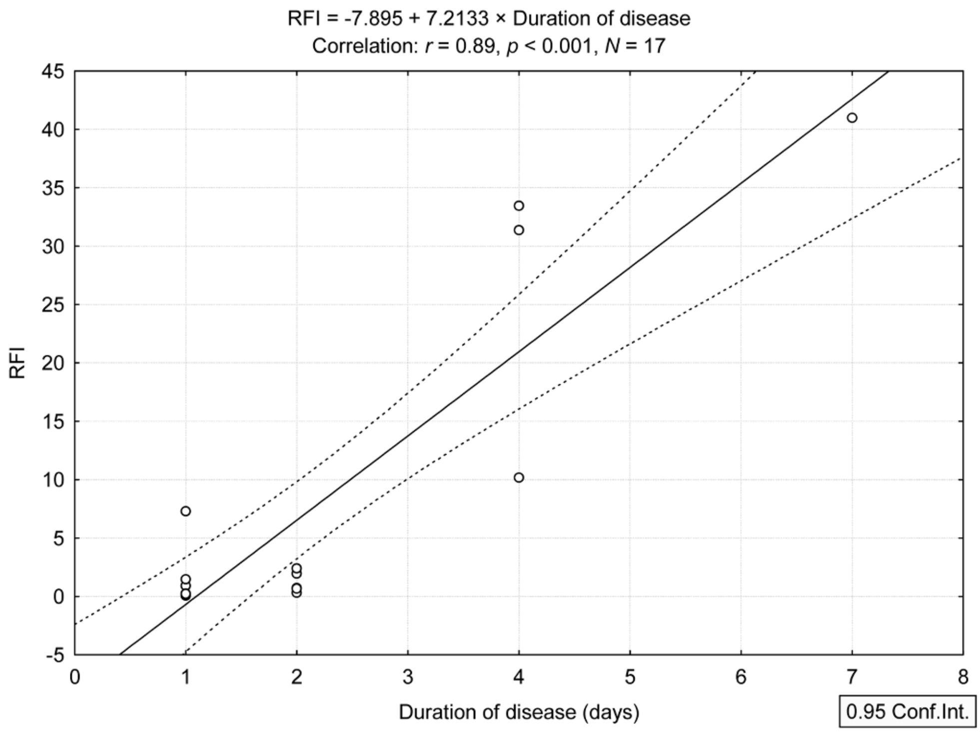

Fig. 6. Correlation between RFI and duration of the disease in 17 dogs infected with *B. canis* (0.95 Conf.Int. – 95% Confidence Interval, r – Pearson's correlation coefficient, p – a value of p, N – number of dogs). The function of the correlation formula: RFI = –7.895 + 7.2133 × Duration of disease

Table II. Results of Mann-Withney U test used to compare the UCr/SCr ratio and RFI between 17 dogs infected with *B. canis* (group A) and 12 healthy dogs (group B), and between 9 azotaemic dogs infected with *B. canis* (subgroup A1) and 8 non-azotaemic dogs infected with *B. canis* (subgroup A2)

Parameter	Group	Median	25%–75%	Min., Max.	U	p
UCr/SCr	A	60	12.5–181.48	3.5, 528.0	44.0	0.011*
	B	229.335	189.585–247.8	140.71, 408.33		
	A1	12.5	5.02– 26.79	3.5, 130.95	4.0	0.002*
	A2	207.825	119.645 – 360.68	40.0, 528.0		
RFI	A	0.92	0.24 – 7.3	0.07, 40.97	65.0	0.11
	B	0.41	0.33 – 0.495	0.19, 0.62		
	A1	7.3	1.47 – 31.36	0.21, 40.97	9.0	0.011*
	A2	0.275	0.215 – 0.69	0.07, 2.41		

UCr/SCr – urinary creatinine to serum creatinine ratio, RFI – renal failure index, 25%–75% – interval between 25th and 75th percentile, Min., Max. – minimal and maximal values, U – a value of U, p – a value of p, *statistical significance.

and the duration of the disease before diagnosis and treatment in 17 dogs infected with *B. canis* was negative ($r = -0.48$, $p = 0.052$, $N = 17$) and statistically insignificant (Fig. 3). However, this correlation was at the limit of statistical significance.

Comparison of RFI between group A and B did not show a statistically significant difference (Fig. 4). Comparison of RFI between subgroup A1 and A2 showed statistically significantly higher median in group A1 (Fig. 5). Correlation between RFI and duration of the disease before diagnosis and treatment in 17 dogs infected with *B. canis* was high, positive ($r = 0.89$, $p < 0.001$, $N = 17$) and statistically significant (Fig. 6).

Results of Mann-Whitney U tests are presented in Table II.

Discussion

A significantly lower UCr/SCr ratio in infected dogs indicates a decrease of tubular water reabsorption (Waldrop 2008). This difference between healthy dogs and dogs infected with *B. canis* resulted from very low values of UCr/SCr ratio in azotaemic dogs. A value of the UCr/SCr ratio lower than 20 indicates acute tubular necrosis (Waldrop 2008). In this work 6 out of 9 azotaemic dogs infected with *B. canis* had values of UCr/SCr ratio lower than 20. One of these 6 dogs had haemolytic serum and dark-brown urine indicating haemolysis what might influence on the result of UCr/SCr ratio. Nevertheless, the result of UCr/SCr ratio lower than 20 in these 6 dogs, indicating acute tubular necrosis, is in agreement with the results of the previous studies (Máthé *et al*. 2007, Zygner *et al*. 2012). In these Máthé *et al*. (2007) observed tubular necrosis in kidneys of dogs infected with *B. canis*, and Zygner *et al*. (2012) noted median of fractional excretion of sodium higher than 1% in azotaemic dogs infected with *B. canis*.

This work did not reveal significant difference between medians of RFI in healthy dogs and infected dogs. This may result from small groups used in this study. However, a significantly higher RFI in azotaemic dogs infected with *B. canis* indicates acute tubular necrosis. In this work 5 out of 9 azotaemic dogs had a value of RFI higher than 2, which is typical for acute tubular necrosis (Waldrop 2008). This result is in agreement with observation on the UCr/SCr ratio in azotaemic dogs infected with *B. canis*.

Changes observed in this study indicate acute tubular necrosis in azotaemic dogs. It should be emphasised that acute tubular necrosis is a continuation of pre-renal azotaemia (Albright 2001). These pathological changes probably results from hypotension and overproduction of TNFα leading to renal ischaemia and hypoxia (Jacobson 2006, Máthé *et al*. 2007). The differentiation between reversible pre-renal azotaemia caused by hypotension and irreversible acute tubular necrosis is important for clinicians. Statistically significant correlation between the duration of the disease and RFI showed that the duration of the period between the first clinical signs and the beginning of proper therapy is extremely important. Early diagnosis of pre-renal azotaemia and appropriate therapy may prevent development of irreversible acute tubular necrosis (Albright 2001). Lack of statistical significance (but at the limit of statistical significance) in the correlation between UCr/SCr ratio and duration of the disease probably resulted from the small group of dogs.

This work confirmed the results of a previous study (Máthé *et al*. 2007) in which acute tubular necrosis was detected in infected dogs in Hungary. Moreover, the authors of this study showed that UCr/SCr ratio and RFI may be useful tools in the diagnosis of pre-renal azotaemia and acute tubular necrosis in canine babesiosis.

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